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Twelve-week secukinumab treatment is consistently efficacious for moderate-to-severe psoriasis regardless of prior biologic and non-biologic systemic treatment: *Post hoc* analysis of six randomised trials

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Abstract

Background The efficacy of biologic therapies is greater among biologic-naïve vs. biologic-experienced psoriasis patients. However, little is known as to whether prior use of other systemic therapies impacts secukinumab efficacy in patients with moderate-to-severe psoriasis.

Objective To investigate the impact of prior exposure to systemic therapies upon the efficacy and safety of secukinumab 300 mg for moderate-to-severe psoriasis.

Methods *Post hoc* analysis of six randomised controlled trials (RCTs) comparing secukinumab with placebo, ustekinumab or etanercept at 12 weeks of treatment. Data comparing secukinumab with placebo and ustekinumab were meta-analysed, while comparisons between secukinumab and etanercept were from a single RCT. Four subgroups of patients were assessed: (i) naïve to non-biologic systemics (NBS) and biologics; (ii) exposed to NBS but naïve to biologics; (iii) naïve to NBS but exposed to biologics; and (iv) exposed to NBS and biologics. Outcomes of interest included the following: investigator's global assessment (IGA) score, absolute psoriasis area and severity index (PASI) response, PASI 75, PASI 90 and PASI 100 responses, and dermatology life quality index (DLQI). Safety was also assessed.

Results One thousand three hundred and eighty-three patients were included in the secukinumab vs. placebo meta-analysis: 1776 in the secukinumab vs. ustekinumab meta-analysis and 653 in the within-trial analyses of secukinumab vs. etanercept. For all subgroups, secukinumab was significantly more efficacious than placebo for all outcomes measured. Secukinumab generated greater responses in biologic-naïve patients, while prior NBS had a negligible impact on treatment response. Furthermore, secukinumab was more efficacious than both ustekinumab and etanercept on many outcomes, with an even greater difference for biologic-naïve than biologic-exposed patients. Safety results were consistent with individual clinical trial results.

Conclusions Twelve-week treatment with secukinumab 300 mg is consistently more efficacious than placebo, etanercept and ustekinumab in patients with moderate-to-severe psoriasis, regardless of prior exposure to biologics or NBS. Secukinumab had a comparable safety profile to both etanercept and ustekinumab.

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Conflict of interest

Dr. Hampton has nothing to disclose. Anna Halliday is a permanent employee of Novartis Pharmaceuticals UK Ltd. Dr. Aassi is an employee of Novartis. Ms. Subramanian is an employee of Novartis Healthcare Pvt. Ltd. Dr. Jain is an employee of Novartis Healthcare Pvt. Ltd. Dr. Griffiths reports grants and personal fees from Almirall, Celgene, Eli Lilly, Janssen and Novartis; personal fees from Amgen, BMS, LEO Pharma and AbbVie; and grants from Sandoz and UCB Pharma, during the conduct of the study.

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Introduction

Psoriasis is a psychologically disabling and often painful skin disorder with no cure, which is estimated to affect at least 60 million individuals worldwide.[1] It has a high disease burden that negatively affects patients' lives to a degree comparable with diseases such as diabetes and cancer and, in severe disease, reduces life span.[2,3]

Treatment can help control the symptoms of psoriasis, with long-term treatment generally required.[4] Guidelines largely recommend topical therapies, such as corticosteroids and vitamin D in the first line; phototherapies, including broad- or narrow-band ultraviolet (UV) B radiation and psoralen plus ultraviolet A radiation (PUVA), and non-biologic systemics (NBS), such as ciclosporin, methotrexate and acitretin in the second line; and biologics in the third line.[5–7] Biologic therapies licensed for the treatment of psoriasis include those targeting tumour necrosis factor-alpha (TNF-α; e.g. adalimumab, etanercept and infliximab), interleukin (IL)-23 (e.g. guselkumab, tildrakizumab and risankizumab), IL-12/23 (e.g. ustekinumab) and agents targeting the IL-17 pathway (e.g. secukinumab, brodalumab and ixekizumab).[4,8–10]

IL-17 is a pro-inflammatory cytokine secreted primarily not only by Th17 cells, but also by natural killer (NK) cells, mast cells and neutrophils, and by some Treg cells during acute infection and under some pathological conditions.[11,12] Th17 cells are a subset of T-helper cells that play a role in many immune-mediated disorders, including psoriasis and psoriatic arthritis.[12] Secukinumab is a fully human monoclonal antibody that targets IL-17A, thereby inhibiting the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage.[13] It has been demonstrated that both IL-23 and IL-17F transcripts were reduced by secukinumab treatment – disrupting an IL-17A-dependent feedback mechanism leading to reduction in both IL-17A and IL-17F as early as Week 4 after treatment, sustained to Week 12.[14] Indeed, secukinumab has been shown to reduce erythema, induration and desquamation in plaques of psoriasis.[13] It gained European approval in 2015 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.[13]

It is well established that, for patients with psoriasis, the efficacy of biologic therapies is greater among biologic-naïve than biologic-exposed patients.[15–18] However, little is known as to whether prior receipt of other systemic therapies, such as methotrexate, impacts the efficacy of secukinumab vs. placebo or other biologic therapies in patients with moderate-to-severe psoriasis.

The objective of the current study was to examine the efficacy and safety of secukinumab for the treatment of moderate-to-severe psoriasis via *post hoc* analysis of six randomised controlled trials (RCTs), according to prior exposure to systemic therapies, including the number of prior NBS.

Materials and methods

Study design and trials

This was a *post hoc* analysis of six large, registrational and postregistration RCTs that directly compared head-to-head secukinumab with placebo and other biologics in plaque psoriasis.[19–23] These six RCTs provided the patient-level data with information on prior systemic therapies required to analyse their impact upon the safety and efficacy of secukinumab in adults with moderate-to-severe, chronic, plaque-type psoriasis (Table 1). Briefly, patients were eligible for inclusion in these six RCTs if they had been diagnosed with moderate-to-severe plaque psoriasis for at least 6 months, affecting ≥10% of body area, with a psoriasis area and severity index (PASI) score ≥12 and investigator's global assessment (IGA) score ≥3. Patients were excluded from the trials if they had forms of psoriasis other than plaque psoriasis, had significant medical problems (such as uncontrolled high blood pressure and congestive heart failure) or had previously received secukinumab or drugs targeting IL-17 or its receptor.

Data analysis

Data from patients who received the licensed dose of secukinumab (300 mg monthly) or placebo, ustekinumab or etanercept were analysed. Patients who did not satisfy inclusion criteria or met any exclusion criterion (also known as screening failures), or those who were taking the drugs of interest but had no information on date of medication (past/concomitant) were excluded.

Table 1 Trials included in the *post hoc* analysis of the efficacy and safety of secukinumab in patients with moderate-to-severe psoriasis

Trial name (registration number)	Treatments	*N*†	Study time	Primary endpoint assessment	Location
ERASURE[21] (NCT01365455)	Secukinumab 150 mg/300 mg vs placebo	951	2011–2012	12 weeks	International
FEATURE[20] (NCT01555125)	Secukinumab 150 mg/300 mg vs placebo	209	2012	12 weeks	International
JUNCTURE[22] (NCT01636687)	Secukinumab 150 mg/300 mg vs placebo	220	2012	12 weeks	International
FIXTURE[21] (NCT01358578)	Secukinumab 150 mg/300 mg vs placebo or etanercept 50 mg	1560	2011–2012	12 weeks	International
CLEAR[23] (NCT02074982)	Secukinumab 300 mg vs ustekinumab‡	808	2014	16 weeks	International
CLARITY[19] (NCT02826603)	Secukinumab 300 mg vs ustekinumab‡	1353	2016–2018	12 weeks	International

†Includes screening failures.
‡Dosing as per approved label.

The secukinumab vs. placebo, and secukinumab vs. ustekinumab comparisons were meta-analysed separately, according to prior exposure to biologics and/or NBS, and the number of prior NBS to which patients had been exposed. These meta-analyses used data from the placebo-controlled trials ERASURE, FEATURE, JUNCTURE and FIXTURE, and the two ustekinumab-controlled CLEAR and CLARITY trials, respectively.[19–23] Similarly, for the comparison between secukinumab vs. etanercept, data from the head-to-head RCT FIXTURE were used. Analysis based on number of prior biologics was not possible, as very few patients had taken more than one biologic. For consistency, all trial data were analysed after 12 weeks of treatment, given that this was the time point for the measurement of the primary endpoint in all RCTs except CLEAR (16 weeks).

Patient groups and therapies

Patients were stratified into one of four subgroups according to their prior exposure to biologic and NBS therapies (Table 2): Subgroup 1: naïve to both NBS and biologics; Subgroup 2: exposed to NBS but naïve to biologics; Subgroup 3: naïve to NBS but exposed to biologics; and Subgroup 4: exposed to both NBS and biologics. Though exposure to biologics before NBS is uncommon, most Subgroup 3 patients were from the United States where biologics can be prescribed before systemics, which may not reflect clinical practice in other regions. Efficacy and safety endpoints were analysed in each of these four subgroups separately, as well as in the following four combinations: biologic-naïve (Subgroups 1 and 2), regardless of prior exposure to NBS; NBS-naïve (Subgroups 1 and 3), regardless of prior exposure to biologics; biologic-exposed (Subgroups 3 and 4), regardless of prior exposure to NBS; and NBS-exposed (Subgroups 2 and 4), regardless of prior exposure to biologics. The therapies included in this analysis and considered to be either NBS or biologics are detailed in Supplementary file 1.

Given the extensive problem of missing data regarding the use of corticosteroids, prior systemic corticosteroid exposure of ≥30 days was disregarded in the analysis. However, this decision should not have influenced results because, based on the limited observations available, the use of corticosteroids for this period of time was evenly distributed across all subgroups.

Outcome measures

All efficacy and safety endpoints analysed here are dichotomous and listed below:

- IGA score (0/1 vs. >1) [5-point discrete scoring system: 0 – clear skin, 4 – severe lesions].[24]
- Absolute PASI (≤3 vs. >3 and ≤1.5 vs. >1.5) [assessment of severity of lesions and the area affected, 0 – no disease, 72 – maximal disease].[25]
- PASI 90/100 [binary indicator, represents 90%, 100% improvement in patient PASI from baseline].[25]
- Dermatology life quality index (DLQI) (0/1 vs. >1) [0/1 – no effect on patient's life; 30 – maximum effect on patient's life].[26]

Safety outcomes were any adverse event (AE) and serious AE, categorised as treatment emergent and occurred during treatment, that were reported after 12 weeks of treatment.

Statistical analyses

Relative risk (RR) estimates with 95% confidence intervals (CI) were reported for each subgroup, as well as for the combination groups. The analysis was carried out using a meta-package and R statistical software (version 3.5.1; https://www.r-project.org). Cochran's Q test and I^2 statistic were used to determine the statistical heterogeneity arising due to variation in the included studies. An I^2 value >50% was considered as substantial heterogeneity[27] and, where this was observed,[28] random-effect models were used to compute the RR. However, if the inter-study heterogeneity was not substantial, the inverse variance method was used to calculate the fixed-effects estimate. It should be noted that heterogeneity factor is less reliable if fewer studies are meta-analysed. RR values for within-trial analysis were obtained using the standard formula.

Statistical significance of RR value can be inferred from the 95% confidence interval. If the 95% CI of the ratio contains the value 1, the *P*-value will be >0.05, indicating it is not statistically

Table 2 Patient distribution across the six included trials, according to prior systemic therapy exposure. NBS, non-biologic systemic

		Biologic-naïve				Biologic-exposed			
		Placebo	Ustekinumab	Etanercept†	Secukinumab	Placebo	Ustekinumab	Etanercept†	Secukinumab
NBS-naïve		Subgroup 1				Subgroup 3			
	4 trials†	256 (118)	274	–	110	67 (8)	51	–	7
	CLEAR	112	–	107	–	8	–	6	–
	CLARITY	246	–	247	–	45	–	64	–
NBS-exposed		Subgroup 2				Subgroup 4			
	4 trials†	299 (176)	280	–	178	69 (25)	87	–	31
	CLEAR	182	–	191	–	34	–	34	–
	CLARITY	199	–	178	–	60	–	63	–

†ERASURE/FEATURE/JUNCTURE and FIXTURE.

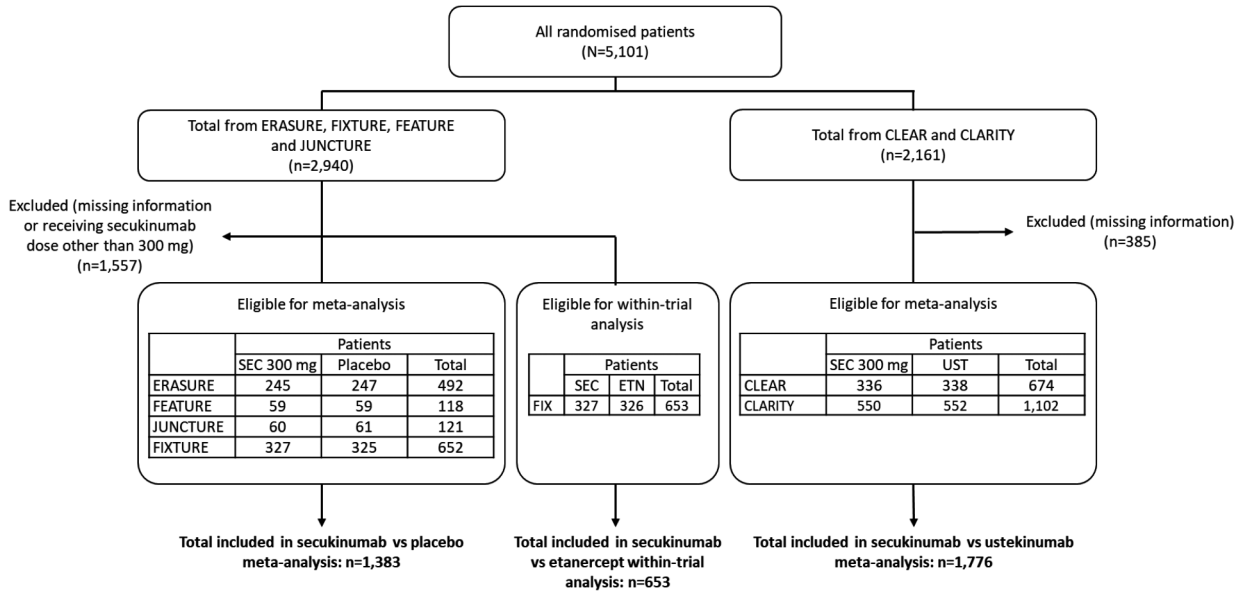

Figure 1 Patient flow in the six included trials and number of patients included in the analyses. ETN, etanercept; SEC, secukinumab; UST, ustekinumab.

significant. Alternatively, if the 95% CI does not contain the value 1, the *P*-value is strictly <0.05.[29]

Results

A total of 5101 patients were enrolled across six RCTs. After removing patients who failed screening, had missing medication dates or received secukinumab doses other than 300 mg (Fig. 1), 1383 patients were included in the secukinumab vs. placebo meta-analysis: 1776 in the secukinumab vs. ustekinumab meta-analysis and 326 in the within-trial analyses of secukinumab vs. etanercept.

Efficacy of secukinumab relative to placebo

Efficacy of secukinumab vs. placebo, according to prior biologic or NBS therapy exposure For all subgroups, regardless of prior biologic or NBS therapy exposure, secukinumab was significantly more efficacious than placebo for all outcomes measured (Tables 3 and 4).

IGA scores. Overall, the likelihood of secukinumab-treated patients achieving IGA scores ≤1 when compared with placebo-treated patients was similar across Subgroups 1, 2 and 4 (RRs: 20.34–23.38), whereas the likelihood for patients naïve to NBS but exposed to biologics (Subgroup 3) was halved [RR 9.90 (2.56–38.22); Table 3]. When analysed in combination, there was little difference between biologic-naïve, biologic-exposed, NBS-naïve and NBS-exposed patients in terms of their likelihood of achieving IGA ≤1 while receiving secukinumab vs. placebo (Table 4).

PASI. When analysed both separately and in combination, biologic-naïve patients (Subgroups 1 and 2) were the most likely of the four subgroups to achieve PASI 90 or PASI 100 (Tables 3 and 4). Patients receiving secukinumab were over 25 times more likely to achieve such an improvement than patients receiving placebo. When combined, the biologic-naïve secukinumab patients were also more likely than the biologic-exposed patients to achieve absolute PASI ≤3 [RR, secukinumab vs. placebo, 33.92 (19.10–60.24) vs. 12.37 (5.60–27.33)] and PASI ≤1.5 [RR, secukinumab vs. placebo, 47.06 (21.15–104.74) vs. 24.24 (6.98–84.15), Table 4].

When compared with placebo, patients naïve to NBS but exposed to biologics (Subgroup 3) were over eight and four times more likely to achieve PASI 90 or PASI 100, respectively, on secukinumab. However, these results should be interpreted with caution because of the small sample size for this subgroup (n = 118).

DLQI. Patients on secukinumab who were biologic-exposed (Subgroups 3 and 4) were the most likely of the four subgroups to achieve DLQI ≤1, when analysed both separately and together (Table 3), possibly due to the extremely low response rates seen among placebo patients in these groups. When analysed separately, biologic-exposed patients receiving secukinumab were at least 5 times more likely to achieve such scores than patients receiving

Table 3 Single group meta-analysis of secukinumab vs. placebo, according to prior systemic therapy exposure

Subgroup		Likelihood of, and proportion of patients, achieving outcome, (RR [95% CI]); %‡															
		IGA ≤1		DLQI ≤1		PASI 75		PASI 90		PASI 100		Absolute PASI (≤3)		Absolute PASI (≤1.5)			
		SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO		
Naïve to both NBS and biologics (Subgroup 1; *n* = 530)	RR	20.34 [10.64–38.88]		5.00 [3.53–7.08]		14.21 [8.67–23.29]		32.10 [13.39–76.96]		30.89 [8.88–107.50]		24.69 [12.44–49.03]		30.22 [12.59–72.51]			
	%‡	71	3	60	11	82	5	58	1	30	0	73	3	55	1		
Exposed to NBS but naïve to biologics (Subgroup 2; *n* = 579)	RR	23.28 [11.70–46.30]		5.69† [3.10–10.43]		21.62 [11.55–40.46]		40.93 [14.40–116.34]		25.79 [6.39–104.04]		33.07 [13.86–78.92]		45.08 [13.09–155.18]			
	%‡	67	3	58	9	79	3	56	1	26	0	69	1	48	0		
Patients taken 1 prior NBS in Subgroup 2 (*n* = 398)	RR	20.57 [9.30–45.46]		5.04† [2.13–11.92]		17.80 [8.81–35.97]		27.69 [9.76–78.54]		20.63 [5.14–82.80]		21.96 [9.24–52.20]		31.90 [9.29–109.46]			
	%‡	65	3	56	9	75	4	54	1	26	0	67	2	47	1		
Patients taken >1 prior NBS in Subgroup 2 (*n* = 181)	RR	16.16 [5.77–45.24]		5.30 [2.68–10.46]		20.25 [7.29–56.26]		15.42 [3.91–60.85]		10.60 [2.01–55.96]		19.27 [4.97–74.65]		13.53 [3.41–53.72]			
	%‡	69	2	62	8	87	2	60	0	24	0	71	0	51	0		
Naïve to NBS but exposed to biologics (Subgroup 3; *n* = 118)	RR	9.90 [2.56–38.22]		9.19 [2.38–35.47]		11.25 [3.37–37.61]		8.87 [2.29–34.36]		4.64 [1.11–19.48]		10.42 [3.11–34.92]		8.12 [2.08–31.69]			
	%‡	63	0	52	0	69	2	52	0	28	0	63	2	49	0		
Exposed to both NBS and biologics (Subgroup 4; *n* = 156)	RR	20.54 [5.96–70.84]		9.82 [3.90–24.73]		13.53 [5.14–35.62]		16.91 [4.80–59.59]		8.57 [2.34–31.37]		8.55 [3.56–20.52]		15.60 [4.41–55.19]			
	%‡	59	1	54	5	77	3	51	1	22	1	61	5	46	1		

CI, confidence interval; DLQI, dermatology life quality index; IGA, investigator's global assessment; NBS, non-biologic systemic; PASI, psoriasis area and severity index; PBO, placebo; RR, relative risk; SEC, secukinumab.
†Random-effects model used due to observed heterogeneity: I^2 >50%.
‡Proportions of patients with outcomes across all studies calculated using 'naïve-pooling' approach, not results of the meta-analysis, in which larger studies get more weight.

Table 4 Combination group meta-analysis of secukinumab vs. placebo, according to prior systemic therapy exposure

Group		Proportion of patients achieving outcome, % (RR‡ [95% CI])															
		IGA ≤1		DLQI ≤1		PASI 75		PASI 90		PASI 100		Absolute PASI (≤3)		Absolute PASI (≤1.5)			
		SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO	SEC	PBO		
Biologic-naïve (*n* = 1109) (Subgroups 1 + 2)	RR	22.29 [13.71–36.25]		5.65 [4.36–7.32]		18.05 [12.13–26.87]		44.75 [21.35–93.76]		51.25 [14.77–177.85]		33.92 [19.10–60.24]		47.06 [21.15–104.74]			
	%‡	68	3	59	10	80	4	57	1	28	0	71	2	51	1		
NBS-naïve (*n* = 648) (Subgroups 1 + 3)	RR	22.68 [11.86–43.39]		5.98 [4.22–8.46]		15.13 [9.36–24.45]		36.93 [15.40–88.60]		35.95 [10.34–125.00]		25.02 [13.10–47.79]		34.72 [14.46–83.35]			
	%‡	69	2	59	10	79	5	57	1	30	0	71	2	54	1		
Biologic-exposed (*n* = 274) (Subgroups 3 + 4)	RR	31.85 [9.25–109.61]		15.10 [6.02–37.90]		17.93 [7.56–42.55]		26.61 [7.69–92.06]		13.11 [3.68–46.66]		12.37 [5.60–27.33]		24.24 [6.98–84.15]			
	%‡	61	1	53	3	73	3	51	1	25	1	62	4	48	1		
NBS-exposed (*n* = 735) (Subgroups 2 + 4)	RR	26.25 [13.71–50.25]		6.63† [3.65–12.04]		22.04 [12.76–38.06]		49.93 [18.76–132.90]		30.07 [8.61–104.98]		25.24 [12.96–49.17]		54.21 [17.48–168.05]			
	%‡	65	2	57	8	78	3	55	1	25	0	67	2	48	1		

CI, confidence interval; DLQI, dermatology life quality index; IGA, investigator's global assessment; NBS, non-biologic systemic; PASI, psoriasis area and severity index; PBO, placebo; RR, relative risk; SEC, secukinumab.
†Random-effects model used due to observed heterogeneity: I^2 >50%.
‡Proportions of patients with outcomes across all studies calculated using 'naïve-pooling' approach, not results of the meta-analysis, in which larger studies get more weight.

Table 5 Within-trial analysis (single groups) of secukinumab vs. etanercept, according to prior systemic therapy exposure

Subgroup		Likelihood of, and proportion of patients, achieving outcome, (RR [95% CI]); %†													
		IGA ≤1		DLQI ≤1		PASI 75		PASI 90		PASI 100		Absolute PASI (≤3)		Absolute PASI (≤1.5)	
		SEC	ETN	SEC	ETN	SEC	ETN	SEC	ETN	SEC	ETN	SEC	ETN	SEC	ETN
Naïve to both NBS and biologics (Subgroup 1; *n* = 228)	RR	2.46 [1.74–3.49]		1.92 [1.40–2.63]		1.78 [1.40–2.28]		2.50 [1.65–3.79]		6.29 [2.27–17.41]		2.35 [1.69–3.25]		3.66 [2.16–6.20]	
	%	63	25	59	31	75	42	50	20	23	4	66	28	47	13
Exposed to NBS but naïve to biologics (Subgroup 2; *n* = 354)	RR	2.30 [1.78–2.97]		1.57 [1.23–1.99]		1.81 [1.50–2.18]		2.71 [1.97–3.71]		5.82 [2.83–11.96]		2.40 [1.84–3.13]		3.00 [2.04–4.40]	
	%	66	29	55	35	77	43	56	21	26	4	65	27	45	15
Patients taken 1 prior NBS in Subgroup 2 (*n* = 239)	RR	2.31 [1.68–3.17]		1.63 [1.21–2.20]		1.76 [1.39–2.22]		3.06 [2.01–4.67]		5.04 [2.18–11.63]		2.35 [1.70–3.25]		3.29 [2.00–5.41]	
	%	64	27	55	33	74	41	55	17	26	5	64	26	45	13
Patients taken >1 prior NBS in Subgroup 2 (*n* = 115)	RR	2.30 [1.51–3.52]		1.44 [0.95–2.18]† 0.084937		1.93 [1.41–2.64]		2.25 [1.40–3.61]		8.18 [1.96–34.17]		2.52 [1.60–3.99]		2.58 [1.41–4.71]	
	%	69	30	53	37	84	43	60	27	27	3	67	27	47	18
Naïve to NBS but exposed to biologics (Subgroup 3; *n* = 15)	RR	1.75 [0.45–6.82]† 0.427618		3.50 [0.5–24.41]† 0.208209		0.88 [0.34–2.25]† 0.803016		1.75 [0.45–6.82]† 0.427618		Cannot be determined‡		1.17 [0.39–3.51]† 0.791778		1.75 [0.45–6.82]† 0.427618	
	%	50	29	50	14	50	57	50	29	13	0	50	43	50	29
Exposed to both NBS and biologics (Subgroup 4; *n* = 56)	RR	1.74 [0.94–3.22]† 0.07746		1.35 [0.72–2.53]† 0.354975		1.55 [1.05–2.30]		2.48 [1.09–5.67]		2.48 [0.49–12.45]† 0.274455		1.69 [0.95–3.00]† 0.073266		2.07 [0.87–4.90]† 0.09871	
	%	56	32	48	35	80	52	48	19	16	6	60	35	40	19

CI, confidence interval; DLQI, dermatology life quality index; ETN, etanercept; IGA, investigator's global assessment; NBS, non-biologic systemic; PASI, psoriasis area and severity index; RR, relative risk; SEC, secukinumab.
†95% CI for RR includes 1, i.e. the groups are not statistically significantly different.
‡It was not possible to calculate RRs for response for those outcome measures not achieved by any patients in one of the treatment arms.

placebo (Table 3). When analysed together, the RR for response for patients in these subgroups was 15.10 (95% CI: 6.02–37.90; Table 4).

Efficacy of secukinumab vs. placebo, according to number of prior NBS therapies

Further analysis of Subgroup 2 (NBS-exposed, biologic-naïve) confirmed that, regardless of the number of prior NBS therapies, secukinumab was significantly more efficacious than placebo for all outcomes measured (Table 3). Although this analysis was conducted on small patient numbers, numerical comparison between the patient groups previously exposed to one, or more than one, NBS indicated that secukinumab efficacy was even greater among patients with exposure to just one prior NBS. This was particularly evident with the more stringent PASI response criteria, where exposure to only one NBS, compared with more than one, doubled the likelihood of reaching PASI 90 [RR 27.69 (9.76–78.54) vs. 15.42 (3.91–60.85)], PASI 100 [RR 20.63 (5.14–82.80) vs. 10.60 (2.01–55.96)] and absolute PASI score ≤1.5 [RR 31.90 (9.29–109.46) vs. 13.53 (3.41–53.72), Table 3].

Efficacy of secukinumab relative to active comparators

Efficacy of secukinumab vs. etanercept and ustekinumab, according to prior biologic or NBS therapy exposure While not all results were statistically significant, for Subgroup 1 and Subgroup 2 secukinumab was found to be more efficacious than etanercept or ustekinumab on almost all outcomes assessed (Tables 5 and 6, respectively). For Subgroups 3 and 4, while secukinumab was numerically better than either etanercept or ustekinumab, in the main, these results were not significant, potentially due to small sample sizes.

IGA scores. The likelihood of achieving IGA scores ≤1 was significantly higher for secukinumab-treated patients than either etanercept- or ustekinumab-treated patients in Subgroups 1, 2 and 3 (ustekinumab-treated patients only) but did not reach statistical significance in Subgroup 4 (Tables 5 and 6 for etanercept and ustekinumab, respectively). Similar effects were seen when these subgroups were analysed in combination, where significant changes were seen in all groups, apart from in the biologic-exposed cohort (Subgroups 3 + 4) for both the etanercept and

Table 6 Single group meta-analysis of secukinumab vs. ustekinumab, according to prior systemic therapy exposure

Subgroup		Likelihood of, and proportion of patients achieving outcome, (RR [95% CI]); %§													
		IGA ≤1		DLQI ≤1		PASI 75		PASI 90		PASI 100		Absolute PASI (≤3)		Absolute PASI (≤1.5)	
		SEC	UST	SEC	UST	SEC	UST	SEC	UST	SEC	UST	SEC	UST	SEC	UST
Naïve to both NBS and biologics (Subgroup 1; *n* = 712)	RR	1.19† [1.00–1.41]‡ 0.05		1.10 [0.97–1.24]‡ 0.1232		1.10† [0.99–1.23]‡ 0.0755		1.21 [1.08–1.37]		1.52 [1.22–1.88]		1.16 [1.06–1.27]		1.29 [1.13–1.48]	
	%§	73	63	63	57	86	79	66	55	40	26	79	68	61	48
Exposed to NBS but naïve to biologics (Subgroup 2; *n* = 750)	RR	1.30 [1.18–1.43]		1.26 [1.11–1.43]		1.17† [1.04–1.31]		1.47 [1.30–1.65]		1.81 [1.44–2.27]		1.33 [1.21–1.46]		1.55 [1.35–1.78]	
	%§	79	60	64	51	89	76	72	49	40	22	81	61	66	43
Patients taken 1 prior NBS in Subgroup 2 (*n* = 471)	RR	1.25 [1.11–1.40]		1.19 [1.02–1.39]		1.14† [0.94–1.38]‡ 0.1752		1.41 [1.22–1.64]		1.78 [1.32–2.39]		1.29† [1.04–1.60]		1.55 [1.31–1.84]	
	%§	79	63	64	54	89	78	72	51	39	22	82	63	68	44
Patients taken >1 prior NBS in Subgroup 2 (*n* = 279)	RR	1.38 [1.17–1.63]		1.38 [1.11–1.71]		1.22 [1.09–1.37]		1.56 [1.28–1.92]		1.84 [1.28–2.66]		1.41 [1.20–1.66]		1.53 [1.20–1.94]	
	%§	79	57	64	46	88	73	72	46	42	23	80	58	63	41
Naïve to NBS but exposed to biologics (Subgroup 3; *n* = 123)	RR	1.54 [1.10–2.17]		1.45 [1.07–1.96]		1.30 [1.05–1.61]		1.99 [1.37–2.88]		2.06 [1.06–4.02]		1.48 [1.14–1.93]		1.62 [1.10–2.39]	
	%§	62	41	68	47	81	63	66	34	32	16	75	51	57	36
Exposed to both NBS and biologics (Subgroup 4; *n* = 191)	RR	1.33† [0.84–2.12]‡ 0.2267		1.26 [0.97–1.63]‡ 0.0867		1.32 [1.10–1.57]		1.33† [0.68–2.58]‡ 0.4066		2.19† [0.62–7.68]‡ 0.2213		1.23† [0.84–1.82]‡ 0.2861		1.43 [0.98–2.07]‡ 0.0613	
	%§	62	44	61	48	83	63	53	38	24	10	66	52	45	30

CI, confidence interval; DLQI, dermatology life quality index; IGA, investigator's global assessment; NBS, non-biologic systemic; PASI, psoriasis area and severity index; RR, relative risk; SEC, secukinumab; UST, ustekinumab.
†Random-effects model due to observed heterogeneity: I^2 >50%.
‡95% CI for RR includes 1, i.e. the groups are not statistically significantly different.
§Proportions of patients with outcomes across all studies calculated using 'naïve-pooling' approach, not results of the meta-analysis, in which larger studies get more weight.

ustekinumab comparisons (Supplementary file 2 and Supplementary file 3).

PASI. Patients on secukinumab in Subgroups 1 and 2 were significantly more likely than patients on etanercept or ustekinumab to achieve PASI 90 or PASI 100 at 12 weeks, with similar results observed for the comparison with ustekinumab in Subgroup 3 (Tables 5 and 6, respectively). Subgroup 1 and Subgroup 2 patients were more than twice as likely to achieve PASI 90, and more than 5 times as likely to achieve PASI 100, on secukinumab than on etanercept (Table 5). Secukinumab-treated patients in these subgroups were also more likely to achieve absolute PASI scores ≤3 and ≤1.5 than patients on etanercept or ustekinumab, respectively (Tables 5 and 6).

DLQI. The likelihood of achieving DLQI scores ≤1 was significantly higher for secukinumab-treated patients than etanercept-treated patients in Subgroups 1 and 2, and numerically higher in Subgroups 3 and 4 (Table 5). And, when compared with ustekinumab, secukinumab-treated patients in Subgroups 2 and 3 had a significantly higher likelihood of achieving a DLQI score ≤1. Numerically higher likelihoods were seen in Subgroups 1 and 4 (Table 6).

Efficacy of secukinumab vs. active comparators, according to number of prior NBS therapies Further analysis of Subgroup 2 (NBS-exposed, biologic-naïve) showed that, regardless of the number of prior NBS therapies, secukinumab was more efficacious than both etanercept and ustekinumab (Tables 5 and 6, respectively). The additional benefit with secukinumab was almost always statistically significant, except in two comparisons where significance was not reached.

Safety analysis Across all subgroups, at 12 weeks post-treatment, the likelihood of the patient experiencing an adverse event was similar between all active treatment arms (Table 7). Quantitatively, no new clinically reported safety signals were identified during the analysis.

Discussion

Meta-analysis of four placebo-controlled RCTs showed that secukinumab was significantly more efficacious than placebo for

Table 7 Safety analysis with outcomes as any adverse event and serious adverse event

Comparator	Adverse event		Likelihood of, and proportion of patients, experiencing adverse events, (RR [95% CI]); %							
			Subgroup							
			Subgroup 1		Subgroup 2		Subgroup 3		Subgroup 4	
			SEC	Comp	SEC	Comp	SEC	Comp	SEC	Comp
Placebo	Any adverse event	RR	1.18 [1.00–1.40]§ 0.0548		1.18 [1.01–1.38]		0.92 [0.75–1.13]§ 0.4136		1.05 [0.78–1.42]§ 0.7393	
		%‡	54	46	58	49	57	55	54	51
	Serious adverse event	RR	2.10 [0.37–11.98]§ 0.4041		1.33 [0.37–4.86]§ 0.6618		1.18 [0.22–6.17]§ 0.8475		1.02 [0.21–5.11]§ 0.9766	
		%‡	2	1	2	1	4	2	3	3
Etanercept	Any adverse event	RR	0.81 [0.63–1.02]§ 0.086142		1.11 [0.92–1.34]§ 0.280184		1.53 [0.77–3.06]§ 0.229114		0.77 [0.49–1.20]§ 0.255509	
		%	48	56	59	53	88	57	52	68
	Serious adverse event	RR	0.93 [0.06–14.72]§ 0.96254		3.03 [0.32–28.89]§ 0.339808		Cannot be determined¶		Cannot be determined¶	
		%	1	1	2	1	0	0	0	0
Ustekinumab	Any adverse event	RR	1.00 [0.90–1.11]§ 0.9652		1.03† [0.87–1.23]§ 0.7319		0.96 [0.72–1.29]§ 0.8009		1.04 [0.87–1.24]§ 0.6798	
		%‡	66	66	68	66	58	61	73	70
	Serious adverse event	RR	1.19 [0.52–2.72]§ 0.6827		1.46 [0.74–2.90]§ 0.2751		1.42 [0.21–9.73]§ 0.7195		0.78† [0.04–15.92]§ 0.8713	
		%‡	3	3	5	4	4	3	3	4

CI, confidence interval; Comp, comparator; RR, relative risk; SEC, secukinumab.
†Random-effects model due to observed heterogeneity: I^2 >50%.
‡Proportions of patients with outcomes across all studies calculated using 'naïve-pooling' approach, not results of the meta-analysis in which larger studies get more weight.
§95% CI for RR includes 1, i.e. the groups are not statistically significantly different.
¶For within-trial analysis, it was not possible to calculate RRs where patients in one treatment arm did not experience an adverse event.

all outcomes measured, regardless of prior biologic or NBS therapy exposure. Compared with placebo, 12-week secukinumab treatment significantly increased the likelihood of achieving optimal IGA, PASI (across all response levels) and DLQI outcomes. Furthermore, all significant results from the analyses in which secukinumab was compared with two licensed biologics, etanercept and ustekinumab showed superior efficacy for secukinumab. These results agree with those of two recently published network meta-analyses: the first of which found secukinumab to be superior to placebo in terms of reaching PASI 90 (12–16 weeks after randomisation);[4] and the second found secukinumab to be more efficacious in terms of PASI (75, 90 and 100) than both etanercept and ustekinumab (52 weeks).[15]

Treatment with secukinumab was associated with improved responses compared with placebo on all outcomes assessed among biologic-naïve patients, regardless of NBS exposure. This finding was consistent among biologic-exposed patients, although responses were generally lower. Similarly, outcomes for patients on secukinumab were consistently better than for patients on etanercept and ustekinumab; again, biologic-naïve patients were generally more likely to respond than biologic-exposed patients, regardless of NBS exposure. These findings are in agreement with both clinical trial and real-world findings demonstrating that prior exposure to biologic therapies reduces the likelihood of efficacy of subsequent biologic therapies.[16–18,30]

In general, prior treatment with NBS had little effect on secukinumab efficacy; overall, the RRs for IGA, PASI and DLQI responses on secukinumab vs. placebo were similar in NBS-naïve patients (combined Subgroups 1 and 3) and NBS-experienced patients (combined Subgroups 2 and 4). This finding supports previous studies of biologics, which have found similar efficacy regardless of prior exposure to NBS.[15,31]

However, little is currently known about whether the number of prior NBS taken by a patient will affect the efficacy of treatment with a biologic. To address this, the RR values achieved by

patients exposed to one, or more than one, prior systemic were reported. Numerically, (vs. placebo) patients exposed to just one prior NBS appear to have better outcomes than those with multiple exposure, but these findings should be interpreted with caution due to small sample sizes.

Some limitations to the study should be noted. Although sample sizes within the groups were sufficiently large to generate robust estimates, low frequency of outcomes in the placebo groups led to relatively wide confidence intervals. Small sample sizes for the within-trial analyses of secukinumab vs. etanercept meant that RR for response could not be determined for all subgroups and outcomes. Moreover, statistical analysis was limited to within-group comparisons (e.g. secukinumab vs. comparator for each group); across-group statistical comparisons could not therefore be made. Heterogeneity was observed in some of the data sets; while all the included trials had similar inclusion and exclusion criteria, with minor variability in baseline characteristics, the observed heterogeneity could be due to the variation in baseline characteristics within the subgroups.

As further research, across-group statistical comparisons could be made using a comprehensive framework such as network meta-analysis. Additionally, this study assessed response at 12 weeks (the common primary endpoint for most studies); however, as psoriasis is a long-term condition, it would be interesting to observe whether these findings are sustainable in the long term. Finally, this was a *post hoc* analysis using clinical trial data and was not conducted using 'real-world' patients. Thus, the validity of these findings in relation to clinical practice may be limited.

Conclusions

This study demonstrated that 12-week treatment with secukinumab 300 mg is consistently more efficacious than placebo, etanercept and ustekinumab in patients with moderate-to-severe psoriasis, regardless of prior exposure to biologics or NBS. Safety analyses revealed that secukinumab had a comparable safety profile to both etanercept and ustekinumab, regardless of previous NBS or biologic exposure, supporting previous findings from head-to-head studies and real-world evidence.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Supplementary file 1. Biologic and non-biologic systemic therapies included in the meta-analyses.
Supplementary file 2. Within-trial analysis (combination groups) of secukinumab versus etanercept, according to prior systemic therapy exposure.
Supplementary file 3. Combination groups meta-analysis of secukinumab versus ustekinumab, according to prior systemic therapy exposure.