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Secukinumab in adult patients with lichen planus: efficacy and safety results from the randomized placebo-controlled proof-of-concept PRELUDE study

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Abstract

Background Patients with lichen planus (LP) refractory to available therapies often experience a high disease burden, representing a population with a clear unmet need for new treatments.

Objectives To evaluate the efficacy and safety of secukinumab 300 mg over 32 weeks in adult patients with biopsy-proven cutaneous LP (CLP), mucosal LP (MLP) or lichen planopilaris (LPP) that is inadequately controlled by topical corticosteroids.

Methods PRELUDE was a randomized double-blind placebo-controlled phase II proof-of-concept study that enrolled patients with CLP, MLP or LPP. Eligible patients were randomized to either secukinumab 300 mg every 4 weeks for 32 weeks (SECQ4W) or placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks (SECQ2W) for 16 weeks. The primary endpoint was achievement of the newly designed Investigator's Global Assessment (IGA) score ≤ 2 at week 16.

Results Overall, 111 patients were randomized ($n=37$ each) to CLP, MLP and LPP cohorts. As the proof-of-concept criteria were not met for any of the three cohorts, the primary objective was not met. A numerically higher proportion of patients achieved IGA ≤ 2 response at week 16 with SECQ4W vs. placebo in the MLP {37.5% [95% credibility interval (CrI) 20.3–57.2] vs. 23.1% (95% CrI 6.5–49.2)} and LPP cohorts [37.5% (95% CrI 20.2–57.3) vs. 30.8% (95% CrI 10.8–57.6)]. In the LPP cohort, a sustained response for IGA ≤ 2 from week 16 to week 32 was achieved with SECQ4W (week 16, 37.5%; week 32, 45.8%), and a substantial improvement was observed in IGA ≤ 2 response in patients from this cohort who switched from placebo (week 16, 30.8%) to SECQ2W after week 16 (week 32, 63.6%). The safety profile was consistent with the known profile of secukinumab and showed no new or unexpected signals.

Conclusions PRELUDE is the first randomized controlled basket trial evaluating interleukin (IL)-17A inhibition with secukinumab across three subtypes of LP. Secukinumab was well tolerated and safe, showing different response rates across the three subtypes, with numerical IGA improvements in MLP and LPP, and no response in CLP. The study raises the question of a differential role of IL-17A across LP subtypes. The novel IGA score showed significant correlation with both patient- and physician-reported outcome measurements.

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Lay summary

Lichen planus (LP) is a skin disease that causes itchy, reddish-purple bumps on the skin. LP can affect different parts of the body, including the skin, mouth, genitals and nails. People with LP often experience intense itch, pain and discomfort, which can affect their daily lives.

Secukinumab is a drug specifically designed to target and block a protein called 'interleukin-17A', which is found in high amounts in the lesions of LP.

We carried out a clinical study to look at the effect of secukinumab separately in three different types of LP: cutaneous LP (CLP), mucosal LP (MLP) and lichen planopilaris (LPP). The study was conducted in the USA, France and Germany. A total of 111 adults who had not responded to topical treatment (treatment applied directly on the skin) took part in the study. Patients were divided into two groups. In one group, patients were treated with secukinumab 300 mg every 4 weeks for 16 weeks and continued with the treatment for another 16 weeks. In the other group, patients received placebo for 16 weeks and then received secukinumab 300 mg every 2 weeks for the next 16 weeks. All the patients were followed up for 8 weeks after stopping treatment. We measured whether secukinumab could reduce symptoms associated with LP using both doctor- and patient-assessed severity and quality-of-life measures. We also measured the side-effects related to the drug.

We found that secukinumab was safe for people with LP, but it did not substantially reduce symptoms in people with CLP and only showed a tendency for improvement in people with MLP and LPP.

What is already known about this topic?

- About 30–50% of patients with lichen planus (LP) are refractory to current therapies and experience a high burden of disease owing to a lack of clinical symptom control.
- There is a lack of targeted systemic treatment options for patients with LP who are refractory to current topical treatments.

What does this study add?

- This phase II clinical trial shows different results for secukinumab 300 mg across the three studied subtypes of LP with numerical Investigator's Global Assessment (IGA) improvements in MLP and LPP, but no response in CLP.
- For this trial, a novel 5-point IGA grading system was developed to assess disease severity and treatment response, which showed significant correlation with both patient- and physician-reported outcome measurement tools.
- We hope to enable future clinical research in LP by making this new IGA score available at a later date.

Lichen planus (LP) is an immune-mediated skin disease with a prevalence of 1–2%.[1–3] It can present with a broad spectrum of clinical manifestations affecting primarily the skin [cutaneous LP (CLP)], the mucosae [mucosal LP (MLP)] or hair follicles [lichen planopilaris (LPP)].[4] The often treatment-refractory nature of the disease, the pronounced itch of CLP lesions, the pain of erosive MLP lesions and the visible impact of LPP-induced hair loss contribute to poor quality of life in patients with LP.[5] The pathogenesis of LP is yet to be fully understood. CLP and MLP lesions are infiltrated with T cells, including $CD8^+$ and $CD4^+$ populations. $CD8^+$ T cells, mainly located around the basal layer of the epidermis, can trigger apoptosis of epidermal keratinocytes.[6–11] A number of recent studies have suggested a potential role for interleukin (IL)-17A in the pathogenesis of LP; elevated IL-17A serum concentrations, increased numbers of T helper (Th)17 cells, and upregulation of IL-17A and Th17-derived cytokines in lesions of patients with LP have been described.[12–14] Specific autoreactive Th17 cells have been detected in the serum of patients with LP with a distinct Th17 cell infiltrate underneath the basal membrane zone in LP skin lesions.[12,13,15,16] Furthermore, an open-label case series has reported positive results for targeting the Th17 axis with IL-17A-, IL-12- or IL-12/23-directed monoclonal antibodies in LP.[17,18] These findings have led to the hypothesis that therapeutic targeting of IL-17A could lead to clinical improvement of LP.

Secukinumab is a fully human monoclonal antibody that selectively neutralizes IL-17A, a central cytokine of the Th17 axis, involved in the pathophysiology of other inflammatory skin diseases such as psoriasis or hidradenitis suppurativa. PRELUDE (ClinicalTrials.gov NCT04300296) is the first randomized controlled basket trial to evaluate a systemic treatment across three major subtypes of LP.

Patients and methods

Study design

PRELUDE was a multicentre randomized double-blind placebo-controlled parallel-group study evaluating the efficacy and safety of secukinumab 300 mg over 32 weeks in adult patients with three different biopsy-proven subtypes of LP. The study was conducted from July 2020 to May 2022 in three countries (USA, France, Germany) and recruited 111 patients at 36 sites. The study had a basket design, consisting of three separate cohorts, one per LP subtype, to ensure a homogeneous population within each cohort, i.e. CLP, MLP and LPP. PRELUDE had four study periods: screening

[screening (4 weeks) to baseline], treatment period (TP)1 (baseline to week 16), TP2 (week 16 to week 32), and a treatment-free safety follow-up period (week 32 to week 40) (Figure 1, Appendix S1; see Supporting Information). The study protocol and all amendments were reviewed by the Independent Ethics Committee and/or Institutional Review Board for each centre. The study was conducted according to the International Council for Harmonisation E6 Guidelines for Good Clinical Practice, which have their origin in the Declaration of Helsinki. Informed consent was obtained from each patient in writing at the screening visit and before any study-specific procedure was performed.

Participants

Eligible patients aged ≥ 18 years with biopsy-proven CLP, MLP or LPP; moderate or severe disease [based on an Investigator's Global Assessment (IGA) score of ≥ 3 on a scale from 0 to 4] at screening and baseline; and an inadequate response to topical corticosteroids of high/ultrahigh potency and eligible for systemic therapy in the opinion of the investigator were included. Detailed eligibility criteria are provided in Table S1 (see Supporting Information).

Endpoints

The primary objective of this study was to demonstrate the efficacy of secukinumab 300 mg administered every 4 weeks in patients with CLP, MLP or LPP that was inadequately controlled by topical therapies, with respect to achievement of IGA ≤ 2 at week 16, compared with placebo. Given the lack of well-established clinical assessment scores for LP, a novel, 5-point IGA grading system was developed for this trial to assess disease severity and treatment response in all three subtypes of LP in a harmonized way (Table S2; see Supporting Information). As an anchor variable for validation of the IGA score, a Patient Global Impression of Change (PGIC) patient-reported outcome (PRO) score was used across all cohorts.

Secondary endpoints were assessed over 32 weeks (from baseline to weeks 16 and 32, and throughout the duration of the study) and included the following: (i) achievement of ≥ 2 points improvement in IGA score (all cohorts); (ii) achievement of IGA 0/1 response (all cohorts); (iii) Physician Assessment of Surface Area of Disease (PSAD) (CLP); (iv) change from baseline in Reticular Erythematous Ulceration (REU) score (MLP); and (v) change from baseline in LPP Activity Index (LPPAI) score and proportion of LPPAI responders (LPP). PRO assessments included the following: (i) Dermatology Life Quality Index (DLQI) (all cohorts), (ii) patient assessment of itch over time (CLP and LPP) and (iii) patient assessment of pain and Oral Lichen Planus Symptoms Severity Measure (OLPSSM) score over time (MLP). Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory evaluations and vital signs, throughout the study.

Statistical analysis

All data were analysed separately for each cohort (CLP, MLP, LPP), if not otherwise specified. The analysis of the

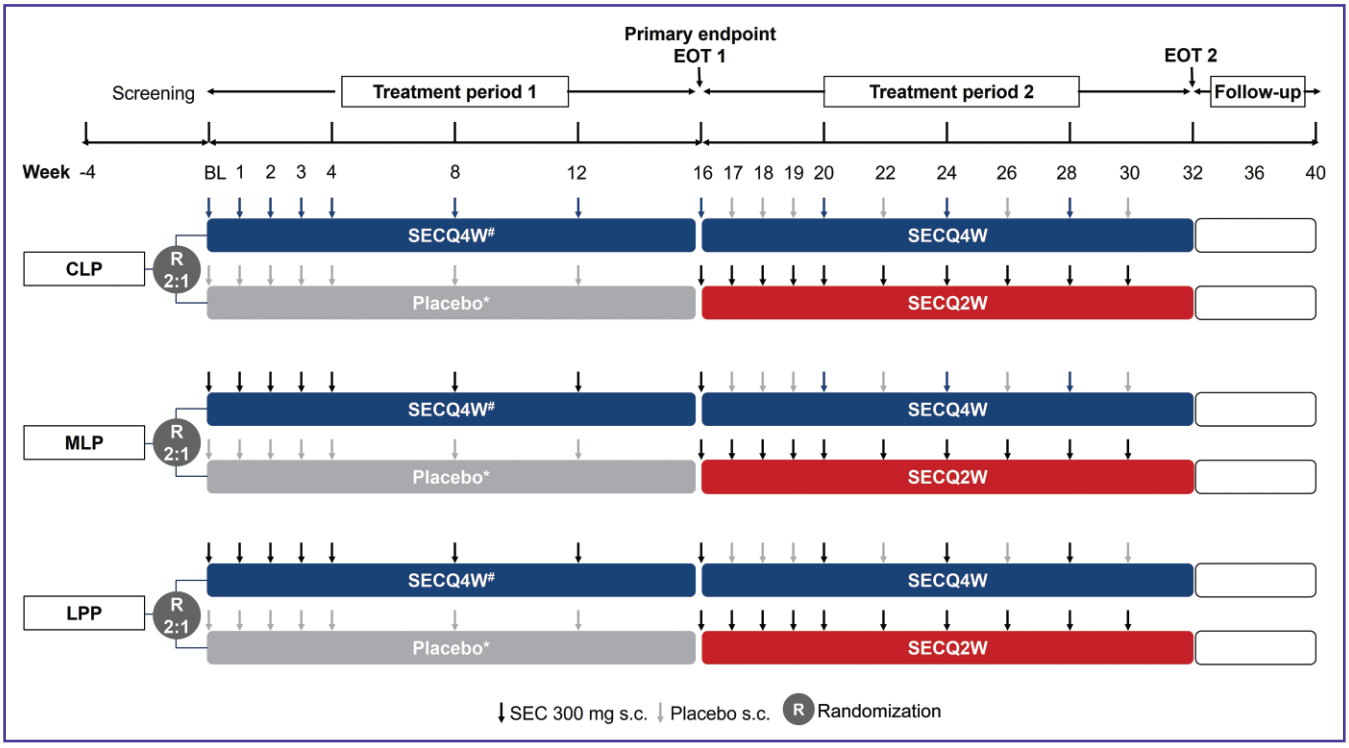

Figure 1 Basket study design.*Patients in the TP1 placebo treatment groups roll over to a SECQ2W dosing regimen after week 16, including a weekly induction for 5 weeks, with the exception of patients who achieved an IGA of 0 or 1 at week 16. #Patients receiving secukinumab in TP1 continued SECQ4W plus matching placebo injections. CLP, cutaneous lichen planus; EOT, end of treatment; LPP, lichen planopilaris; MLP, mucosal lichen planus; R, randomization; s.c., subcutaneous; SEC, secukinumab 300 mg; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks.

primary endpoint was based on the full analysis set (FAS). Bayesian inference based on the noninformative prior of beta (1/3, 1/3) for each treatment group was used to obtain the posterior distribution of the treatment difference between secukinumab and placebo for the three subtypes. Secondary efficacy endpoints were analysed separately for each cohort. For discrete data, the number and proportions (%) of each category were presented by visit for each treatment group. For continuous data, the absolute and percentage change from baseline by visit for each treatment group were provided. For safety analysis, exposure-adjusted incidence rates (EAIRs) for AEs were expressed as the incidence rate per 100 patient-years (PYs) of exposure based on the entire TP. Correlations between the IGA score and other endpoints (both measured as week-16 change from baseline) were evaluated using Spearman's rank correlation. The level of statistical significance was set at 5% ($P<0.05$). Further details of statistical procedures are described in Appendix S1.

Results

Patient disposition and demographics

Overall, 163 patients (across all three cohorts) were screened, 111 of whom were randomized to the CLP, MLP and LPP cohorts (Table 1). Overall, baseline demographics and disease characteristics were balanced between the treatment groups and across cohorts (Table 2). In the MLP cohort, the proportion of male patients was higher in the secukinumab group than in the placebo group (41.7% vs. 7.7%). In the CLP and MLP cohorts, patients in the secukinumab group had a higher mean body weight (kg) than those in the placebo group (CLP, 88.8 vs. 77.2; MLP, 83.0 vs. 73.0). In the MLP cohort, the proportion of patients with severe disease was higher in the placebo group than in the secukinumab group (38.5% vs. 8.3%).

Efficacy

Investigator's Global Assessment ≤ 2 response at week 16 for all cohorts

At week 16, the IGA ≤ 2 response rates in the secukinumab group vs. placebo group were 44.0% [95% credibility interval (CrI) 25.8–63.3] vs. 58.3% (95% CrI 31.0–82.6) in the CLP cohort, 37.5% (95% CrI 20.3–57.2) vs. 23.1% (95% CrI 6.5–49.2) in the MLP cohort and 37.5% (95% CrI 20.2–57.3) vs. 30.8% (95% CrI10.8–57.6) in the LPP cohort (Tables 3 S3; see Supporting Information). Although the secukinumab 300 mg every 4 weeks (SECQ4W) response rates were numerically higher than the placebo response rates for the MLP and LPP cohorts, the predefined proof-of-concept (PoC) criteria were not met for all three cohorts, and therefore the primary objective of the study was not met.

Secondary efficacy results by cohort

Cutaneous lichen planus cohort

Investigator's Global Assessment response. Overall, the IGA ≤ 2 response achieved at week 16 (44.0%) was maintained up to week 32 (37.5%) for the SECQ4W group. No improvement was seen in the placebo-secukinumab 300 mg every 2 weeks (placebo-SECQ2W) group from week 16 (50.0%) to week 32 (22.2%) (Figure 2). The correlation analysis showed a moderate correlation of IGA with PSAD ($r=0.64$, $P<0.001$) and PGIC ($r=0.58$, $P<0.001$). Other key endpoints evaluated included PSAD, patient assessment of itch and DLQI (Table 4). No relevant differences between secukinumab and placebo could be detected for these endpoints.

Mucosal lichen planus cohort

Investigator's Global Assessment response. At week 16, a numerically higher proportion of patients achieved an IGA ≤ 2 response in the SECQ4W group (37.5%) compared with placebo (23.1%). In the SECQ4W group, the response was sustained up to week 32 (39.1%). In the placebo-SECQ2W group, the IGA ≤ 2 response increased from 9.1% at week 16 to 20.0% at week 32 (Figure 3). A similar pattern was observed for the IGA improvement of ≥ 2 points and the IGA 0/1 response (Figure 3).

Given the numerically higher response of secukinumab vs. placebo in the MLP cohort, a post hoc analysis was conducted pooling all patients with predominant (from the MLP cohort) and concomitant MLP (patients from the CLP cohorts who had concomitant MLP). Patients in the secukinumab

Table 1 Patient disposition by cohort

	CLP (*N*=37)		MLP (*N*=37)		LPP (*N*=37)	
Treatment disposition/reason	**SECQ4W**	**Placebo-SECQ2W**	**SECQ4W**	**Placebo-SECQ2W**	**SECQ4W**	**Placebo-SECQ2W**
Randomized, *n*	25	12	24	13	24	13
Completed TP1 treatment	22 (88.0)	10 (83.3)	23 (95.8)	13 (100.0)	23 (95.8)	12 (92.3)
Entered TP2	22 (88.0)	8[a] (66.7)	23 (95.8)	11[a] (84.6)	23 (95.8)	12 (92.3)
Completed TP2 treatment	16 (64.0)	7 (58.3)	16 (66.7)	10 (76.9)	18 (75.0)	11 (84.6)
Primary reason for discontinuing treatment during entire TP						
Adverse event	1 (4.0)	0 (0.0)	2 (8.3)	0 (0.0)	2 (8.3)	0 (0.0)
Progressive disease	2 (8.0)	0 (0.0)	4 (16.7)	0 (0.0)	2 (8.3)	1 (7.7)
Patient decision	3 (12.0)	0 (0.0)	1 (4.2)	1 (7.7)	1 (4.2)	1 (7.7)
Protocol deviation	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as *n* (%) unless otherwise stated. CLP, cutaneous lichen planus; LPP, lichen planopilaris; MLP, mucosal lichen planus; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks; TP, treatment period. [a]Two patients in the placebo group in each of the CLP and MLP cohorts did not enter TP2 because they achieved spontaneous remission (Investigator's Global Assessment 0/1) at week 16.

Table 2 Baseline demographic and disease characteristics by cohort

	CLP		MLP		LPP	
Characteristic	**SECQ4W, *N*=25**	**Placebo, *N*=12**	**SECQ4W, *N*=24**	**Placebo, *N*=13**	**SECQ4W, *N*=24**	**Placebo, *N*=13**
Age group, *n* (%)						
<65 years	22 (88.0)	9 (75.0)	14 (58.3)	8 (61.5)	19 (79.2)	12 (92.3)
≥65 years	3 (12.0)	3 (25.0)	10 (41.7)	5 (38.5)	5 (20.8)	1 (7.7)
Sex, *n* (%)						
Female	15 (60.0)	8 (66.7)	14 (58.3)	12 (92.3)	20 (83.3)	10 (76.9)
Weight (kg)						
Mean (SD)	88.8 (20.46)	77.2 (17.24)	83.0 (24.45)	73.0 (15.75)	76.0 (17.11)	80.3 (25.20)
Median (Q1–Q3)	88.5 (73.0–95.25)	78.5 (61.0–82.5)	78.4 (69.0–92.96)	75.0 (68.0–83.3)	74.0 (63.2–84.3)	77.2 (63.0–86.0)
Race, *n* (%)						
Black or African American	6 (24.0)	4 (33.3)	2 (8.3)	1 (7.7)	1 (4.2)	0 (0.0)
White	19 (76.0)	8 (66.7)	19 (79.2)	12 (92.3)	23 (95.8)	13 (100.0)
Other	0 (0.0)	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking status, *n* (%)						
Never	11 (44.0)	7 (58.3)	18 (75.0)	7 (53.8)	17 (70.8)	11 (84.6)
Former	9 (36.0)	1 (8.3)	4 (16.7)	4 (30.8)	7 (29.2)	1 (7.7)
Current	5 (20.0)	4 (33.3)	2 8.3)	2 (15.4)	0 (0.0)	1 (7.7)
Baseline IGA score, *n* (%)						
1=Almost clear	1[a] (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3=Moderate	16 (64.0)	9 (75.0)	22 (91.7)	8 (61.5)	17 (70.8)	10 (76.9)
4=Severe	8 (32.0)	3 (25.0)	2 (8.3)	5 (38.5)	7 (29.2)	3 (23.1)
Patients with a concomitant second LP subtype, *n* (%)[b]	7 (28.0)	2 (16.7)	9 (37.5)	3 (23.1)	NA	NA
Anatomical location of MLP, *n* (%)[c]						
Oral	7 (28.0)	2 (16.7)	21 (87.5)	12 (92.3)	NA	NA
Genital	1 (4.0)	0 (0.0)	5 (20.8)	7 (53.8)	NA	NA
Oesophageal	0 (0.0)	0 (0.0)	1 (4.2)	1 (7.7)	NA	NA
Time since diagnosis (years)						
Mean (SD)	5.7 (7.17)	5.3 (3.62)	7.3 (7.54)	7.9 (4.35)	5.9 (6.34)	5.7 (5.05)
Median	2.0	4.8	4.5	7.0	3.4	3.6
Previous exposure to nonbiologic systemic medication for LP						
Yes	12 (48.0)	8 (66.7)	15 (62.5)	8 (61.5)	15 (62.5)	10 (76.9)

CLP, cutaneous LP; IGA, Investigator's Global Assessment; LP, lichen planus; LPP, lichen planopilaris; MLP, mucosal LP; *N*, total number of patients; *n*, number of patients with assessments available; SEC, secukinumab 300 mg. [a]Patient had both CLP (baseline=1) and MLP (baseline=3). This case was randomized in the CLP cohort at site based on investigator's judgement. [b]Patients with CLP and MLP also had concomitant MLP and CLP, respectively. [c]Patient may have MLP in more than one anatomical location.

Table 3 Outcomes of primary endpoint: achievement of Investigator's Global Assessment (IGA) ≤2 at week 16

Cohort	IGA ≤2 response rate at week 16 (SECQ4W vs. placebo)	Detailed data
CLP	44.0% vs. 58.3%	Figure 2a
MLP	37.5% vs. 23.1%	Figure 3a
LLP	37.5% vs 30.8%	Figure 4a

CLP, cutaneous lichen planus; LPP, lichen planopilaris; MLP, mucosal lichen planus; SECQ4W, secukinumab 300 mg every 4 weeks.

group showed a 23.9% higher IGA≤2 response rate than those in the placebo group at week 16 with a 95% CrI of −5.1 to 48.7 (posterior median, Table S5; see Supporting Information). The statistical correlation between IGA and REU score ($r=0.55$, $P<0.001$), PGIC ($r=0.55$, $P<0.001$) and OLPSSM ($r=0.5$, $P<0.001$) was moderate at week 16.

Reticular Erythematous Ulceration score in mucosal lichen planus cohort

There was no meaningful difference in the REU score between the SECQ4W and the placebo groups by week 16 in the MLP cohort. No improvements beyond week 16 were observed in the SECQ4W group, nor could a response be detected in the placebo-SECQ2W group (Figure S3; see Supporting Information). Other key endpoints evaluated included patient assessment of pain and DLQI (Table 4). No significant differences between secukinumab and placebo could be detected for these endpoints.

Lichen planopilaris cohort

Investigator's Global Assessment response. At week 16, a numerically higher proportion of patients achieved an IGA≤2 response in the SECQ4W group (37.6%) compared with placebo (30.9%) (Figure 4). The SECQ4W group continued to improve beyond week 16, with the IGA≤2 response rate increasing to 45.8% at week 32 (Figure 4). In the placebo-SECQ2W group, substantial improvements were observed with the IGA≤2 response increasing from 30.8% at week 16 to 63.6% at week 32. The proportion of patients in the placebo-SECQ2W group achieving an IGA improvement of ≥2 points improved from 0% at week 16 to 45.5% at week 32 (Figure 4). At week 16, a moderate correlation was observed between IGA and LPPAI ($r=0.59$, $P<0.001$) and a weak correlation was observed between IGA and PGIC ($r=0.39$, $P<0.001$). In line with these findings, there was a numerically higher LPPAI response in the SECQ4W arm at week 16 compared with placebo,

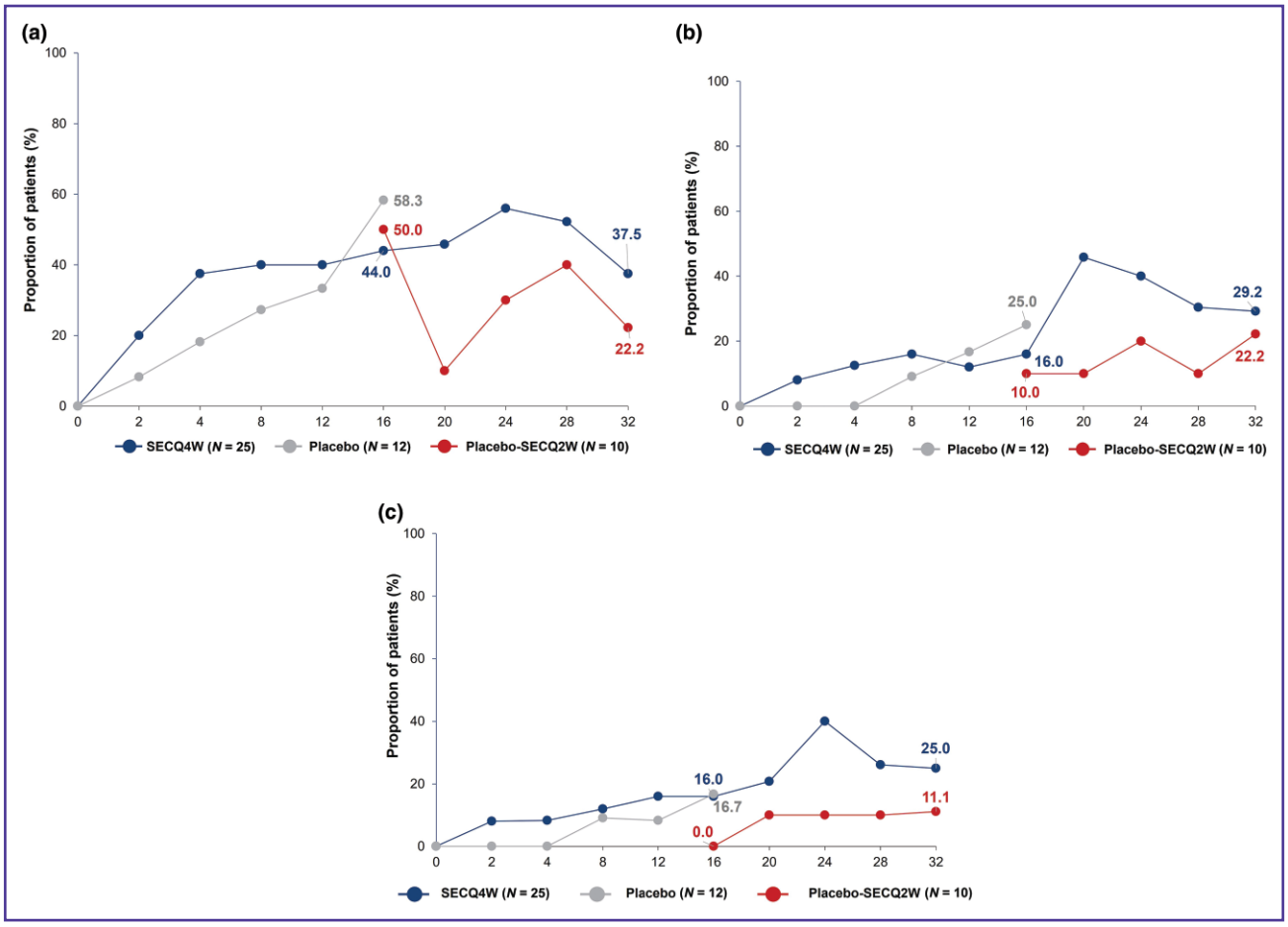

Figure 2 Percentage of patients with (a) IGA $\leq$2, (b) IGA improvement of $\geq$2 points, and (c) IGA 0/1 in the CLP cohort.CLP, cutaneous lichen planus; FAS, full analysis set; IGA, Investigator's Global Assessment; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks. Entire treatment period (FAS). Missing assessment was imputed with baseline value after treatment discontinuation.

Table 4 Outcomes of key secondary endpoints

			Detailed data	
Cohort	**Endpoint**	**Treatment group**	**Week 16**	
CLP	PSAD	SECQ4W	Improvement from BL	Figure S1
		Placebo/placebo-SECQ2W[a]	Improvement from BL	
	Patient assessment of itch (NRS)	SECQ4W	Improvement from BL	Table S4
		Placebo/placebo-SECQ2W[a]	Improvement from BL	
	DLQI 0/1	SECQ4W	Improvement from BL	Figure S2a
		Placebo/placebo-SECQ2W[a]	Improvement from BL	
MLP	REU	SECQ4W	No improvement	Figure S3
		Placebo/placebo-SECQ2W[a]	No improvement	
	OLPSSM	SECQ4W	No improvement	Figure S4
		Placebo/placebo-SECQ2W[a]	No improvement	
	Patient assessment of pain (NRS)	SECQ4W	No improvement	Table S5
		Placebo/placebo-SECQ2W[a]	No improvement	
	DLQI 0/1	SECQ4W	Improvement from BL	Figure S2b
		Placebo/placebo-SECQ2W[a]	Improvement from BL	
LLP	LPPAI	SECQ4W	Improvement from BL	Figure 5
		Placebo/placebo-SECQ2W[a]	Improvement from BL	
	Patient assessment of itch (NRS)	SECQ4W	Improvement from BL	Table S6
		Placebo/placebo-SECQ2W[a]	No improvement	
	DLQI 0/1	SECQ4W	Improvement from BL	Figure S2c
		Placebo/placebo-SECQ2W[a]	Improvement from BL	

BL, baseline; CLP, cutaneous lichen planus; DLQI, Dermatology Life Quality Index; LPP, lichen planopilaris; LPPAI, LPP Activity Index; MLP, mucosal lichen planus; NRS, numeric rating scale; OLPSSM, Oral Lichen Planus Symptoms Severity Measure; PSAD, Physician Assessment of Surface Area of Disease; REU, Reticular Erythematous Ulcerative; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks.
[a]Week-16 data are for 'placebo' and week-32 data are for 'placebo-SECQ2W'.

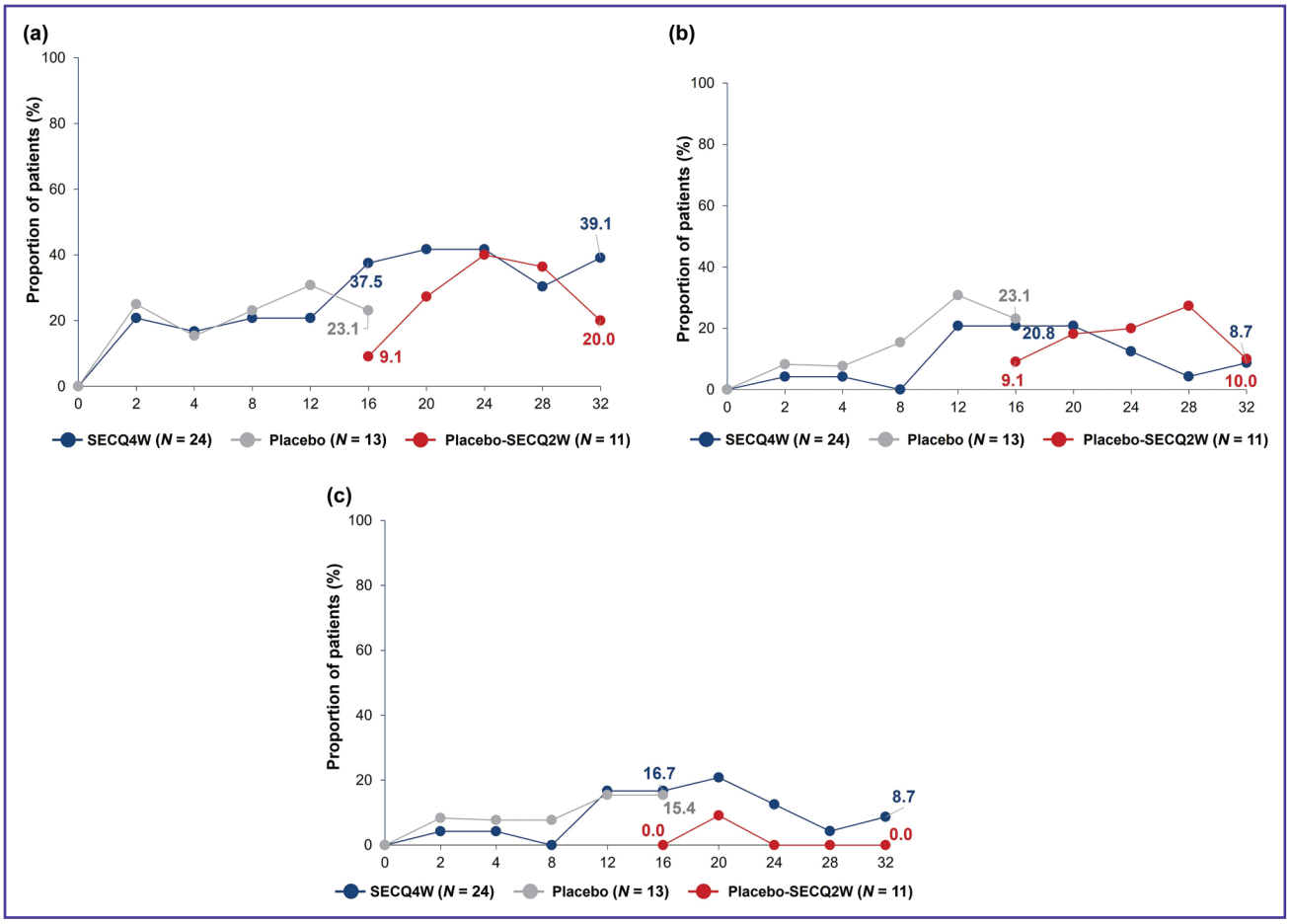

Figure 3 Percentage of patients with (a) IGA ≤ 2, (b) IGA improvement ≥ 2 points, and (c) IGA 0/1 in the MLP cohort.FAS, full analysis set; IGA, Investigator's Global Assessment; MLP, mucosal lichen planus; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks. Entire treatment period (FAS). Missing assessment was imputed with baseline value after treatment discontinuation.

with continued improvement up to week 32, in addition to improvements in the LPPAI response in the SECQ2W group between weeks 16 and 32 (Figure 5). Other key endpoints evaluated included patient assessment of itch and DLQI (Table 4). No significant differences between secukinumab and placebo could be detected for these endpoints.

In all three cohorts, no relevant efficacy differences were observed for current smokers vs. nonsmokers or patients pretreated with systemic therapies vs. patients who were treatment naïve. However, the sample size for this subgroup analysis was very limited.

Safety

The cumulative exposure across cohorts ranged from 16.17 to 16.73 PYs for the SECQ4W group, 3.23 to 5.39 PYs for the SECQ2W group, 19.39 to 22.12 PYs for the any secukinumab 300 mg group, and 3.85 to 4.22 PYs for the placebo group for the entire TP. The overall incidence of AEs was comparable across the cohorts (Table 5). The most frequently reported AEs by preferred term were LP worsening and headache across the cohorts (Table S7; see Supporting Information). The majority of AEs were mild to moderate in severity. The overall incidence of serious AEs (SAEs) was low, and no death was reported during the study. Ulcerative colitis in a patient from the MLP cohort (secukinumab group) was reported as an SAE, considered to be related to study treatment and led to treatment discontinuation during TP1. It is noteworthy that this patient had concomitant plaque psoriasis. The EAIRs of AEs leading to discontinuation during the entire TP were low and similar across treatment groups and cohorts. No new or unexpected safety signals were detected for secukinumab.

Discussion

To date, there are no approved systemic treatments available for patients with LP inadequately controlled by topical therapies, which constitutes a significant unmet need. To the authors' knowledge, this is the first double-blind randomized clinical trial to assess the efficacy and safety of a systemic therapy (i.e. IL-17A blockade) in the three major subtypes of LP. The trial studied secukinumab in each subtype in a separate cohort, including a separate placebo arm for each cohort. The subtype diagnosis had to be clinically confirmed (by a dermatologist) and histopathologically confirmed (by a dermatopathologist). Patients were required to present with an IGA ≥ 3 (using the subtype-specific IGA definitions) and prior inadequate response to topical corticosteroids in

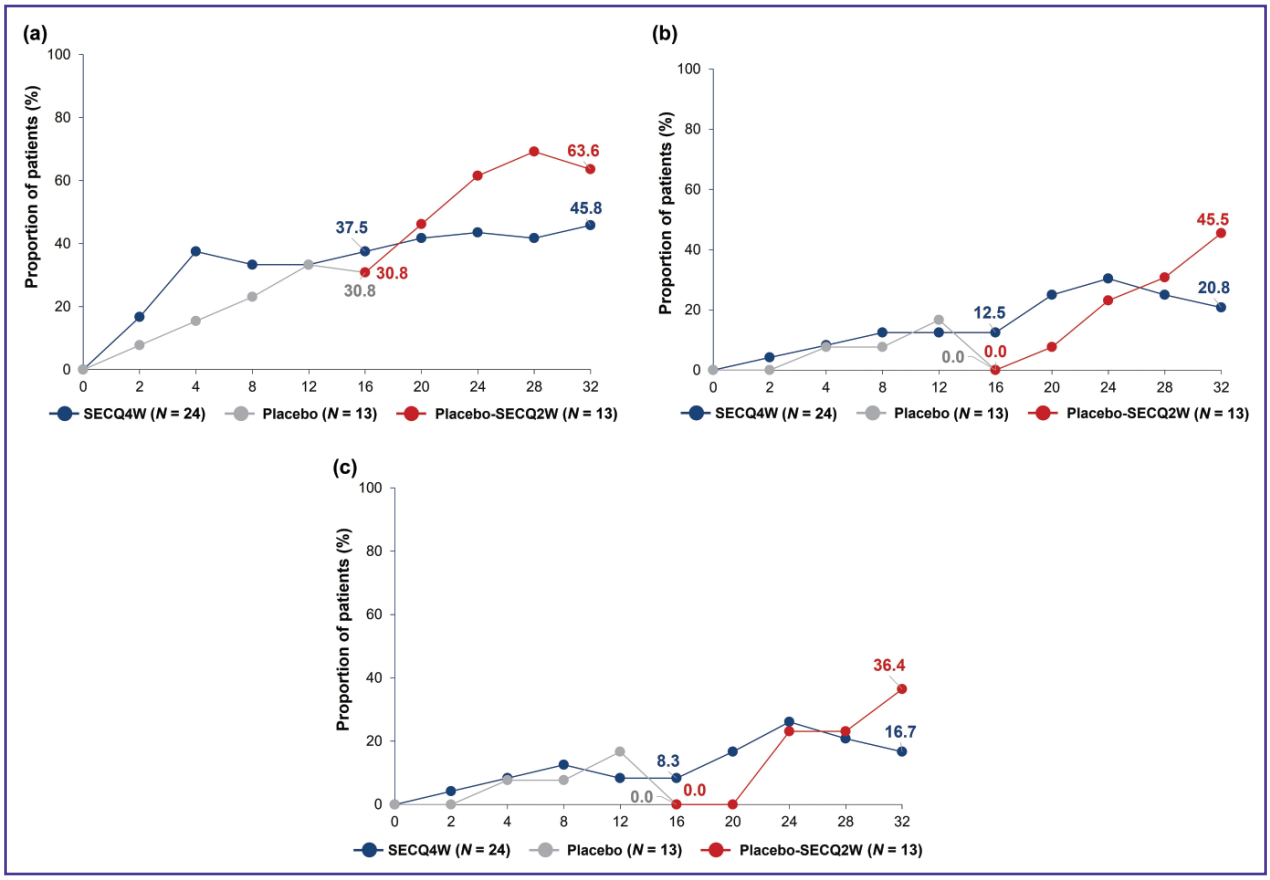

Figure 4 Percentage of patients with (a) IGA ≤ 2, (b) IGA improvement ≥ 2 points, and (c) IGA 0/1 in the LPP cohort.FAS, full analysis set; IGA, Investigator's Global Assessment; LPP, lichen planopilaris; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks. Entire treatment period (FAS). Missing assessment was imputed with baseline value after treatment discontinuation.

order to ensure homogeneity within the individual cohort with regard to subtype and severity. As expected, a relevant number of patients presented with two subtypes at the same time (CLP and MLP). Such patients were enrolled in one cohort only, the cohort of their predominant subtype (defined by higher IGA score), and only the data from this subtype were used for the primary endpoint analysis.

The primary objective of this study was to demonstrate the efficacy of SECQ4W in patients with moderate-to-severe (IGA ≥ 3) CLP, MLP or LPP with respect to improvement in IGA score (IGA ≤ 2) by week 16, compared with placebo. The secukinumab 300 mg Q4W dosing regimen showed numerically greater efficacy in achieving an IGA score ≤ 2 compared with placebo in the MLP and LPP cohorts at week 16. However, PoC criteria were not met for any of the three cohorts.

Secukinumab was well tolerated across all three cohorts, and the safety results observed were consistent with the well-characterized favourable safety profile of secukinumab in other approved indications.[19–21]

In the CLP cohort, no improvement was observed with any secukinumab dose in IGA-related endpoints, PSAD scores or PROs, indicating that IL-17A blockade was not effective in CLP in this study. In the MLP cohort, a numerically higher proportion of patients achieved an IGA score ≤ 2 in the SECQ4W group compared with the placebo group at week 16, which was sustained up to week 32. Furthermore, when pooling the IGA response data for MLP from patients with predominant (full MLP cohort) and concomitant MLP (CLP cohort who had concomitant MLP), a significant difference between SECQ4W and placebo was observed in a post hoc analysis. However, this benefit was not substantiated by the REU data.

In the LPP cohort, the response to SECQ4W was numerically higher compared with placebo at week 16 and continued to improve over time up to week 32 across all IGA-related endpoints (IGA 0/1, IGA ≤ 2 and IGA improvement by ≥ 2 points response). Furthermore, after the switch from placebo to SECQ2W at week 16, good control over the disease (with regard to IGA 0/1, IGA ≤ 2, IGA improvement by ≥ 2 points response and LPPAI response) was achieved in a notable percentage of patients receiving SECQ2W treatment, indicating potential efficacy of secukinumab in the treatment of LPP.

In a previously published case series secukinumab treatment led to clinical improvement in three patients with CLP or MLP that was resistant to topical steroids.[17] Further publications reported successful therapeutic targeting of IL-17A with secukinumab in a patient with recalcitrant genital LP and in a patient with cutaneous LP.[15,18] These positive individual observations could not be fully confirmed by the current randomized controlled trial. The difference in sample size, the fluctuant disease course of LP, the different pretreatments and concomitant treatments could be potential reasons

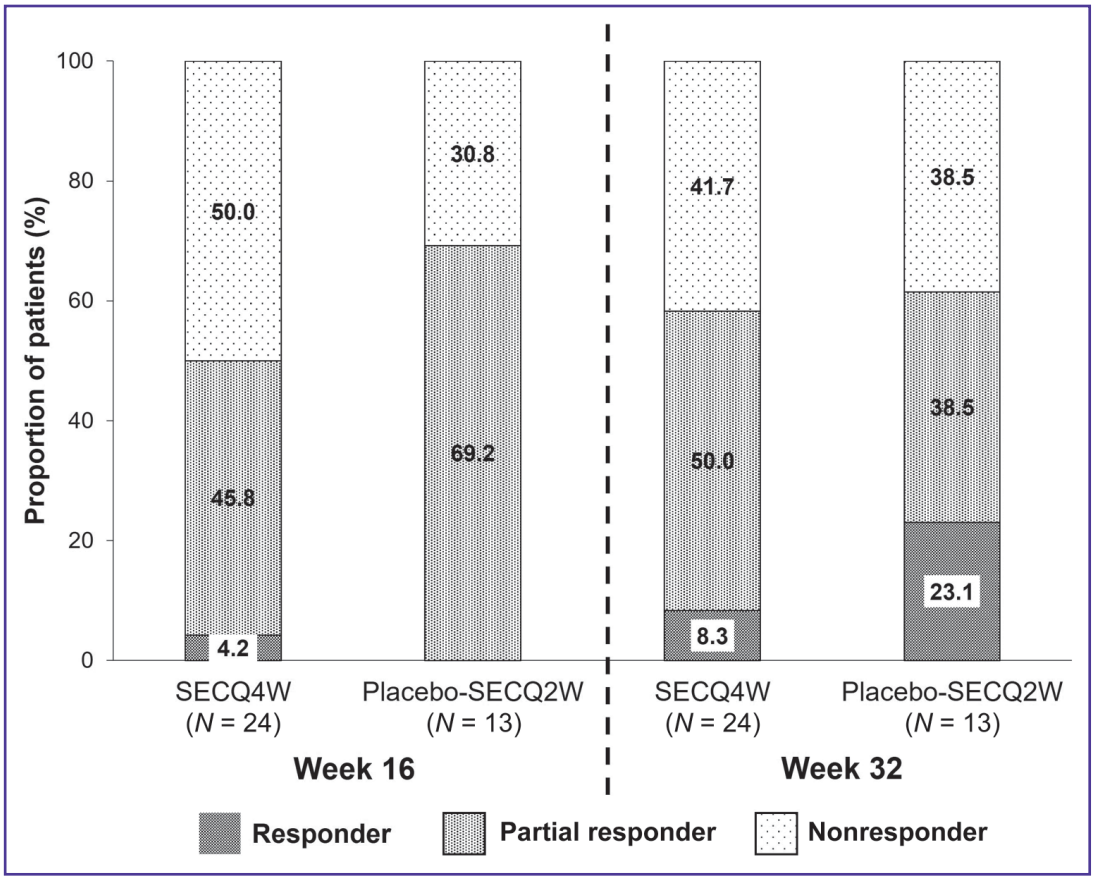

Figure 5 LPPAI responder, partial responder and nonresponder patients in the LPP cohort.LPPAI, Lichen Planopilaris Activity Index; LPP, lichen planopilaris; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks.

Table 5 Summary of safety of secukinumab treatment through week 32

Events

EAIR/100 PYs (95% CI)	SECQ4W	Placebo-SECQ2W	Any SEC	Placebo
CLP	*N*=25	*N*=8	*N*=33	*N*=12
Any AEs	313.4 (188.7–489.5)	423.1 (155.3–920.8)	334.2 (216.3–493.4)	381.0 (164.5–750.7)
Any SAEs	0 (0–22.8)	0 (0–114.4)	0 (0–19)	27.3 (0.7–151.9)
Discontinued study treatment owing to any AEs	19.0 (3.9–55.4)	0 (0–114.4)	15.8 (3.2–46.0)	0 (0–95.7)
Important identified and potential risks based on all adverse events (AESI)				
Infections and infestations (SOC)	77.5 (35.4–147.0)	125.9 (26.0–368.1)	85.7 (44.3–149.7)	122.2 (33.3–312.8)
Malignant or unspecified tumours (SMQ)	6.5 (0.2–36.0)	0 (0–114.4)	5.3 (0.1–29.8)	27.3 (0.7–151.9)
Hypersensitivity (SMQ) (narrow)	6.2 (0.2–34.8)	0 (0–114.4)	5.2 (0.1–29.0)	0 (0–95.7)
MLP	*N*=24	*N*=11	*N*=35	*N*=13
Any AEs	327.3 (199.9–505.5)	360.7 (155.7–710.8)	336.2 (223.4–485.9)	359.0 (155.0–707.3)
Any SAEs	6.1 (0.2–34.1)	21.1 (0.5–117.7)	9.5 (1.1–34.3)	0 (0–87.4)
Discontinued study treatment owing to any AEs	32.4 (10.5–75.6)	0 (0–75.5)	24.6 (8.0–57.4)	0 (0–87.4)
Important identified and potential risks based on all adverse events (AESI)				
Infections and infestations (SOC)	84.2 (42.0–150.6)	101.2 (27.6–259.2)	88.1 (49.3–145.3)	51.9 (6.3–187.4)
Hypersensitivity (SMQ) (narrow)	6.3 (0.2–34.9)	0 (0–75.5)	4.8 (0.1–26.7)	0 (0–87.4)
LPP	*N*=24	*N*=12	*N*=36	*N*=13
Any AEs	307.4 (182.2–485.8)	212.7 (85.5–438.3)	272.3 (176.9–403.5)	284.4 (114.3–586.0)
Any SAEs	0 (0–22.1)	19.9 (0.5–110.9)	4.6 (0.1–25.6)	26.9 (0.7–149.6)
Discontinued study treatment owing to any AEs	18.2 (3.8–53.1)	19.5 (0.5–108.7)	18.5 (5.0–47.4)	0 (0–95.6)
Important identified and potential risks based on all adverse events (AESI)				
Infections and infestations (SOC)	43.3 (15.9–94.3)	40.2 (4.9–145.2)	42.5 (18.3–83.7)	87.7 (18.1–256.4)
Malignant or unspecified tumours (SMQ)	6.0 (0.2–33.7)	0 (0–68.5)	4.6 (0.1–25.4)	0 (0–95.6)
Hypersensitivity (SMQ) (narrow)	26.0 (7.1–66.5)	18.7 (0.5–104.1)	24.1 (7.8–56.2)	0 (0–95.6)

AEs, adverse events; AESI, AEs of special interest; CI, confidence interval; CLP, cutaneous lichen planus LP; EAIR, exposure-adjusted incidence rate; LP, lichen planus; LPP, lichen planopilaris; MLP, mucosal lichen planus LP; PY, person-years; SEC, secukinumab 300 mg; SECQ2W, secukinumab 300 mg every 2 weeks; SECQ4W, secukinumab 300 mg every 4 weeks; SECQ2W, secukinumab 300 mg every 2 weeks; SMQ, Standardized Medical Dictionary for Regulatory Activities MedDRA query; SOC, system organ class.

why these findings could not be confirmed. Furthermore, the case series[17] lacked a placebo control, whereas in the current clinical trial a relatively high placebo effect was observed. Lastly, even though patients were asked to maintain a concomitant topical glucocorticoid at a stable dose, its mild-to-moderate potency remains a potential source of bias. To the best of our knowledge, no published data are available on the efficacy of IL-17A-directed therapies in LPP.

The results of this study only partially substantiate the previously published findings of IL-17A-driven mechanisms in the pathophysiology of LP.[12–16,22] Interestingly, different response rates for IL-17A blockade have been observed across the three cohorts in this trial. Based on these findings, one could hypothesize a differential role of IL-17A in the pathophysiology of the three subtypes. With no robust comparison of the molecular mechanisms of the three subtypes existing so far, this hypothesis raises a question for further exploration. Also, the understanding of the different sources of IL-17A ($CD4^+$ T cells/Th17 cells, $CD8^+$ T cells/Tc17 cells, $\gamma\delta$ T cells, natural killer cells and neutrophils) in inflammatory skin disease has improved in recent years and could be a differential mechanism between LP subtypes.[15] Moreover, a recent study showed that the major cellular source of IL-17A in the skin lesions of patients with CLP was neither granulocytes nor T cells.[23]

In the context of previous evidence on LP being a Th1-driven immune disease with a Th17 component,[10,15,23,24] the results of this study raise questions about the relevance of the Th17 component, particularly in CLP, and whether the balance between Th1 and Th17 might differ across subtypes.

The study has several limitations. Firstly, the number of patients enrolled per cohort was relatively small, which limits the robustness of the results, and the results of any additional subgroup analyses (e.g. by smoking status or previous treatment) and makes imbalances in baseline characteristics more likely to occur. Larger trials are required in order to confirm the observed results. Secondly, as there is a lack of a placebo treatment group after week 16, a direct comparison between the two different dosing regimens, SECQ4W and SECQ2W is not possible. Given the lack of widely used and well-validated scoring tools for LP, a new IGA scoring system was developed specifically for this study, which showed significant correlation with patient- (PGIC and OLPSSM) and physician-reported (PSAD, REU and LPPAI) outcome measurement tools. We hope to enable future clinical research in LP by making this new score available at a later date.

In conclusion, secukinumab was safe and well tolerated, and showed different response rates across the three studied subtypes, with no response in CLP, and numerical IGA improvements in MLP and LPP, which would need to be confirmed in larger trials. This raises important questions regarding the mechanistic role of IL-17A across LP subtypes and warrants robust comparisons of the molecular mechanisms.

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Conflicts of interest

T.P. has received honoraria and/or consultation fees from AbbVie, Almirall, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, GSK, Incyte, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Sanofi Genzyme, Sun Pharma, UCB Pharma and Vyne Therapeutics. He is a cofounder of YUKIN Therapeutics. B.E. has served as a consultant and/or clinical study investigator for AbbVie, Acelyrin, Aclaris, Allakos, Almirall, Alumis, Amgen, AnaptysBio, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Concert Pharma, Dermavant Sciences, Dermira Inc., Eli Lilly, Evelo Biosciences, Evommune, Incyte, Janssen, Kymab, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Priovant, Regeneron, Sanofi Genzyme, Sun Pharma, UCB Pharma and Ventyx, and as a paid speaker for Dermavant, Incyte, LEO Pharma, Eli Lilly, Novartis, Ortho Dermatologics, Regeneron and Sanofi Genzyme. J.W. has served as an investigator/advisor and/or speaker for AbbVie, Aclaris, Almirall, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dr Reddy's, EPI Health, Foamix/Vyne, Galderma, Incyte, Janssen, LEO Pharma, Lilly, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, UCB Pharma and Verrica. M.S. 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. P.R. has been an investigator, speaker, or member of an advisory board for Bristol Myers Squibb, Concert Pharmaceutical, Ducray, Legacy Healthcare, LEO Pharma, Lilly, L'Oreal Research, Novartis, Pfizer, Pierre Fabre Dermatologie and Vichy Laboratories. J.W. has received grants for scientific projects, clinical studies, lectures or consultancy from the following companies in the last 5 years: Abbott, AbbVie, Actelion, Allergika, Almirall, Aristo, BayPharma, Beiersdorf, Biogen, BMS, Boehringer Ingelheim, Celltrion, Dermapharm, Evolva, Galderma, GSK, Helm, Hexal, Incyte, Infectopharm, Janssen-Cilag, Jenapharm, Johnson & Johnson, Klinge, LEO, Lilly, L'Oréal, Medac, Medice, Mibe, MSD, Mylan, Novaliq, Novartis, Pierre Fabre, Pfizer, Regeneron, Rigi, Skinomics and Wolff. M.H. has received honoraria and/or consultation fees from AbbVie, Argenx, Biotest, Janssen, Novartis, Pfizer, Sanofi Genzyme and Topas Therapeutics. M.R., E.M., H.F., and I.H. are employees and stockholders of Novartis. N.C. was an employee of Novartis Pharma AG at the time of the study and is a stockholder of Novartis.

Data availability

The datasets generated and/or analysed during the current study are not publicly available. Novartis is committed to sharing access to patient-level data and supporting clinical

documents from eligible studies with qualified external researchers. 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 manuscript.

Ethics statement

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each centre. The study was conducted according to the International Council for Harmonisation E6 Guidelines for Good Clinical Practice, which have their origin in the Declaration of Helsinki. Informed consent was obtained from each patient in writing at the screening visit and before any study-specific procedure was performed.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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