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Original article

Filgotinib or lanraplenib in moderate to severe cutaneous lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study

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Abstract

Objectives. To explore the safety and efficacy of filgotinib (FIL), a Janus kinase 1 inhibitor, and lanraplenib (LANRA), a spleen kinase inhibitor, in cutaneous lupus erythematosus (CLE).

Methods. This was a phase 2, randomized, double-blind, placebo-controlled, exploratory, proof-of-concept study of LANRA (30 mg), FIL (200 mg) or placebo (PBO) once daily for 12 weeks in patients with active CLE. At week 12, PBO patients were rerandomized 1:1 to receive LANRA or FIL for up to 36 additional weeks.

Results. Of 47 randomized patients, 45 were treated (PBO, $n=9$; LANRA, $n=19$; FIL, $n=17$). The primary endpoint [change from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) score at week 12] was not met. The least squares mean CLASI-A score change from baseline was −5.5 (S.E. 2.56) with PBO, −4.5 (1.91) with LANRA and −8.7 (1.85) with FIL. Numerical differences between FIL and PBO were greater in select subgroups. A ≥5-point improvement in the CLASI-A score at week 12 was achieved by 50.0%, 56.3% and 68.8% in the PBO, LANRA and FIL arms, respectively. A numerically greater proportion of patients in the FIL arm (50%) also achieved ≥50% improvement in the CLASI-A score at week 12 (37.5% PBO, 31.3% LANRA). Most adverse events (AEs) were mild or moderate in severity. Two serious AEs were reported with LANRA and one with FIL.

Conclusion. The primary endpoint was not met. Select subgroups displayed a numerically greater treatment response to FIL relative to PBO. LANRA and FIL were generally well tolerated.

Trial registration. ClinicalTrials.gov identifier NCT03134222

Key words: systemic lupus erythematosus and autoimmunity, skin, cytokines and inflammatory mediators, clinical trials and methods, inflammation

CLINICAL SCIENCE

Rheumatology key messages

- Cutaneous lupus represents an underserved patient population with high unmet need.
- This study evaluated the JAK1 inhibitor filgotinib and SYK inhibitor lanraplenib in patients with lupus.
- JAK1 inhibition may provide a therapeutic benefit in lupus based on filgotinib responses observed in select subgroups.

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Introduction

Lupus erythematosus (LE) is a multifactorial, heterogeneous autoimmune disease with broad clinical manifestations, from cutaneous LE (CLE) to SLE, potentially involving multiple organ systems [1, 2]. CLE may present in isolation or as a clinical manifestation in the setting of SLE [3]. CLE-specific skin lesions present with varied morphology and histopathology, including acute, subacute (SCLE) and chronic (CCLE). CCLE is categorized further into several subtypes, of which discoid is the most common [1]. Treatments for CLE are adapted from SLE, as there is no US Food and Drug Administration–approved CLE therapy at present [4]. The current treatment strategy of CLE includes topical corticosteroids, antimalarials, retinoids, dapsone, immunosuppressants and immunomodulatory agents, all with highly variable levels of effectiveness or with dose-limiting toxicities [1, 4, 5]. Thus there is an unmet need for safe and effective therapy for the cutaneous manifestations of LE.

Activation of the IFN pathway, a key driver of CLE disease activity, occurs through the chronic production of various pro-inflammatory cytokines, notably type I IFN (IFN-I) and an increased expression of IFN-I-regulated genes [2]. IFN-I is produced by a variety of cells, primarily dendritic cells and keratinocytes [1, 2], and drives an inflammatory autoimmune process resulting in possible tissue damage, particularly in the skin and joints [2]. Antibody blockade of IFN-I signalling through the IFN receptor reduced disease activity in SLE in a phase 2b trial [6] and phase 3 trials [7, 8]. Treatment with a monoclonal antibody targeting blood dendritic cell antigen 2 on plasmacytoid dendritic cells reduced the expression of IFN-I response biomarkers in blood and skin and was associated with reduced skin disease activity in a phase 1 study that enrolled SLE patients with active cutaneous disease [9] and a phase 2 study in CLE [10].

Janus kinases (JAKs) mediate intracellular signalling downstream of IFN and other inflammatory cytokines, ultimately regulating the expression of numerous genes contributing to the inflammatory autoimmune processes in LE [4, 11, 12]. Filgotinib (FIL), a preferential inhibitor of JAK1, is associated with transcriptional inhibition of multiple inflammation-associated immune signalling pathways [13, 14]. Spleen tyrosine kinase (SYK) is recruited and activated by ligand-engaged immunoreceptors and in turn activates pathways that increase pro-inflammatory cytokine production [15]. Increased SYK activity and SYK-associated gene expression are evident within CLE tissue and SYK inhibition reduced pro-inflammatory cytokine levels in cultured keratinocytes [16]. Lanraplenib (LANRA), a second-generation selective SYK inhibitor, showed benefits in preclinical models of SLE [17]. FIL and LANRA efficacy in LE are unknown.

In this proof-of-concept study, the safety and efficacy of JAK1 inhibition with FIL and SYK inhibition with LANRA were examined in patients with CLE.

Methods

Study oversight

Trial conduct was in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol was approved by the central institutional review board (IRB), Copernicus Group IRB or by the local IRB at the study's site (Western IRB; Penn State Milton S. Hershey Medical Center, Penn State College of Medicine Human Subjects Protection Office; Duke University Health System IRB; University of Pennsylvania Office of Regulatory Affairs IRB; Wake Forest University Health Sciences IRB; University Health Network Research Ethics Board; Research Review Board Inc.). All patients provided written informed consent prior to participation in the study.

Study design and patients

In this phase 2, randomized, double-blind, placebo-controlled study, patients were enrolled at 16 study sites (9 rheumatology, 7 dermatology) in the USA and Canada (ClinicalTrials.gov identifier NCT03134222). Sites were required to undergo Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) training prior to patient enrolment.

Given the predominance of lupus in women and ongoing studies to assess the effect of FIL on semen parameters at the time of starting this study (ClinicalTrials.gov NCT03926195), recruitment was restricted to female patients ages 18–75 years. Patients had a diagnosis of active SCLE or CCLE (CLASI-A score $\geq$10 at screening and day 1) with or without SLE and prior intolerance or inadequate response to at least one medication for CLE. Although patients were required to present with active SCLE or CCLE, mixed skin presentations were allowed. Patients were required to maintain stable dosing of permissible background medications for 28 days prior to study treatment initiation through study week 12 or discontinue use 28 days prior to study treatment initiation. Exclusion criteria included active SLE or Sjögren's syndrome requiring the use of a prohibited medication or other inflammatory, rheumatic or autoimmune diseases that could compromise patient safety or conduct of the study per investigator judgment. Exclusion criteria included the use of JAK or SYK inhibitors within 3 months prior to screening or previous use of cyclophosphamide at any time. Full eligibility and exclusion criteria are listed in the supplementary methods (Supplementary Data S1, available at *Rheumatology* online).

Randomization and treatment

Eligible patients were randomized 2:2:1 using an interactive web response system to receive FIL (200 mg),

LANRA (30 mg) or placebo (PBO) plus matching PBO. Randomization was stratified by disease subtype (SCLE *vs* CCLE) and concurrent DMARD use *vs* no use. Allowed continued stable medications were class V–VII topical corticosteroids for CLE, oral corticosteroids (≤10 mg/day prednisone equivalent), antimalarials (e.g. chloroquine ≤250 mg/day, HCQ ≤400 mg/day or quinacrine ≤100 mg/day), dapsone (≤100 mg/day), MTX (≤20 mg/week) and AZA (≤2 mg/kg body weight/day or 300 mg/day). Concomitant MMF use was not permitted because of its known safety profile. A full list of permitted and prohibited medications is provided in Supplementary Data S1 (available at *Rheumatology* online).

Procedures and endpoints

Study drugs were orally administered daily for 12 weeks. Following completion of assessments at week 12, PBO patients were rerandomized 1:1 to receive blinded treatment with either FIL or LANRA for an additional 12 weeks, while patients randomized to FIL or LANRA maintained their dose. Patients who had not discontinued treatment during the 24 week study period were eligible to enter a 24 week extension period. Study assessments were conducted at screening; on day 1 (baseline); at weeks 2, 4, 8, 12, 14, 16, 20 and 24 of the initial study; and at 6 week intervals during the 24 week extension period.

The primary endpoint was the change in the CLASI-A score from baseline at week 12. Secondary endpoints were the proportion of patients with a decrease of ≥5 points in the CLASI-A score from baseline at weeks 12 and 24 and the proportion of patients with no worsening (≥3 point increase) in the CLASI-A score from baseline at weeks 12 and 24. Given the enrichment for patients with higher baseline disease activity based on inclusion criteria, the secondary endpoint threshold of 5 points was prespecified. This value represents a CLASI-A score reduction slightly more stringent than 4 points, the lowest respective CLASI-A minimal clinically important difference (MCID) reported.

Exploratory analyses included the proportion of patients achieving a ≥50% improvement in CLASI-A score, Physician's Global Assessment of CLE Disease Activity, Patient's Global Assessment of CLE Disease Activity, Dermatology Life Quality Index (DLQI), Treatment Satisfaction Questionnaire for Medication and Visual Analog Scale assessment of fatigue at weeks 12 and 24. Blood samples were collected pre-dose on day 1 for assessment of biomarker activity at baseline. Primary and secondary endpoints were examined in subgroups, including age (<50 years and ≥50 years), disease subtype (CCLE or SCLE), concurrent background conventional synthetic DMARD (csDMARD) use at baseline (yes or no), concurrent use of systemic corticosteroids at baseline (yes or no), diagnosis of SLE (yes or no), time from CLE diagnosis (<10 years or ≥10 years) and baseline CLASI-A score (<15 or ≥15).

Safety assessments included monitoring of adverse events (AEs), clinical and laboratory analyses, vital sign measurement, electrocardiograms and physical examinations. AEs of interest were identified using either the standardized Medical Dictionary for Regulatory Activities Queries or Medical Search Terms. These included all infections, serious infections, infections of special interest (herpes zoster, active tuberculosis, opportunistic and hepatitis B or C infections), venous thromboembolic events and pulmonary embolism, malignancies, gastrointestinal perforations, liver transaminase elevations and serious major cardiovascular events (MACEs). Venous thromboembolic events and MACEs were not adjudicated.

Biomarker assessments are described in Supplementary Data S1, available at *Rheumatology* online.

Statistical methods

A sample size of 50 patients (20 per active group and 10 in the PBO group) was chosen based on the assumption of a 2 point difference between each active group and the PBO group in the primary endpoint (change from baseline in the CLASI-A score at week 12) with a SD of 2. Efficacy and safety analyses included all randomized patients who received at least one dose of study drug. Patients who received at least one dose of study drug and had a baseline measurement available for the specific parameter of interest were included in the biomarker analysis set.

Analysis of FIL or LANRA superiority over PBO was assessed using a mixed-effects model for repeated measures that included terms for baseline CLASI-A score, treatment, stratification factors, visit and treatment by visit interaction. Week 12 secondary endpoints were analysed separately by a Cochran–Mantel–Haenszel test stratified by disease subtype and DMARD use at randomization. No correction for multiple comparisons was implemented in this proof-of-concept study. For exploratory endpoints and subgroup analyses, descriptive statistics are provided for each treatment group. No formal statistical testing was planned for exploratory endpoints, and where conducted, nominal *P*-values are provided.

Summaries of treatment-emergent AEs (TEAEs) are provided by treatment group and period. Statistical methods for biomarker analyses are provided in Supplementary Data S1, available at *Rheumatology* online.

Results

Study patients

Of the 72 screened patients, 47 were randomized and 45 received at least one study dose (PBO, $n=9$; LANRA, $n=19$; FIL, $n=17$; Supplementary Fig. S1, available at *Rheumatology* online). Treatment groups had generally similar baseline demographics and disease characteristics (Table 1). Most patients were <50 years of age and white. The proportion of black

Table 1 Baseline demographics and disease characteristics (full analysis set)*

Characteristics	PBO ($n = 9$)	LANRA ($n = 19$)	FIL ($n = 17$)	Total ($N = 45$)
Age, years, mean (S.D.)	46 (7.3)	51 (9.0)	43 (11.5)	47 (10.1)
Race, *n* (%)				
White	6 (66.7)	12 (63.2)	7 (41.2)	25 (55.6)
Black	1 (11.1)	6 (31.6)	8 (47.1)	15 (33.3)
Asian	2 (22.2)	0	0	2 (4.4)
American Indian, Alaska Native, or Other	0	1 (5.3)	2 (11.8)	3 (6.6)
Ethnicity, *n* (%)				
Hispanic or Latino	2 (22.2)	3 (15.8)	4 (23.5)	9 (20.0)
BMI, kg/m^2, mean (S.D.)	28.5 (6.52)	30.2 (6.67)	30.1 (4.12)	29.8 (5.70)
Time from CLE diagnosis to enrolment, years, mean (S.D.)	12.1 (8.42)	11.8 (8.09)	9.6 (8.95)	11.0 (8.37)
Baseline CLASI-A score, mean (S.D.)	14.8 (4.8)	17.1 (6.1)	19.7 (14.4)	17.6 (9.9)
≥15, *n* (%)	4 (44.4)	10 (52.6)	8 (47.1)	22 (48.9)
Concurrent SLE diagnosis, *n* (%)	2 (22.2)	7 (36.8)	7 (41.2)	16 (35.6)
Concurrent systemic csDMARD use at baseline, *n* (%)	5 (55.6)	13 (68.4)	11 (64.7)	29 (64.4)
Antimalarial use at baseline, *n* (%)	5 (55.6)	12 (63.2)	10 (58.8)	27 (60.0)
Immunosuppressant use at baseline, *n* (%)†	1 (11.1)	2 (10.5)	5 (29.4)	8 (17.8)
MTX use at baseline, *n* (%)	0	1 (5.3)	4 (23.5)	5 (11.1)
Systemic corticosteroid use at baseline, *n* (%)	2 (22.2)	6 (31.6)	3 (17.6)	11 (24.4)
Corticosteroid dose at baseline, mg/day, mean (S.D.)	7.5 (3.54)	8.4 (2.30)	8.3 (2.89)	8.2 (2.39)

*Full analysis set includes patients who were randomized and received at least one dose of study drug. csDMARDs and corticosteroids reported were orally administered. Smoking status was available for only a limited number of subjects and therefore is not shown. †Oral immunosuppressants were MTX, MMF and AZA.

patients was higher in the active treatment groups. The baseline mean CLASI-A score was 17.6 (S.D. 9.89) across treatment groups. Most patients had CCLE (82.2%) and 35.6% had a diagnosis of SLE. Sixty-four percent of patients were on systemic csDMARDs that included antimalarials (60.0%), AZA (2.1%), MTX (11.1%) and MMF [4.3% (2 patients with protocol deviations)]. Systemic corticosteroids were taken by 24.4% of patients (Table 1).

Primary, secondary and key exploratory endpoints

The least squares (LS) mean CLASI-A score changes from baseline at week 12 (primary endpoint) were −5.5 (S.E. 2.56) in the PBO arm, −4.5 (1.91) in the LANRA arm and −8.7 (1.85) in the FIL arm (Fig. 1). The magnitude of the PBO response was larger than expected. A post hoc analysis revealed that the removal of a single study site (2 PBO, 2 LANRA, 1 FIL patients) with multiple CLASI-A scoring discrepancies reduced the PBO response to −3.9 (S.E. 2.73), while the LANRA and FIL effects remained consistent with the response in the full population [LANRA −4.6 (S.E. 1.87) and FIL −8.3 (1.76); Supplementary Fig. S2, available at *Rheumatology* online].

The proportion of patients with a ≥5-point improvement in CLASI-A score during the PBO-controlled study period at week 12 was 50.0% for PBO, 56.3% for LANRA and 68.8% for FIL (Fig. 2). At week 24, 50.0% achieved a ≥5-point improvement in the LANRA arm and 83.3% in the FIL arm. At weeks 12 and 24, no patients showed worsening of the CLASI-A score (>3-point increase). A numerically greater proportion of patients in the FIL arm achieved ≥50% improvement in the CLASI-A score at week 12 (Fig. 2) and week 24 (35.7% of the LANRA and 66.7% of the FIL arms).

Among health-related quality of life (HRQoL) assessments (Fig. 2), an LS mean improvement of −5.8 (S.E. 1.47) points in the DLQI was observed in the PBO arm, −0.6 (1.10) in the LANRA arm and −4.4 (0.98) in the FIL arm.

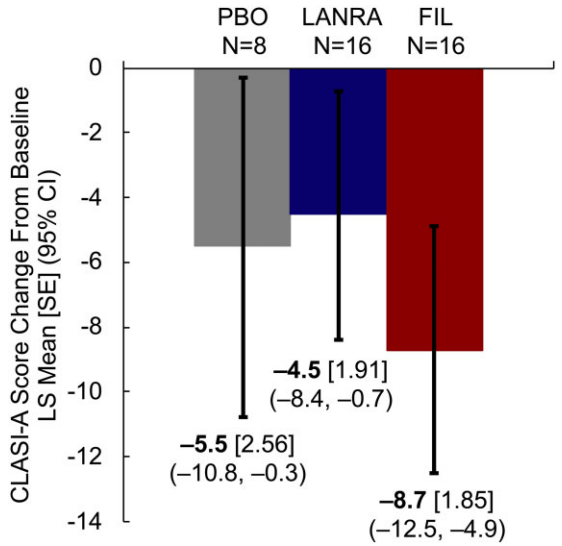
Subgroup analyses

Patients with a diagnosis of SLE at baseline, a CLASI-A score ≥15 at baseline, SCLE disease subtype, concomitant use of DMARDs and concomitant use of corticosteroids showed a numerically greater change in CLASI-A score from baseline at week 12 with FIL compared with PBO; however, there were a small number of patients in these subgroups (Fig. 3).

Transcriptional analyses

IFN pathway gene activity decreased over time with FIL treatment and was statistically significant (compared with PBO) after 2 weeks (Supplementary Fig. S3, available at *Rheumatology* online) but not at other time points. Of the four FIL patients with the highest IFN activity at baseline, three had the largest reduction in the CLASI-A score after 12 weeks across all arms and two achieved a CLASI-A score of 0 over the course of treatment (Supplementary Fig. S4, available at *Rheumatology*

Fig. 1 CLASI-A score least squares mean change from baseline to week 12



Full analysis set includes patients who were randomized and received at least one dose of study drug. Baseline value was the last available value collected on or prior to the day of the first dose of study drug. The adjusted means were obtained from a mixed effects model for repeated measures with baseline CLASI-A score, stratification factors, visit and treatment*visit as fixed effects and patient as a random effect.

online). All six patients with IFN activity within the range of the healthy volunteers at baseline were randomized to the PBO or LANRA groups; no patients with normal IFN activity were randomized to FIL. The median [quartile 1 (Q1), quartile 3 (Q3)] change from baseline in the CLASI-A score by IFN activity subgroup is shown by treatment group in Fig. 3.

Safety summary

During the PBO-controlled period, TEAEs were observed in 6 (66.7%) PBO, 14 (73.7%) LANRA and 9 (52.9%) FIL patients (Table 2). Most AEs were mild to moderate in severity and non-serious. Serious AEs (SAEs) were reported in two patients in the LANRA arm (coronary artery occlusion and hypersensitivity). Premature discontinuation of study drug due to an AE occurred in one (11.1%) PBO patient, four (21.1%) LANRA patients and one (5.9%) FIL patient. The most common AEs, reported for two or more patients in any treatment group during the PBO-controlled period, were upper respiratory tract infection and headache. TEAEs of interest (Table 2) during the PBO-controlled period included infections and infestations, which occurred in 22.2%, 47.1% and 36.8% patients in the PBO, LANRA and FIL arms, respectively. Other TEAEs of interest were infrequent and occurred only in the LANRA arm, including liver transaminase elevation in two patients and a serious MACE in one patient. This patient had cardiovascular risk factors, including hypertension, mitral valve stenosis, positive smoking status and long-term contraceptive use.

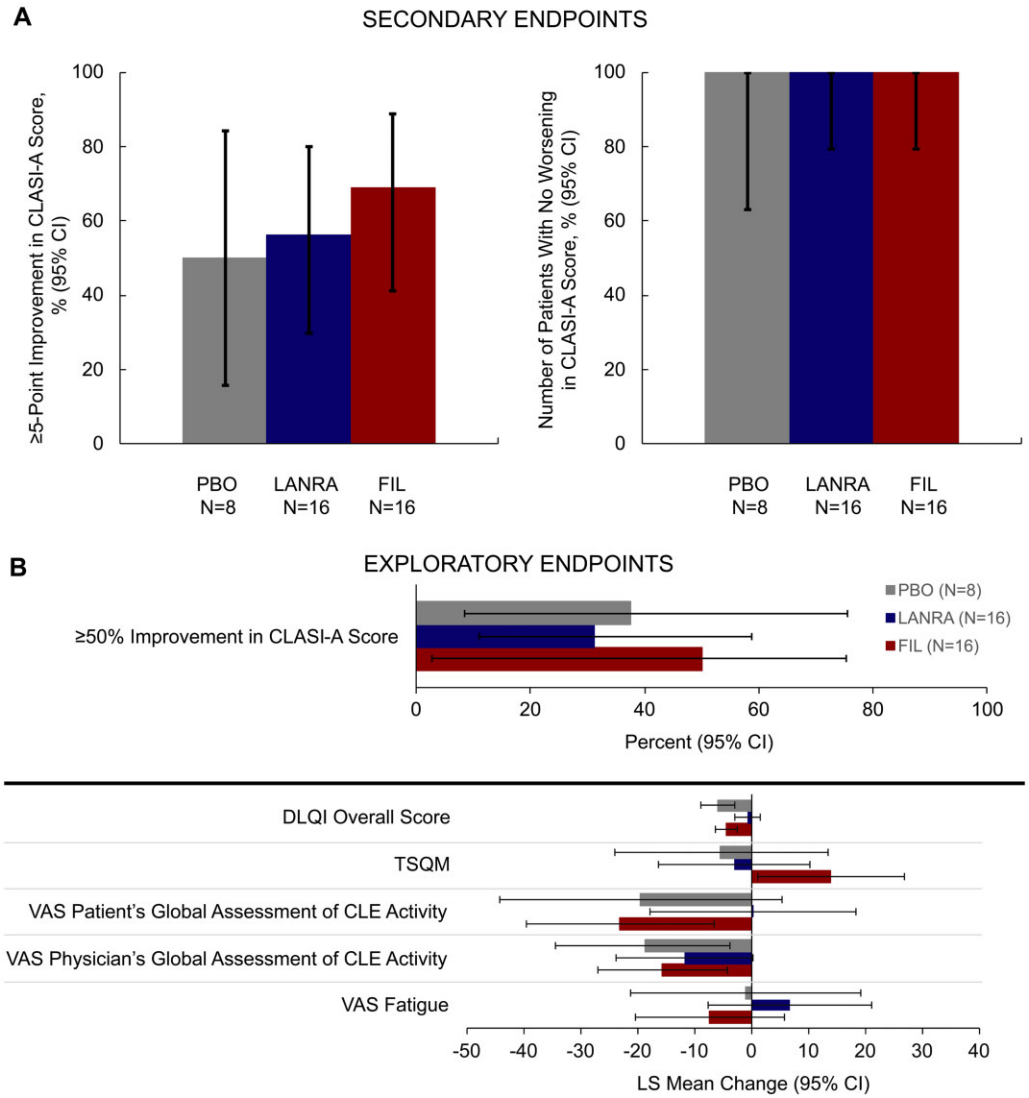
TEAEs during the overall study period were consistent with those of the PBO-controlled period (Supplementary Table S1, available at *Rheumatology* online). One additional SAE of haemorrhoids occurred following the PBO-controlled period in the FIL group. There were no serious infections, opportunistic infections, venous thrombotic events, gastrointestinal perforations, malignancies or deaths during the study. During the entire study, most laboratory abnormalities were grade 1 or 2 in severity (using Common Terminology Criteria for Adverse Events version 4.03) and no patient had a grade 4 laboratory abnormality.

Discussion

Development of safe and effective treatments for patients with LE is an area of high unmet need, as there are many patients who do not respond well to current therapies or who have unacceptable toxicity. This proof-of-concept study explored the safety and efficacy of JAK1 inhibition with FIL or SYK inhibition with LANRA in females with CLE. The primary endpoint was not met for either investigational treatment. This may be due to a lack of efficacy of both agents, the small number of patients studied, that the patient-reported outcomes (PROs) assessed were unsuitable in this population or to the unexpectedly high PBO response. However, FIL treatment resulted in a trend suggesting improvement in skin manifestations of CLE with several measures and in subgroups of patients. PRO results were highly variable, with no clear trend observed for either FIL or LANRA *vs* PBO.

High PBO responses have been observed previously in SLE studies; this is problematic in trying to determine the efficacy of a new molecule [18–22]. The high PBO response in this proof-of-concept study limits the ability to draw conclusions about the efficacy of LANRA or FIL in CLE. Concomitant use of background medications, particularly when initiated at the start of the trial, has been suggested as a component of the high PBO response observed in some SLE trials [23]. In the current trial, a criterion for enrolment was an inadequate response to the standard of care (SOC). SOC therapy was allowed if the dose was stable for 28 days prior to study treatment initiation and remained constant during the PBO-controlled period of the trial. It is possible that requiring only 28 days of stable SOC therapy prior to baseline was not long enough to observe the full effects of the SOC. Antimalarial and oral corticosteroid use was highest in the LANRA group and immunosuppressant use was highest in the FIL group, which may have affected the results. Overall background medication use was relatively well balanced across treatment groups. Background treatment adherence was not assessed; adherence to background treatments may possibly have contributed to the observed discrepancies.

FIG. 2 Secondary and exploratory endpoints (change from baseline or meeting criteria at week 12)

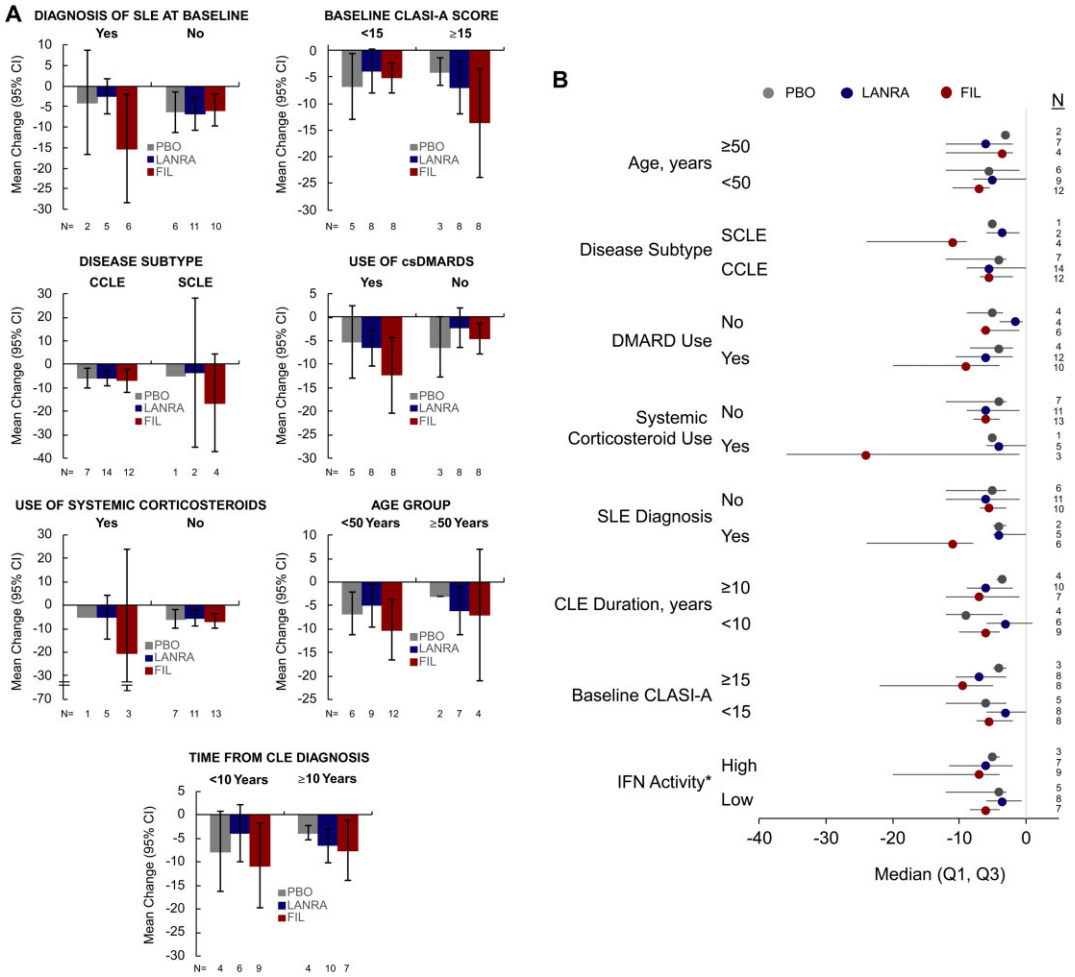


(**A**) Secondary endpoints: proportion of patients with a ≥5-point improvement in the CLASI-A score (left) and proportion with no worsening in the CLASI-A score (right). (**B**) Exploratory endpoints: percentage of patients with ≥50% improvement in the CLASI-A score and patient- and physician-reported QoL assessments. Full analysis set includes patients who were randomized and received at least one dose of study drug. Increase in TSQM indicates improvement. DLQI: Dermatology Life Quality Index; TSQM: Treatment Satisfaction Questionnaire for Medication; VAS: Visual Analog Scale.

It is well recognized that many of the disease activity metrics in SLE may be difficult to assess [23]. The CLASI-A scale was designed as a single instrument to assess heterogeneous CLE presentation. The change in the CLASI-A determined as a meaningful improvement (MCID) is 4–7 points [24–26]. The CLASI-A also correlates with HRQoL [24, 26] and disease biomarkers [9]. It has recently been used to demonstrate efficacy in phase 1 [9, 27], phase 2 [10, 28, 29] and phase 3 [8, 30] trials of therapies for skin disease in LE. In addition, it has shown high inter- and intrarater reliability and responsiveness [8, 9, 28, 31] in trained individuals. Despite these considerations, in this study a post hoc review identified one site with multiple CLASI-A scoring discrepancies and exclusion of this site decreased the primary endpoint PBO response by 1.6 points, while the effects on other treatment group responses were much smaller (maximum difference 0.4 points), indicating that intersite variability may have contributed to the high PBO response. Photo adjudication of CLASI-A findings might be helpful in similar multicentre clinical trials.

FIL treatment appeared to impact cutaneous disease activity in subgroups with more severe manifestations, including those with high disease activity at baseline

Fig. 3 Change in the CLASI-A score from baseline to week 12 by subgroup



(**A**) Mean (95% CI) change from baseline for PBO, LANRA and FIL groups for selected subgroups. (**B**) Forest plot showing the median (Q1, Q3) for the PBO, LANRA and FIL groups for all subgroups. Age (in years) was calculated from date of first study drug administration. Disease subtype as reported in the clinical database was used for subgroup derivation. csDMARD subgroups determined per systemic DMARD use as reported in the clinical database. The following routes of administration were considered for systemic corticosteroids: oral, intravenous, intramuscular and subcutaneous. The duration of CLE was calculated based on the reported date of CLE diagnosis and the date of enrolment in the study. For all treatment groups, the baseline value was the last available value on or prior to the first dose of the study drug. *IFN activity was not a prespecified subgroup analysis. IFN activity was classified into subgroups according to whether the value was below (low) or above (high) the median value at baseline.

(CLASI-A scores ≥15) and those with a concurrent SLE diagnosis. Historically, better discrimination of treatment differences from PBO and lower PBO responses have been shown in analyses of patients with more severe manifestations of disease [23, 32], consistent with our observations. Although the patient number is small, the subgroup analysis in CLE patients with concurrent SLE suggests that JAK inhibition may possibly be effective in populations with more severe disease, consistent with findings from the belimumab BLISS trials [32].

JAK inhibitors have shown clinical benefit and have been approved for RA, psoriatic arthritis and ulcerative colitis and are under investigation in several inflammatory and autoimmune diseases [33–39]. Baricitinib (a JAK1/2 inhibitor) is the first JAK inhibitor with phase 2 results in SLE, showing a significantly greater proportion of patients with resolution of arthritis or rash (primary endpoint) at the 4 mg dose, with similar findings on several other efficacy endpoints [40]. Baricitinib did not lead to improvements in skin disease as assessed by the

Table 2 TEAEs (placebo-controlled period, up to week 12)

n (%)	PBO (*n* = 9)	LANRA (*n* = 19)	FIL (*n* = 17)
TEAE	6 (66.7)	14 (73.7)	9 (52.9)
Infections and infestations	2 (22.2)	7 (36.8)	8 (47.1)
Serious infections	0	0	0
Herpes zoster	0	1 (5.3)	0
Active tuberculosis	0	0	0
Opportunistic infection	0	0	0
Hepatitis B or C	0	0	0
VTE and pulmonary embolism (unadjudicated)	0	0	0
Malignancies	0	0	0
Gastrointestinal perforation	0	0	0
Liver transaminase elevation	0	2 (10.5)	0
Serious MACE (unadjudicated)	0	1 (5.3)	0
TEAE grade ≥3	0	2 (10.5)	0
TE SAE	0	2 (10.5)	0
Death	0	0	0

Safety analysis set includes patients who received at least one dose of study drug. AEs were coded according to MedDRA version 22.0. Severity grades were defined by the CTCAE version 4.03. CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event; VTE: venous thromboembolic event.

CLASI-A scale in patients with SLE; however, this may have been due in part to mild skin disease [mean CLASI-A 4.2 (S.D. 5)] at baseline [40]. Our results with FIL in the subpopulations of CLE support further development of JAK1 inhibitors in LE.

Some evidence supports the use of SYK inhibitors in lupus models [41], and SYK activity and SYK-associated gene expression are evident in CLE tissue [16]. However, this is the first trial of oral SYK inhibitors in LE. Although a very small study, the results of LANRA treatment reported here suggest that SYK inhibition appears to lack therapeutic efficacy in CLE.

High expression of IFN-stimulated genes in the periphery may represent a biomarker to identify a population responsive to FIL, as patients with the highest IFN activity at baseline had the largest CLASI-A responses, including remission during treatment in two cases. The skin manifestations of SLE are known to be IFN-I-associated [1, 2] and are improved by treatment that reduces IFN-I response biomarkers in the blood and skin [9]. IFN-I receptors are known to signal via JAK1 [42], but the role of IFN signalling in the pathogenesis of CLE is less established [43, 44]. Because all patients with IFN pathway activity within the range of healthy volunteers at baseline received PBO or LANRA (none were randomized to FIL), the therapeutic benefit of FIL in patients with normal IFN activity cannot be determined from this study. Future investigations that include biomarkers within these subpopulations may elucidate the role of IFN signalling via JAK1 in the pathogenesis of CLE.

Both study drugs were generally well tolerated in this small sample size. There were no deaths during the study and few SAEs were reported. There were no serious infections; only one infection of interest (herpes zoster) was reported in the LANRA group. Venous thrombosis with JAK inhibitors is an area of concern [40], and patients with SLE may be at increased risk [45]; no deep vein thrombosis or pulmonary embolism was observed. Liver function test elevations reported with fostamatinib [46] were also observed with LANRA treatment. However, other safety concerns for fostamatinib observed in the RA development program—such as hypertension, diarrhoea and rashes—were not observed with the use of the highly selective SYK inhibitor LANRA. The safety profile observed with FIL in this study is consistent with that observed in trials of FIL in RA [47].

This study has several limitations, including the limited number of patients evaluated. The PBO-controlled period was only 12 weeks of the 48 week study. The high PBO response that limited data interpretation, in addition to the acknowledged challenge of assessing disease activity in LE, suggests that central adjudication of the CLASI, if possible, may help reduce outcome variability in future studies. Imbalances in gene signatures between the treatment groups at baseline limit interpretation of exploratory biomarker data, but selection of those with high IFN activity at baseline may help clarify the extent of such signalling through JAK1 in CLE pathogenesis. Despite these limitations and the inability to achieve the primary endpoint, these results collectively suggest that JAK1 inhibition with FIL in CLE warrants further investigation while SYK inhibition does not.

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Data availability statement

Anonymised individual patient data will be shared upon request for research purposes depending on the nature of the request, the merit of the proposed research, the availability of the data, and its intended use. The full data-sharing policy for Gilead Sciences can be found at https://www.gilead.com/about/ethics-and-code-of-conduct/policies.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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