

Pharmacodynamic Effects of Litifilimab in Lupus in a Randomized, Placebo-Controlled Phase 2 Study: Rapid and Sustained Reductions in Type I Interferon-Associated Gene Expression and Cytokines

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Objective. The pharmacodynamic effects of litifilimab on type I interferon (IFN) response and correlations with clinical outcomes were investigated in systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE).

Methods. Participants from part A (SLE) or part B (CLE with or without SLE) of the randomized phase 2 LILAC trial who received litifilimab (at 50 mg, 150 mg, or 450 mg) or a placebo were included. IFN gene signature (IFNGS) scores were assessed from whole-blood samples using a 22-gene panel in 120 and 131 participants (parts A and B, respectively). IFN α and other IFN-regulated cytokine concentrations were measured in serum in 112 and 131 participants (parts A and B, respectively).

Results. Most participants were IFNGS-high at baseline (79–91%), and no baseline IFNGS-low participant results were reported. In IFNGS-high participants, litifilimab induced rapid, significant (nominal $P < 0.05$), and sustained reductions in IFNGS scores and IFN α concentrations versus a placebo for litifilimab at 450 mg in part A and for litifilimab at 150 mg and 450 mg in part B. In part A, IFN α reductions with litifilimab were correlated with clinical response measures. In part B, dose-response relationships for IFNGS score and IFN α concentration were observed, similar to those for disease activity measured with the Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity (CLASI-A) score.

Conclusion. Administration of litifilimab resulted in reductions in both IFNGS scores and IFN α concentrations, pharmacodynamic effects that correlated with clinical responses. These findings support the mechanism of action of litifilimab and its continued evaluation in larger studies of patients with SLE or CLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory disease that affects multiple organs, with the musculoskeletal and mucocutaneous systems being most frequently involved.^{1–3} Cutaneous lupus erythematosus (CLE), which occurs with or without concomitant SLE, is categorized into chronic CLE (CCLE), subacute CLE (SCLE), or acute CLE subtypes.³

The interferon (IFN) family of cytokines include type I, type II, and type III IFNs and play an important role in the immune response

against pathogens.⁴ Although the pathogenesis of lupus is not fully understood, there is substantial evidence that the type I IFN cytokine family plays a central role in the pathogenesis of both SLE and CLE.^{5–10} Patients with SLE have been shown to have increased serum IFN α concentrations compared with healthy controls.^{11–14} Up-regulation of IFN expression in SLE has been reported in both active disease and in remission, although IFN expression may vary over time in SLE.^{14–16} Patients with SCLE or discoid lupus erythematosus (DLE) (a subtype of CCLE) have increased IFN signaling and activation of IFN downstream

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mediators, regardless of whether they have concomitant SLE.¹⁷ Overexpression of myxovirus resistance protein 1 (MxA), a specific marker of type I IFN signaling, is observed in lesional skin of patients with active CLE, regardless of CLE subtype.¹⁸

IFN downstream activity can be quantified using an IFN gene signature (IFNGS) score, which is an integrated score based on measurements of expression of a subset of IFN-induced genes. IFNGS scores were shown to be elevated in up to ~80% of patients with active SLE or CLE.^{17,19–21} Increased IFNGS scores have been correlated with disease activity in both SLE and CLE.^{6,17,19} Based on the overall evidence, IFNs are appropriate therapeutic targets for lupus. Indeed, blocking subunit 1 of the type I IFN receptor (IFNAR1) with anifrolumab in patients with SLE led to a down-regulation of type I IFN-induced genes.²² The clinical data for anifrolumab generated by the phase 2 and 3 studies supported its approval by the US Food and Drug Administration^{23–26} in 2021. Furthermore, subgroup analyses of the anifrolumab trials in SLE demonstrated robust effects in patients with cutaneous involvement.^{23–25}

Although several other cell types secreting type I IFN are believed to participate in lupus pathogenesis, plasmacytoid dendritic cells (pDCs) are suggested to be one of the major producers of type I IFN and contributors to lupus disease activity.^{27–34} Litifilimab, an investigational therapy that is a potential first-in-class, humanized Ig G1 monoclonal antibody, targets blood dendritic cell antigen 2 (BDCA2), a receptor expressed on the surface of pDCs.^{35,36} Litifilimab induces rapid and sustained internalization of BDCA2, inhibiting the Toll-like receptor (TLR)-induced production of type I IFN (IFN α) and other pDC-derived proinflammatory mediators, including type III IFN (IFN λ), tumor necrosis factor α (TNF α), and interleukin-6 (IL-6).^{35,36} In the phase 1 study, litifilimab led to a decrease in expression of MxA (a specific marker of type I IFN signaling) and other proteins downstream of IFN in skin biopsies.³⁶ The Fc γ R1a (CD32a) membrane receptor, expressed by pDCs and other cell types, facilitates the uptake of immune complexes that, through internalization, initiate TLR7 and TLR9 signaling and ultimately secretion of type I IFN.^{35,37} Binding of litifilimab to BDCA2 also leads to the internalization of Fc γ R1a and may limit the number of autoreactive immune complexes that can bind and activate TLR7/9 signaling pathways.³⁵ Whether these effects on type I IFN-inducible genes are exerted via an autocrine effect only, and/or via an effect on distant cells, is still under evaluation.³²

A randomized, double-masked, placebo-controlled phase 1 study (ClinicalTrials.gov identifier: NCT02106897) in participants with SLE and active skin disease confirmed that litifilimab BDCA2 internalization on pDCs and decreased cutaneous MxA expression; the latter correlated with improvements in Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity (CLASI-A) scores.³⁶ The subsequent multicenter, randomized, double-masked, placebo-controlled phase 2 LILAC study (ClinicalTrials.gov identifier: NCT02847598) was conducted in two parts to evaluate the efficacy and safety of litifilimab in participants with

SLE and active joint and skin manifestations (part A) or active CLE with or without SLE (part B). Both parts of the LILAC study met their primary end points. In part A, litifilimab was associated with a significantly greater reduction in the number of swollen and tender joints compared with placebo over 24 weeks.³⁸ In part B, litifilimab significantly improved CLASI-A scores compared with placebo over 16 weeks, and a significant dose effect was demonstrated.³⁹

We investigated the effects of litifilimab administration on IFNGS scores and concentrations of IFN α as well as other IFN-regulated cytokines in SLE and CLE. Correlations between pharmacodynamic effects and clinical outcomes were performed.

PATIENTS AND METHODS

Study design and patients. Inclusion and exclusion criteria for LILAC, and its protocol amendments, have been previously reported.^{38,39} Adult participants (aged 18–75 years) were enrolled across the United States, Europe, Latin America, and Asia. Participants in part A had SLE that met the 1997 classification criteria of the American College of Rheumatology,⁴⁰ with active skin manifestations, defined as CLASI-A score ≥ 8 under protocol version 1 (PV1) or meeting the Systemic Lupus Erythematosus Disease Activity Index–2000 (SLEDAI-2K) cutaneous descriptor with no requirement for CLASI-A score under protocol versions 2 through 5 (PV2–5). Part A participants enrolled under PV2–5 were also required to have ≥ 4 tender joints and ≥ 4 swollen joints according to a 28-joint assessment. Participants in part B had histologically confirmed active CLE (SCLE or CCLE, including DLE), with or without SLE, and a CLASI-A score of ≥ 8 .

A total of 120 and 132 participants were randomized in part A and part B, respectively, to receive litifilimab at 450 mg or a placebo for 24 weeks (part A) or to receive litifilimab at 50 mg, 150 mg, or 450 mg or a placebo for 16 weeks (part B). Study treatment was administered every four weeks, with an additional dose at week 2. Under PV1, an additional 12 participants in part A received litifilimab at 50 mg ($n = 6$) or 150 mg ($n = 6$); these 12 participants were excluded from these analyses owing to the small group sizes.

The analyses included the LILAC participants who were randomized and received at least one dose of study treatment (the modified intent-to-treat population) and who also had available measures at baseline and at least one postbaseline time point; the additional 12 participants described earlier were excluded. A description of the study design can be found in Supplementary Figure 1.

Sample collection. IFNGS was assessed in whole-blood samples, and the concentrations of IFN α and other cytokines were measured in serum samples. Blood samples were collected at baseline and weeks 1, 2, 4, 8, 12 or 16, 20, and 24 in part A and at baseline and weeks 1 or 2, 4, and 12 or 16 in part B. Serum samples were collected at baseline and weeks 1, 4, 16, and 24 in part A and at baseline and weeks 1, 4, 12, and

16 in part B. Variations in sample collection time points were due to the differences in protocol versions and the designs of part A and part B. Data from participants enrolled under PV1 were pooled with data from participants enrolled and/or reconsented under PV2–5.

IFNGS assay. Total RNA was extracted from whole-blood samples (PAXgene Blood RNA samples) using an automated procedure (QIA-symphony RNA Kit, QIA-symphony SP Platform; QIAGEN). RNA quantification and quality control were determined using a Nanodrop-8000 spectrophotometer. RNA was normalized and then reverse-transcribed using High-Capacity cDNA Reverse Transcription Kits (Life Technologies). The resulting complementary DNA was analyzed by TaqMan Gene Expression assays (custom or standard off-the-shelf) using 96.96 chips on the Fluidigm Biomark HD real-time polymerase chain reaction analyzer (Eurofins Genomics Europe Genotyping A/S). Each sample was analyzed in triplicate on the same chip alongside the appropriate controls.

A panel of 22 IFN response genes and 4 housekeeping genes (Supplementary Table 1) was selected based on previous literature⁴¹ and on genes evaluated in previous litifilimab studies with sufficiently low variation and high expression to allow for the detection of measurable changes following litifilimab treatment.^{36,41,42} The gene expression levels of the individual genes were normalized to the housekeeping genes in the same run. The average normalized expression values for the 22 IFN-inducible genes on the panel were calculated to give a single IFNGS score per sample.

Participants were classified at screening into IFNGS-high or IFNGS-low subgroups using a 3-gene panel (*G1P2/ISG15*, *LY6E*, and *EPSTI1*), rather than the 22-gene panel used for the longitudinal data analysis. Classifications by these two panels were highly concordant ($\geq 90\%$). See the Supplementary Methods for further details.

IFN α and other cytokine assays. IFN α serum concentrations (specifically IFN α -2a) were measured using the Simoa IFN α assay (Quanterix). Briefly, anti-IFN α antibody-coated paramagnetic capture beads were incubated with the samples. Following the addition of a biotin anti-IFN α detection antibody, a streptavidin- β -galactosidase conjugate was added, and the capture beads were resuspended in a resorufin β -D-galactopyranoside (RGP) substrate solution and transferred to the Simoa disc. IFN α was detected by a fluorescent signal produced by the hydrolysis of the RGP substrate by the β -galactosidase. Appropriate controls were used for each run.

A panel of 10 other cytokines (IFN γ , IL-1 β , IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, and TNF α) was analyzed simultaneously using the Simoa CorPlex Human Cytokine Panel 1 detection assay in serum samples. Quantification signals used streptavidin-horseradish peroxidase and were detected by the

Quanterix SP-X Imaging and Analysis System. Appropriate controls were used for each run. See the Supplementary Methods for further details.

Statistical analysis. IFNGS and each cytokine were analyzed using a mixed model for repeated measures (MMRM) with an unstructured covariance matrix. Least squares mean estimates by visit and treatment group were reported with 95% confidence intervals (CIs). Treatment effect estimates were reported as geometric mean ratios (GMRs), defined as the ratios between the geometric mean fold change from baseline in the litifilimab group and the geometric mean fold change from baseline in the placebo group. Estimates of GMRs were reported with 95% CIs and *P* values for each litifilimab dose group by visit. *P* values were not adjusted for multiple comparisons and should be interpreted as nominal; significance was defined using a two-sided $\alpha = 0.05$. Statistical analyses were performed with SAS (versions 9.4.7 and 9.04.01M7) and R (version 4.0.3). Additional details can be found in the Supplementary Methods.

MMRM. The MMRM outcome in each model was the log₂-transformed ratio of the postbaseline measurement to the baseline measurement, that is, the log₂ fold change from baseline. The model covariates are described in the Supplementary Methods.

For the IFNGS panel, data from weeks 1, 4, 16, and 24 (part A) and weeks 2, 4, and 16 (part B) were used in the final analysis. For IFN α and other cytokine concentrations, data from weeks 1, 4, 16, and 24 (part A) and weeks 1, 4, and 16 (part B) were used in the final analysis. The number of participants who were IFNGS-low at baseline was small, and these participants were excluded from all MMRM analyses reported here.

Correlation analyses. For both part A and part B, correlations between cytokines and the clinical outcome measures (total active joint count score, CLASI-A, and SLEDAI-2K at week 24 for part A; CLASI-A at week 16 for part B) at the end of the study were calculated. Only cytokines with nominally significant treatment effects at week 24 (part A) or week 16 (part B) were included in these analyses. For part A, associations of serum IFN α concentration ratios (after baseline to baseline) at week 24 with Systemic Lupus Erythematosus Responder Index (SRI-4) responder status at week 24 (assessed as previously described³⁸) were also examined.

Multiple Comparisons Procedure—Modeling for dose response in part B. In part B, dose-response relationships for IFNGS score and each cytokine were assessed using the two-step Multiple Comparisons Procedure—Modeling (MCP-Mod) method.^{39,43,44} For each outcome, in the “MCP” step, a test for the presence of a significant dose-response relationship at week 16 was performed in which the placebo arm was treated as a dose of 0 mg. For those outcomes that demonstrated a significant dose-response relationship, the

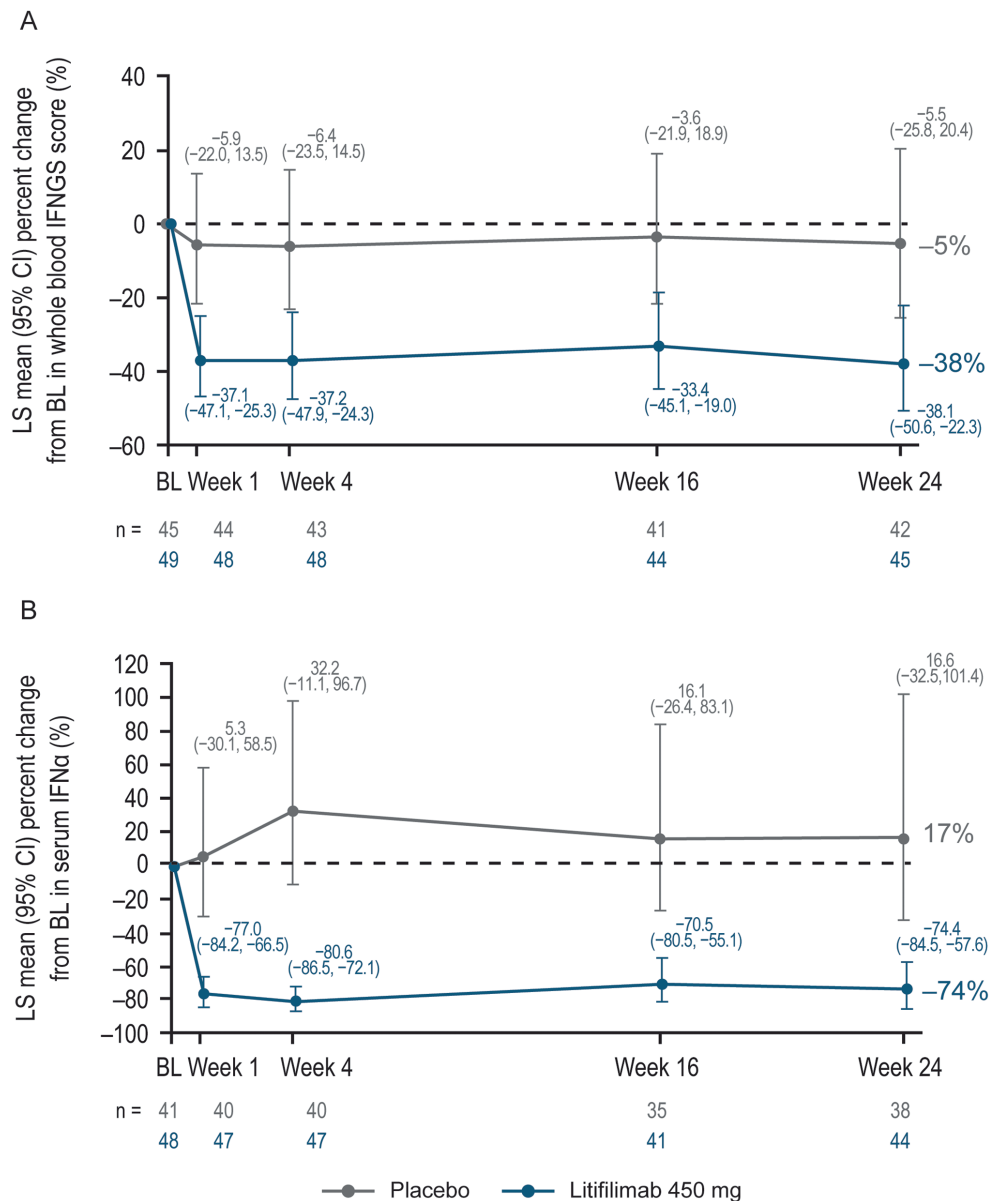


Figure 1. LS mean (95% CI) percent change from baseline in (A) IFNGS score (whole blood) and (B) IFN α concentration (serum) in part A (systemic lupus erythematosus). Variations in the number of participants within each group at any time point were the result of missing samples and/or different analysis populations. BL, baseline; CI, confidence interval; IFN α , interferon α ; IFNGS, interferon gene signature; LS, least squares.

“Mod” step estimated a dose-response curve based on a candidate set of models. Please refer to the Supplementary Methods for a description of the prespecified models used and for further details.

Data availability and ethical statement. Individual participant data collected during the trial may be shared after anonymization and on approval of the research proposal. Biogen commits to sharing patient-level data, study-level data, clinical study reports, and protocols with qualified scientific researchers who provide a methodologically sound proposal. Biogen reviews all data requests internally based on the review criteria and in accordance with our Clinical Trial Transparency

and Data Sharing Policy. Deidentified data and documents will be shared under agreements that further protect against participant reidentification. To request access to data, please visit <https://vivli.org/>.

The LILAC study was conducted in accordance with the principles of the Good Clinical Practice and Good Pharmacovigilance Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before randomization.^{38,39} The present analyses were conducted in accordance with Good Clinical Practice and International Council for Harmonisation Good Clinical Practice regulations.

Table 1. Changes from baseline in IFNGS score (whole blood), IFN α concentration (serum), and other cytokine (serum) concentrations in part A (SLE) and part B (CLE)*

	Litifilimab		
	Placebo	50 mg	150 mg
Part A (SLE)			
Participants, n	45	-	-
Change in IFNGS score, % (95% CI)			
Week 1	-5.9 (-22.0 to 13.5)	-	-
Week 24	-5.5 (-25.8 to 20.4)	-	-
IFNGS GMR ^a vs placebo, % (95% CI), <i>P</i> value			
Week 1	-	-	-
Week 24	-	-	-
Participants, n	41	-	-
Change in IFN α concentration, % (95% CI)			
Week 1	5.3 (-30.1 to 58.5)	-	-
Week 24	16.6 (-32.5 to 101.4)	-	-
IFN α GMR ^a vs placebo, % (95% CI), <i>P</i> value			
Week 1	-	-	-
Week 24	-	-	-
Participants, n	40	-	-
Change in TNF α concentration, % (95% CI)			
Week 1	-0.7 (-10.8 to 10.6)	-	-
Week 24	9.5 (-8.8 to 31.5)	-	-
TNF α GMR ^a vs placebo, % (95% CI), <i>P</i> value			
Week 1	-	-	-
Week 24	-	-	-
Participants, n	40	-	-
Change in IL-10 concentration, % (95% CI)			
Week 1	6.0 (-12.5 to 28.5)	-	-
Week 24	7.8 (-13.8 to 34.8)	-	-
IL-10 GMR ^a vs placebo, % (95% CI), <i>P</i> value			
Week 1	-	-	-
Week 24	-	-	-
Part B (CLE)			
Participants, n	29	24	23
Change in IFNGS score, % (95% CI)			
Week 2	-17.7 (-36.6 to 6.8)	-36.3 (-52.2 to -15.0)	-50.2 (-63.4 to -32.2)
Week 16	-12.2 (-34.3 to 17.3)	-39.7 (-56.1 to -17.2)	-65.1 (-74.9 to -51.6)
IFNGS GMR ^a vs placebo, % (95% CI), <i>P</i> value			
Week 2	-	0.77 (0.53 to 1.13), 0.1839	0.61 (0.41 to 0.89), 0.0123
Week 16	-	0.69 (0.45 to 1.05), 0.081	0.40 (0.26 to 0.61), 0.0001
Participants, n	28	24	23
Change in IFN α levels, % (95% CI)			
Week 1	-13.7 (-50.8 to 51.5)	-63.9 (-78.9 to -38.3)	-75.0 (-85.9 to -55.6)
Week 16	-31.2 (-59.9 to 18.0)	-62.7 (-79.3 to 32.8)	-81.9 (-90.1 to -66.7)
IFN α GMR ^a vs placebo, % (95% CI), <i>P</i> value			
Week 1	-	0.42 (0.2 to 0.89), 0.0248	0.29 (0.13 to 0.63), 0.0023
Week 16	-	0.54 (0.25 to 1.18), 0.123	0.26 (0.12 to 0.58), 0.001

(Continued)

Table 1. (Cont'd)

	Placebo	Litifilimab		
		50 mg	150 mg	450 mg
Participants, n	27	24	22	39
Change in TNF α concentration, % (95% CI)				
Week 1	-0.0 (-9.9 to 11.0)	-9.0 (-17.0 to -0.2)	-2.1 (-11.5 to 8.3)	-4.5 (-13.1 to 4.9)
Week 16	-6.7 (-18.3 to 6.5)	-12.5 (-23.8 to 0.5)	-10.1 (-22.2 to 3.8)	-10.1 (-19.4 to 0.4)
TNF α GMR ^a vs placebo, % (95% CI), <i>P</i> value				
Week 1	-	0.91 (0.79 to 1.04), 0.1764	0.98 (0.85 to 1.13), 0.7705	0.96 (0.83 to 1.1), 0.5145
Week 16	-	0.94 (0.78 to 1.13), 0.507	0.96 (0.79 to 1.17), 0.704	0.96 (0.81 to 1.14), 0.672
Participants, n	27	24	22	39
Change in IL-10 concentration, % (95% CI)				
Week 1	20.8 (-4.1 to 52.2)	2.6 (-16.9 to 26.7)	28.0 (2.0 to 60.7)	5.6 (-14.4 to 30.2)
Week 16	12.7 (-6.6 to 36.0)	-18.9 (-33.5 to -1.2)	5.9 (-13.8 to 30.0)	-4.7 (-18.6 to 11.6)
IL-10 GMR ^a vs placebo, % (95% CI), <i>P</i> value				
Week 1	-	0.85 (0.62 to 1.16), 0.2943	1.06 (0.77 to 1.46), 0.7185	0.87 (0.64 to 1.19), 0.3873
Week 16	-	0.72 (0.55 to 0.94), 0.016	0.94 (0.72 to 1.23), 0.647	0.85 (0.67 to 1.07), 0.168

* Data are least squares means unless otherwise specified. Variations in participant numbers within each group at any time point are the result of missing samples and/or different analysis populations. Nominal significant *P* values (*P* < 0.05). CI, confidence interval; CLE, cutaneous lupus erythematosus; GMR, geometric mean ratio; IFN α , interferon- α ; IFNGS, interferon gene signature; IL-10, interleukin-10; SLE, systemic lupus erythematosus; TNF α , tumor necrosis factor α .

^a Ratios between the geometric mean fold change from baseline in the litifilimab arm and the geometric mean fold change from baseline in the placebo arm; values <1 favor litifilimab.

RESULTS

Baseline characteristics. In part A, IFNGS was assessed in 120 participants (64 participants in the litifilimab 450 mg group and 56 participants in the placebo group), and IFN α concentrations were assessed in 112 participants (60 participants in the litifilimab 450 mg group and 52 participants in the placebo group) (Supplementary Table 2). In part B, IFNGS was assessed in 131 participants (26, 25, 47, and 33 participants in the litifilimab 50 mg, 150 mg, 450 mg, and placebo groups, respectively) and IFN α concentrations were also assessed in 131 participants (26, 25, 48, and 32 participants in the litifilimab 50 mg, 150 mg, 450 mg, and placebo groups, respectively) (Supplementary Table 2).

In both part A and part B, most participants were IFNGS-high at baseline (part A, 94 of 120 participants [78%] for IFNGS and 89 of 112 participants [79%] for IFN α ; part B, 115 of 131 participants [88%] for IFNGS and 115 of 131 participants [88%] for IFN α) (Supplementary Table 2). Too few participants (part A, 25 of 120 participants [21%] for IFNGS and 22 of 112 participants [20%] for IFN α ; part B, 11 of 131 participants [8%] for IFNGS and 11 of 131 participants [8%] for IFN α) were IFNGS-low at baseline to draw meaningful conclusions; therefore, these data are not reported.

Overall, the baseline characteristics were similar between groups (Supplementary Table 3). Part A participants included in the analysis had mean SLEDAI-2K scores that ranged from 9.9 to 11.2. Part B mean CLASI-A scores ranged from 15.5 to 19.0, with approximately half of the part B participants having concomitant SLE. Most participants were taking antimalarials, almost all (98%) participants in part A and 48% to 68% of participants in part B were taking oral glucocorticoids, and between 4% and

18% of participants were taking immunosuppressants in both parts.

Part A (SLE) pharmacodynamic effects. Sharp reductions in IFNGS scores and IFN α concentrations were observed with litifilimab at 450 mg at week 1 (the earliest postbaseline time point), which were sustained through week 24 (Figure 1). The week-24 reduction from baseline was significant ($P < 0.05$) for litifilimab at 450 mg versus placebo (Table 1; Supplementary Table 4). TNF α and IL-10 concentrations were also reduced ($P < 0.05$) with litifilimab at 450 mg at week 24 (Table 1). There was no clear evidence of treatment effects on IFN γ ($P = 0.436$), IL-6 ($P = 0.281$), IL-22 ($P = 0.785$), or IL-8 ($P = 0.806$) concentrations at week 24. Cytokines IL-12, IL-1 β , IL-4, and IL-5 were not quantifiable in a sufficient proportion of participants and were therefore not analyzed. Correlation between change in IFNGS score and IFN α concentration at week 24 is described in Supplementary Figure 2.

Part A (SLE) correlation between pharmacodynamics and clinical response. We next sought to examine correlations between reductions in IFN α and SLEDAI-2K score, active joint count total score, or CLASI-A score. At week 24 in the litifilimab 450 mg group, there were weak positive correlations between changes in IFN α concentration and (1) change in total active joint count and (2) change in CLASI-A score (Table 2). These findings were not observed in the placebo group.

At week 24 in the litifilimab 450 mg group, analyses showed a trend toward greater median IFN α reductions among SRI-4 responders compared with nonresponders (Figure 2), suggesting a possible association between IFN α reduction and SRI-4

Table 2. Spearman correlation estimates between change from baseline in IFN α concentration (serum) at each postbaseline visit and change in clinical responses at week 24 (part A [SLE]) and percent change in CLASI-A score at week 16 (part B [CLE])

	Week 1	Week 4	Week 16	Week 24
Part A (SLE)				
Total active joint count score, estimate (95% CI)				
Placebo	-0.38 (-0.64 to -0.05)	-0.14 (-0.44 to 0.18)	0.16 (-0.18 to 0.47)	-0.15 (-0.41 to 0.16)
Litifilimab 450 mg	0.14 (-0.12 to 0.39)	0.17 (-0.11 to 0.42)	0.29 (0 to 0.53)	0.34 (0.07 to 0.55)
CLASI-A, estimate (95% CI)				
Placebo	-0.06 (-0.37 to 0.28)	0.21 (-0.14 to 0.51)	0.04 (-0.31 to 0.41)	-0.01 (-0.34 to 0.31)
Litifilimab 450 mg	0.21 (-0.10 to 0.49)	0.40 (0.16 to 0.59)	0.29 (0.02 to 0.52)	0.35 (0.10 to 0.58)
SLEDAI-2K, estimate (95% CI)				
Placebo	0.07 (-0.26 to 0.38)	0.13 (-0.18 to 0.43)	0.23 (-0.12 to 0.53)	0.18 (-0.14 to 0.47)
Litifilimab 450 mg	-0.01 (-0.26 to 0.24)	0.10 (-0.17 to 0.35)	0.11 (-0.19 to 0.38)	0.16 (-0.09 to 0.39)
Part B (CLE)				
CLASI-A, estimate (95% CI)				
Placebo	0.34 (-0.13 to 0.71)	0.47 (0.12 to 0.71)	0.43 (0.10 to 0.68)	—
Litifilimab 50 mg	0.13 (-0.32 to -0.50)	0.28 (-0.18 to 0.62)	0.65 (0.32 to 0.85)	—
Litifilimab 150 mg	0.16 (-0.26 to 0.51)	0.15 (-0.26 to 0.52)	0.38 (-0.06 to 0.72)	—
Litifilimab 450 mg	0.30 (-0.08 to 0.61)	0.26 (-0.06 to 0.52)	0.41 (0.10 to 0.62)	—

CI, confidence interval; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; CLE, cutaneous lupus erythematosus; IFN, interferon; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.

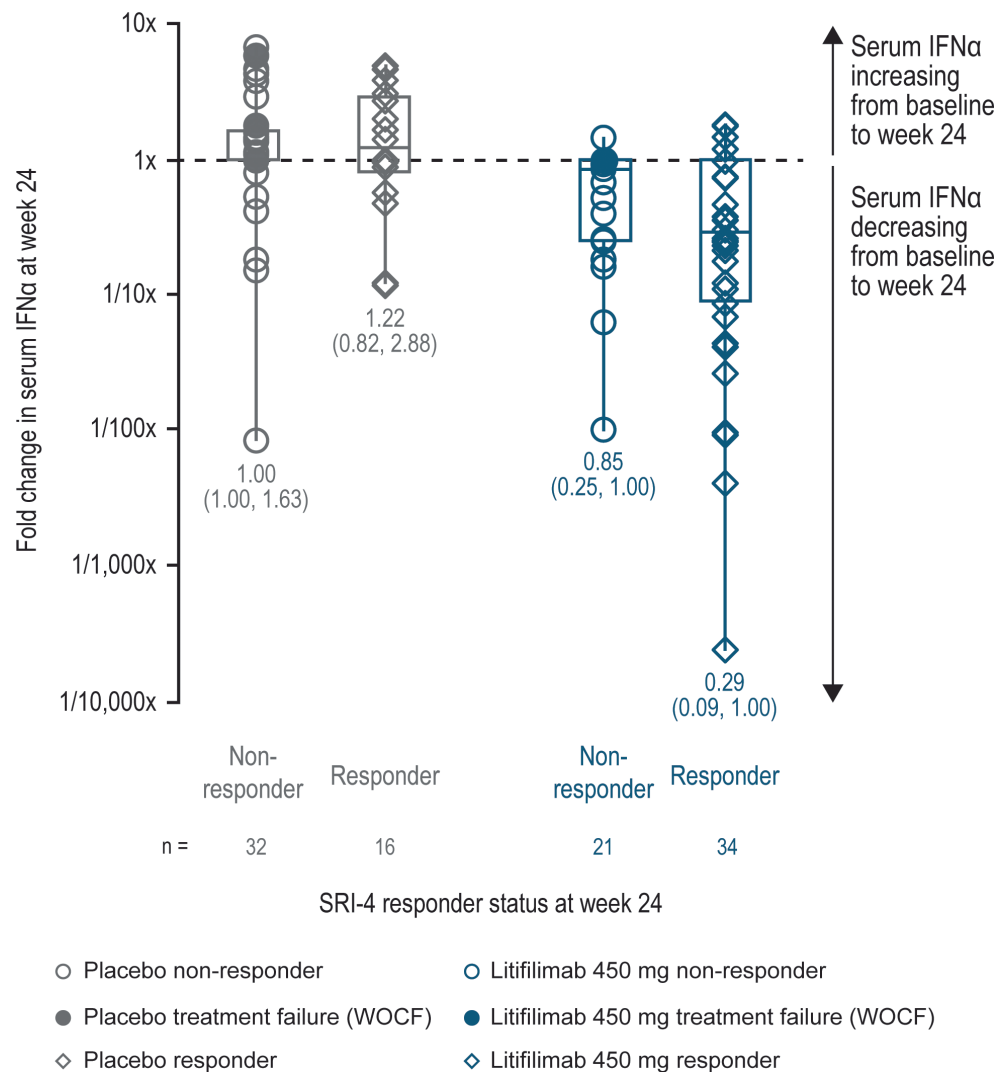


Figure 2. Association of change in IFNα concentration (serum) and SRI-4 responder status at week 24 in part A (systemic lupus erythematosus). The median, 25th percentile, and 75th percentile for the concentration ratio (after baseline/baseline) of serum IFNα by week 24 SRI-4 responder status are presented. IFNα, interferon α; SRI-4, Systemic Lupus Erythematosus Responder Index; WOCF, worst observation carried forward.

response. There was no evidence of meaningful correlations between baseline concentrations of any of the cytokines evaluated (IFNα, IL-10, IL-6, TNFα) with week 24 clinical responses for either the litifilimab or the placebo groups (Supplementary Table 5; data not shown for SRI-4 responder status).

Part B (CLE) pharmacodynamic effects. Similar to part A, IFNGS scores and IFNα concentrations were reduced versus placebo from the first postbaseline measured time point (week 1 or week 2) for all three litifilimab doses, and these reductions were sustained through week 16 (Figure 3). The MMRM analyses determined these reductions to be significant ($P < 0.05$) for the litifilimab 150 mg and 450 mg groups versus placebo (Table 1; Supplementary Table 4). There was no strong evidence of treatment effects in any of the other cytokines analyzed.

Correlation between change in IFNGS score and IFNα concentration at week 16 is described in Supplementary Figure 2.

Among all pharmacodynamic outcomes evaluated, only IFNGS score and IFNα concentration had significant dose-response relationships in the MCP analysis. The estimated dose-response relationship showed similar dose-response shapes for IFNGS score, IFNα concentration, and CLASI-A score at week 16 (Figure 4A). For all three outcomes, the responses appeared greater at the 150-mg dose level, followed by a leveling off, or attenuation, at the highest dose of 450 mg.

Part B (CLE) correlation between pharmacodynamics and clinical response. Correlations between reduction in CLASI-A score at week 16 and (1) reduction from baseline in IFNGS score (Figure 4B) and (2) IFNα concentration (Table 2) were observed in all treatment groups. There was no evidence

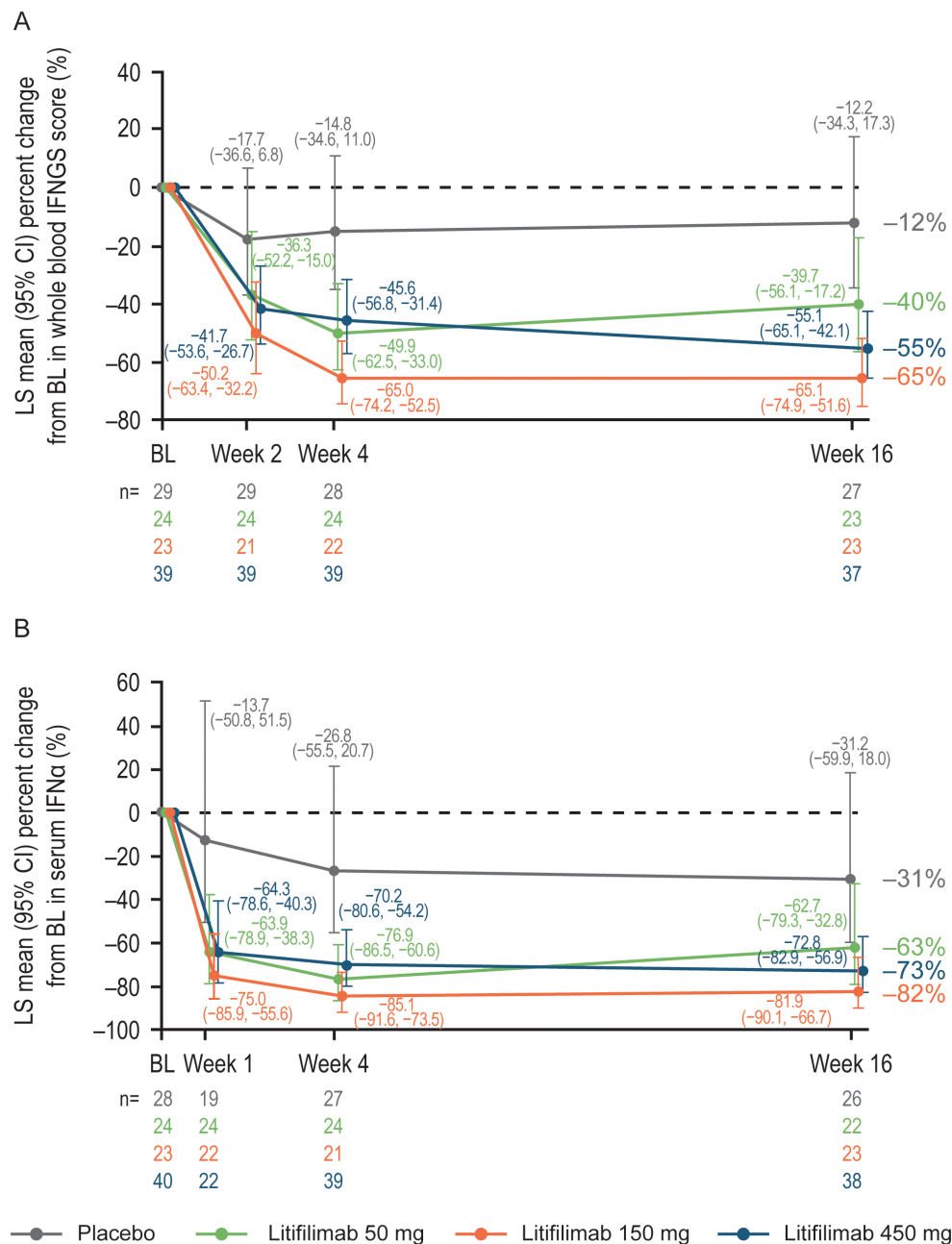


Figure 3. LS mean (95% CI) percent change from baseline in (A) IFNGS score (whole blood) and (B) IFN α concentration (serum) in part B (cutaneous lupus erythematosus). Variations in the number of participants within each group at any time point were the result of missing samples and/or different analysis populations. BL, baseline; CI, confidence interval; IFN α , interferon α ; IFNGS, interferon gene signature; LS, least squares.

of meaningful correlations between baseline cytokine concentrations (IFN α , IL-10, IL-6, and TNF α) and percent change in CLASI-A scores at week 16 (Supplementary Table 5).

DISCUSSION

Treatment with litifilimab rapid and sustained reductions in the whole-blood 22-gene panel IFNGS scores and serum IFN α concentrations in the IFNGS-high subgroup of LILAC study participants with SLE (part A) or CLE (part B). In the litifilimab-treated

participants with SLE (part A), associations between IFN α reductions and clinical responses (total active joint count, CLASI-A score, and SRI-4 responder status) were observed at the end of the study (week 24). Dose-response relationships for IFNGS score and IFN α concentration were observed in the dose-ranging component of the study (part B, CLE), with a similar relationship between dose and CLASI-A score changes from baseline also observed. Associations between reductions in IFNGS or IFN α concentrations and CLASI-A scores were observed in part B (CLE) in all treatment groups including the placebo group.

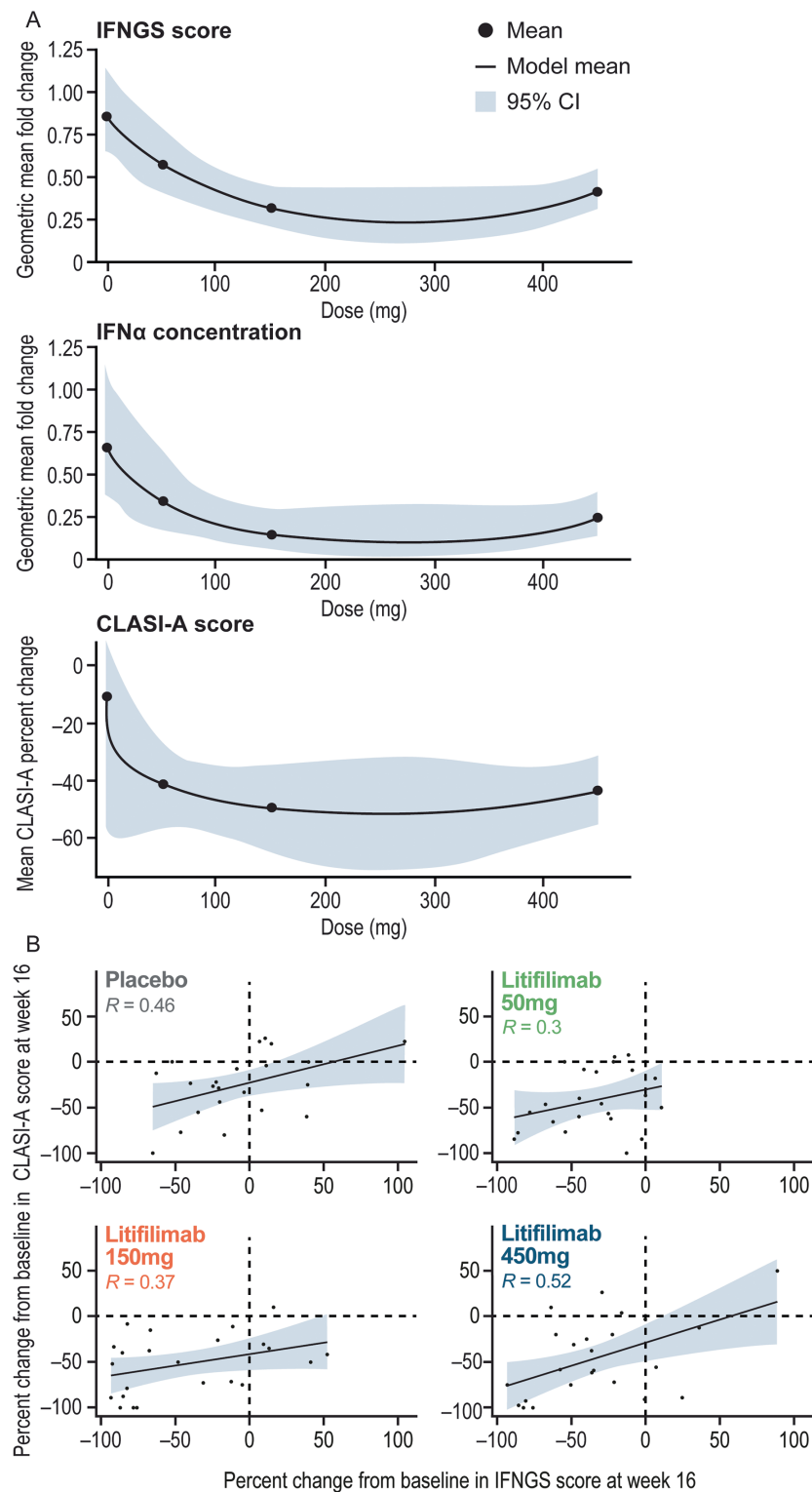


Figure 4. (A) MCP-Mod dose-response relationships for fold changes in IFNGS score (whole blood; top graph), fold changes in IFN α concentration (serum; middle graph), and percent changes in CLASI-A score (clinical response; bottom graph) at week 16 in part B (cutaneous lupus erythematosus [CLE]). Dose-response relationships are based on the MCP-Mod method. The MCP-Mod method uses a two-step process: a multiple comparison step to test for the presence of a significant dose-response relationship, in which placebo serves as a dose of 0 mg, and a modeling step to fit the best dose-response curve. Further details can be found in the study by Werth et al.³⁹; CLASI-A data include the participants with missing baseline data used for these analyses. (B) Pearson correlation estimates between change from baseline in IFNGS score (whole blood) and percent change in CLASI-A score (clinical response) in part B (CLE). CI, confidence interval; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity; IFN α , interferon α ; IFNGS, interferon gene signature; MCP-Mod, Multiple Comparisons Procedure–Modeling.

Most participants in the analyzed LILAC population were classified as IFNGS-high, in line with previous studies in SLE^{19–21}; the baseline characteristics of this IFNGS-high population were generally similar to those of the overall LILAC study population.^{38,39} The LILAC study inclusion requirement for skin activity in both parts may have selected for a disproportionately large IFNGS-high population, as cutaneous lupus is associated with elevated IFN α ¹² levels and IFNGS.¹⁷ In addition, overexpression of type I IFN correlates with the clinical severity of lupus,^{6,17,19} and the overall LILAC study population had moderate-to-severe disease.^{38,39}

Antimalarials and immunosuppressants, which are standard-of-care treatments, have been shown to modulate IFN pathway activity and reduce type I IFN production as part of their broad mechanisms of action.⁶ In this study, similar percentages of participants in the litifilimab and placebo groups were taking antimalarials and/or glucocorticoids (permitted as per study protocol if initiated at least three months before randomization), and it is therefore unlikely that these treatments differentially affected the observed reductions in IFNGS scores and IFN α concentrations.

Several therapeutic agents in development for lupus also directly reduce IFN levels or indirectly modulate its downstream biologic activity. The changes in IFNGS scores and IFN α concentrations generated by the administration of litifilimab were both robust and rapid in part A (SLE) and part B (CLE) of the study. These changes occurred at the earliest time point assessed (week 1 or week 2), when the clinical benefit of a drug might not yet be detectable. These results align with our phase 1 study, in which a single dose of litifilimab led to partial (~50%) reductions in IFN response genes in whole-blood samples of patients with SLE within 24 hours of administration,³⁶ and support the mechanism of action of litifilimab. In this study, improvements in clinical outcomes (active joint count total score and CLASI-A in part A; CLASI-A in part B) were associated with IFNGS score and IFN α concentration reductions between baseline and study end. Additionally, a trend toward greater median IFN α concentration reduction in SRI-4 responders relative to nonresponders was seen with litifilimab in part A. In part B, similar dose-response relationships were observed for IFNGS score, IFN α concentration, and CLASI-A scores.³⁹ In SLE and CLE, type I IFNGS expression correlates with both disease activity and severity,^{6,17,19} and blocking type I IFN signaling with anifrolumab has been shown to result in improvements in clinical outcomes in SLE, including in SLE skin lesions.^{24,25} Although the correlations detected in our study were not very strong, possibly owing to the low sample sizes, these associations warrant further exploration. In part B, associations between reductions in IFNGS or IFN α concentration and decreases in CLASI-A scores were observed for both litifilimab and placebo, which supports the appropriateness of using CLASI-A scores to measure cutaneous disease activity.

It has recently been proposed that the SLE disease activity features associated with type I IFN, such as arthritis and anti-

DNA antibodies, are in fact codetermined by the other types of IFN, and that type I IFN alone is strongly associated with the skin manifestations of patients with SLE.¹⁵ In SLE, anifrolumab treatment downmodulates gene pathways induced by type II IFN as well as type I IFN,²² and litifilimab inhibits pDC-derived IFN- λ 1 (type III IFN) in addition to type I IFN.³⁶ The involvement of type III IFN-producing pathways has also been reported in CLE.⁵ Additionally, the downstream effects of the different IFN types overlap considerably, thus the IFNGS may be reflective of the action of more than one IFN type.¹⁵ The profound effect of litifilimab on IFN α observed in this study provides additional evidence that pDCs play a key role, likely in concert with other cells, in type I IFN production and its downstream IFNGS induction in lupus.

Although the inhibition of IFN α and IFNGS might clearly contribute to the observed clinical response, additional biological effects of litifilimab via other IFN subtypes and/or cytokines may contribute to the clinical response observed in this phase 2 study. Indeed, our results support previous findings showing that BDCA2 is a receptor expressed on the surface of pDCs that plays a critical role in the inhibition of TLR-7 and TLR-9 induced production of type I IFN.^{35,36} In contrast to older research suggesting that BDCA2 is exclusively expressed on classical pDCs,⁴⁵ emerging evidence from single-cell RNA sequencing and flow cytometry has identified a novel DC subset sharing the pDC markers CD123 and BDCA2, and expressing surface CD2, CD5, AXL, and CD33.^{46–48} This indicates that BDCA2 may be expressed on a DC subset that shares properties with pDCs but potentially also has a distinct function, such as activating T cells. The results presented here support that pDCs or BDCA2-expressing cells are certainly critical type I IFN-producing cells but are likely acting in concert with other cells. Initially, it was acknowledged that pDCs were the main producer of type I IFN^{29–31}; however, recent studies in CLE skin suggest that other cell types are important producers of type I IFN, including keratinocytes, macrophages, and classical DCs.^{27,32–34} Taken together, the current evidence reflects the complexity of the disease and the potential multiple cellular pathways associated with different lupus endotypes, in addition to interindividual heterogeneity and variations in IFN expression over time.^{3,15,16,49}

In part A, there was evidence of treatment effects on serum TNF α and IL-10 concentrations. Reduction of TNF α by ligation of BDCA2 has been previously hypothesized⁵⁰ and demonstrated in pDCs of healthy human donors.³⁶ Elevated TNF α levels in patients with SLE and active joint disease has been previously reported,⁵¹ and downmodulation of TNF α was demonstrated in patients with SLE treated with anifrolumab after 52 weeks.²² Therefore, the TNF α decrease observed with litifilimab treatment may contribute to the improvement in lupus arthritis. Reductions in IL-10 concentration were observed with litifilimab treatment; similar effects were observed with anifrolumab in patients with SLE.²² More studies are needed to understand the possible beneficial role of IL-10 modulation in lupus. In our study, no strong

evidence of correlations between reductions in TNF α or IL-10 at any postbaseline visits and changes in total active joint count score at week 24 (data not shown) were observed. Therefore, it is unlikely that reductions in TNF α or IL-10 at an early visit would perform well as a strong predictor of clinical response at the end of the treatment period.

Limitations of this study include the restricted sample size in each cohort, which precludes definitive conclusions on the pharmacodynamic effects of litifilimab in patients with SLE and CLE. In addition, few participants (~20% in part A and 8% in part B) had low IFNGS status at baseline and, for this reason, no results were presented for this subgroup because no firm conclusions could be drawn on the response to treatment. Activated pDCs are decreased in the blood circulation and are found to be increased in lupus lesions.^{29,35,37} A correlation between changes in MxA expression and CLASI-A responses was demonstrated in skin biopsies of participants with SLE.³⁶ However, the pharmacodynamic effects reported here were analyzed from whole-blood and serum samples, rather than directly from lupus-affected tissues, such as the skin. This might constitute a potential limitation in developing a deeper understanding of tissue-specific pharmacodynamic changes induced by litifilimab. Additional studies will be needed to further characterize the pharmacodynamic effects of litifilimab in a larger population of patients with CLE and SLE. In conclusion, the rapid and sustained litifilimab-induced reductions in IFNGS scores and IFN α concentrations, along with the correlation of these pharmacodynamic effects with clinical responses, support the mechanism of action of litifilimab and the important role of type I IFN in lupus.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Barbey confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

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