



ADC 101st Annual Conference

APRIL 19-21, 2024 | HERSHEY LODGE, HERSHEY, PA



Update on New Biologics and Small Molecule inhibitors in Cutaneous Lupus Erythematosus

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DISCLOSURE OF
RELEVANT
RELATIONSHIPS WITH
INDUSTRY

Victoria P. Werth, MD

Cutaneous Lupus and Dermatomyositis

Grants: Pfizer, Corbus, Celgene, Amgen, Janssen,
Biogen, Gilead, Viela, Ventus, CSL Behring, Horizon

Consult: Pfizer, Janssen, Neovacs, Idera, Octapharma,
CSL Behring, Corbus, Rome, Astra-Zeneca, Biogen,
Celgene, Resolve, Gilead, Lilly, BMS, Nektar, Abbvie,
Akira, Viela, GSK, EMD Serona, Sanofi

Developed and validated an outcome measure for
cutaneous lupus (CLASI) and dermatomyositis
(CDASI)

Will be discussing off-label use of medications

Cutaneous Lupus Erythematosus

- Treatment of CLE
- New developments
 - Iberdomide
 - Litifilimab
 - Anti-ILT7
 - Deucravacitinib

LE-specific Skin Lesions

- Chronic Cutaneous LE
 - DLE: localized, generalized, hypertrophic
 - Lupus panniculitis
 - Tumid LE
- Subacute Cutaneous LE
 - Psoriasiform, annular/polycyclic
- Acute cutaneous LE
 - Malar erythema, photodistributed erythema

Cutaneous Lupus Erythematosus



ACLE

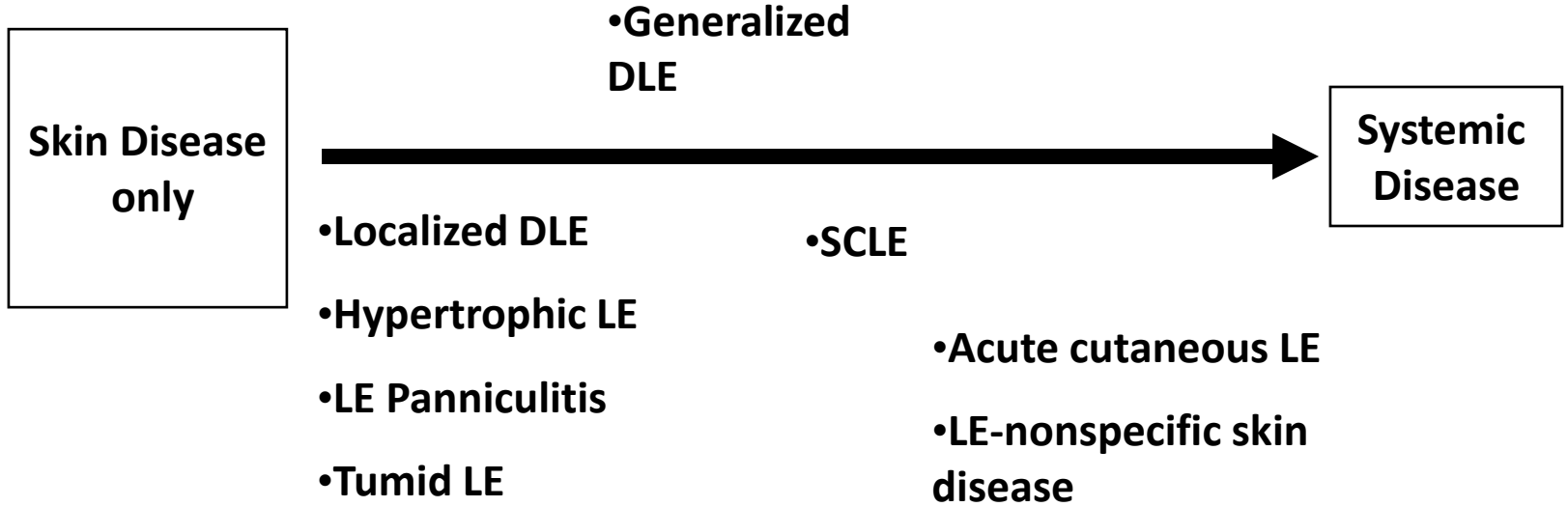


DLE



SCLE

Prognostic Significance of Cutaneous LE



Overview

- Classification criteria
 - SLE
 - DLE
- **Treatment of CLE**
- New developments

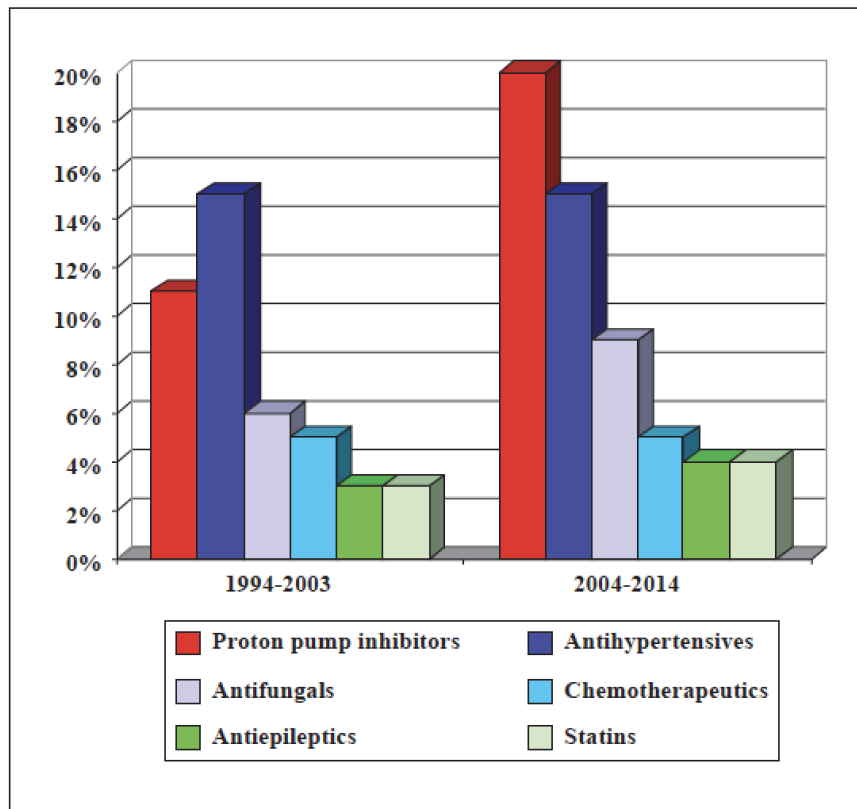
Evaluation of CLE Patients

- Hx and physical
- Skin biopsy
- CBC, CMP, urinalysis, ANA
- dsDNA, anti-Smith, SSA, SSB, complements
- Urine protein:creatinine ratio if any proteinuria on urinalysis
- Check lipids
 - Elevated LDL frequently and increased risk of atherosclerotic heart disease
 - Need evaluation and treatment

Treatment of CLE

- Sun avoidance, sunscreens, sun clothing
- Stop exacerbating medications (if possible)
- Stop smoking
- Topicals: steroids, pimecrolimus, tacrolimus

Causes of Drug-induced SCLE



Laurinaviciene R et al, EJD 27:28, 2017

PPI-induced SCLE



Drug-induced SCLÉ

Thiazide diuretics

Calcium channel blockers

Antifungals

Terbinafine (Lamisil),
griseofulvin

Beta blockers

oxyprenolol

NSAIDS: Piroxicam, naproxen

Antihistamines: Cinnarizine

Chemotherapy: Taxotere,
Paclitaxel, 5-fluorouracil,
checkpoint inhibitors
(ipilimumab and nivolumab)

Biologics: Abatacept, Rituximab,
TNF inhibitors

ACE inhibitors

Cilazapril, captopril

GI Acid inhibitors

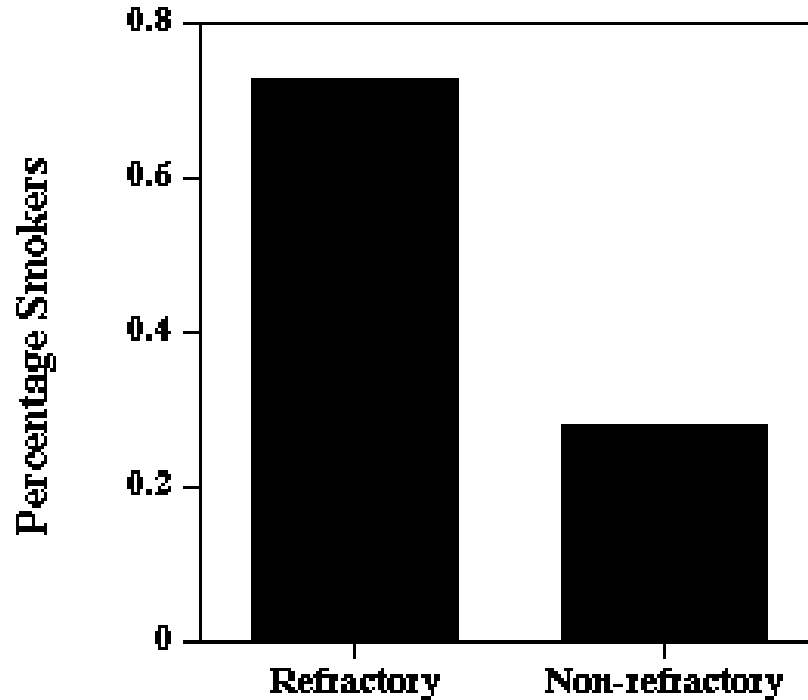
Ranitidine, omeprazole

Platelet inhibitor: Ticlopidine

Miscellaneous:

Interferon α & β , statins,
procainamide, phenytoin,
oxyprenolol, d-penicillamine,
fertilizer/pesticides

Smoking and Refractory Cutaneous LE



n=11
4

*Moghadam-Kia
and Werth, Arch
Dermatol, 145:255,
2009*

Systemic Treatment of CLE

- Antimalarials: Hydroxychloroquine, Chloroquine
 - Quinacrine on import alert for company in India
 - Very difficult to get currently
- Immunosuppressives (methotrexate, mycophenolate mofetil)
- Thalidomide and derivatives
- Other: Steroids, Dapsone, Retinoids, Rituximab, Belimumab (anti-BLyS)

Skin activity change over time with Lenalidomide (5 mg/day)

15 patients
86% with CR

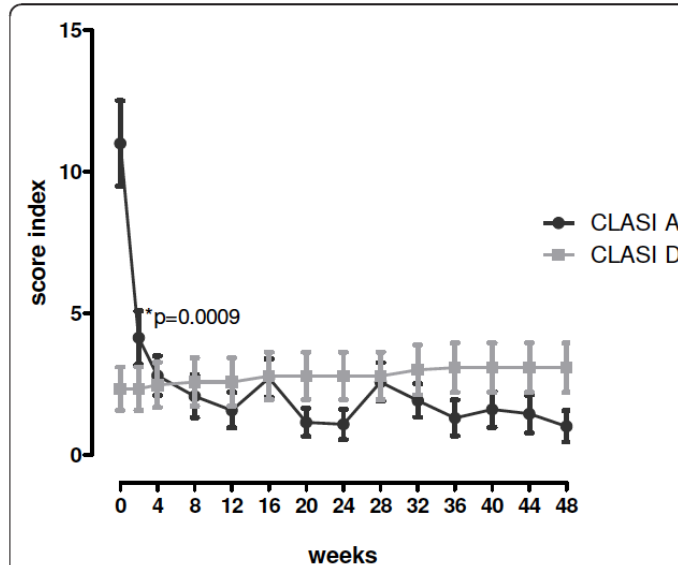


Figure 2 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). CLASI shows a reduction of the CLASI activity (CLASI A (●)) score with no significant changes in the CLASI damage (CLASI D (■)) score over 12 months of follow-up. A significant improvement of the inflammatory rash was already observed by week 2. Data is expressed as mean \pm SEM. **P* value refers to the comparison of CLASI scores between two weeks after treatment and baseline.

*Cortes-
Hernandez J et
al, Arthr Res &
Ther 14:R265,
2012*

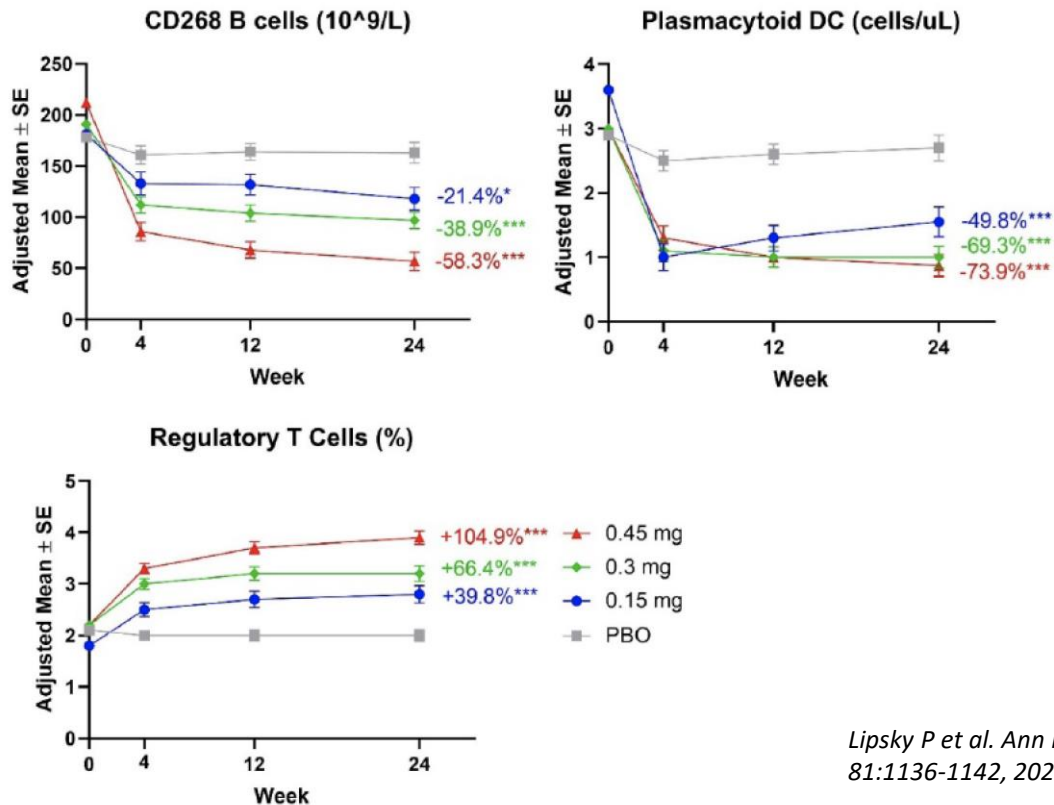
Lenalidomide in CLE

- Side effects: drowsiness, stroke, teratogenicity
- Avoid if antiphospholipid antibodies present
- Requires *Thalidomide* Education and Prescribing Safety (S.T.E.P.S.)
 - Avoid pregnancy
- Less peripheral neuropathy
- Neutropenia, thrombocytopenia, anemia
- Check thyroid function tests before and during therapy

Lenalidomide derivative (Iberdomide)

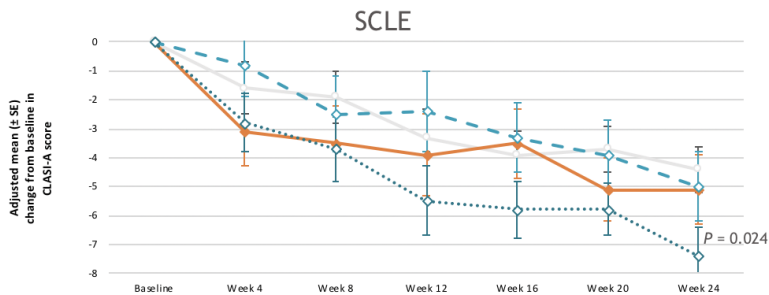
- Degrades Ikaros (*IKZF1*) and Aiolos (*IKZF3*), transcription factors linked to the genetic risk for SLE²⁻⁷
- Decreases B cells, pDCs, and increases T regs

Effects of Iberdomide on Inflammatory Cells

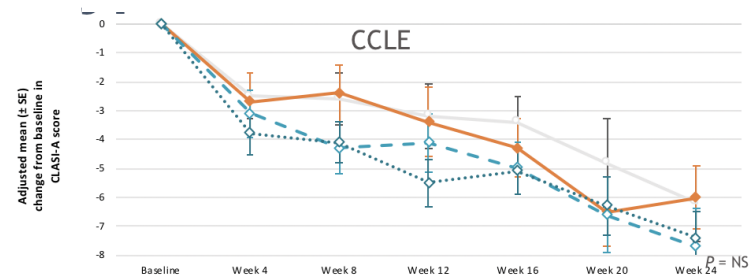


Lipsky P et al. *Ann Rheum Dis*
81:1136-1142, 2022

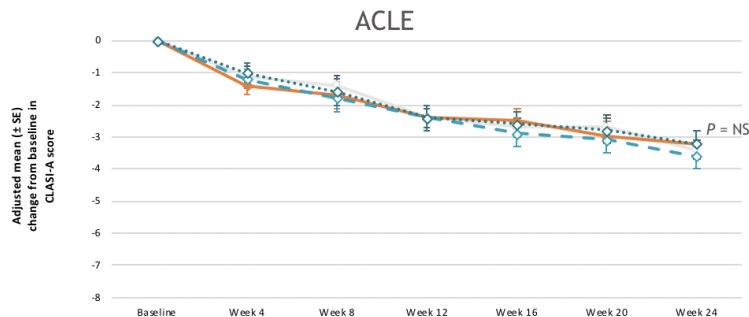
CLASI-A scores: mean improvement from baseline over time by CLE subtype



	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo	17	17	17	16	16	13	14
Iberdomide 0.15 mg	9	9	9	7	7	7	7
Iberdomide 0.3 mg	9	9	8	7	6	6	6
Iberdomide 0.45 mg	12	12	12	12	12	12	12



	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo	18	18	17	16	15	14	13
Iberdomide 0.15 mg	14	14	14	14	13	13	13
Iberdomide 0.3 mg	23	22	20	19	17	15	15
Iberdomide 0.45 mg	29	29	29	26	27	25	25

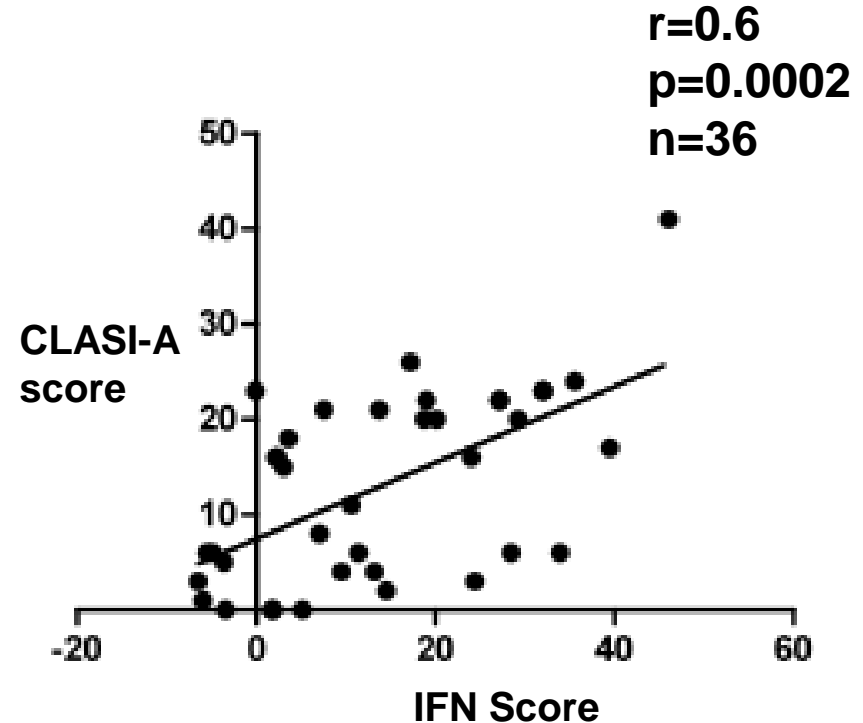
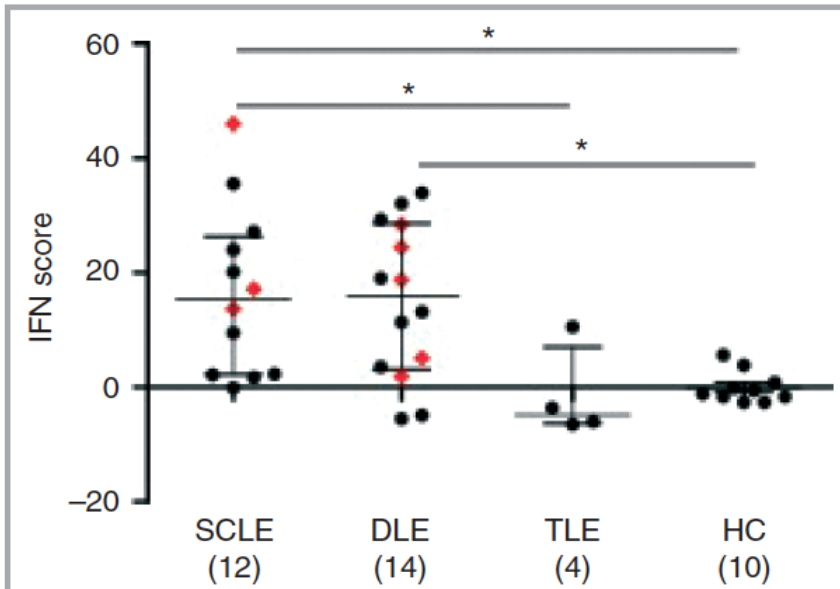


	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo	50	50	46	46	44	43	41
Iberdomide 0.15 mg	30	30	29	28	28	28	28
Iberdomide 0.3 mg	43	43	41	37	35	35	34
Iberdomide 0.45 mg	38	38	38	37	37	34	34

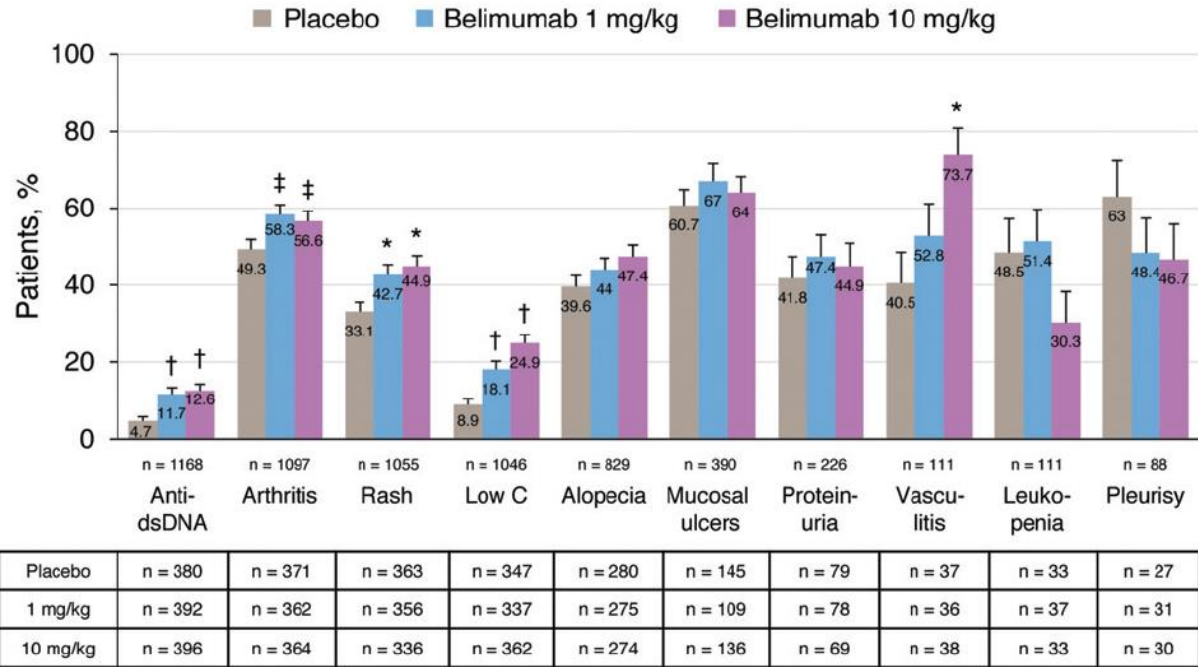
Werth VP et al.
Ann Rheum Dis
(abstr) #132, 2021

2 placebo patients and
4 iberdomide 0.45-mg patients
had a baseline CLASI-A = 0.

Interferon Signature in CLE PBMCs



Belimumab (Anti-BLyS Monoclonal Antibody)



Belimumab (Anti-BLyS Monoclonal Antibody)

Analysis of effects on skin in SLE: Five Phase 3 randomized trials

BILAG

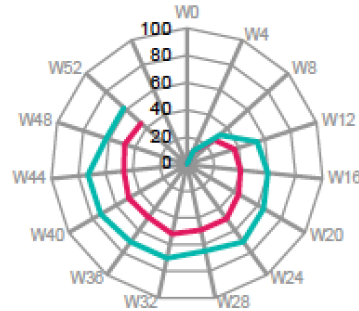
PERNIOTIC SKIN LESIONS

Resolution at Week 52, n (%)

BEL (n=71)	32 (45)
PBO (n=37)	23 (62)

Tx difference
BEL-PBO

-17%; p=0.1075



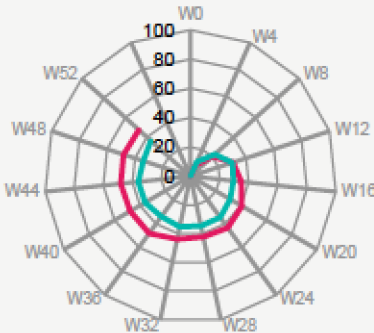
ACTIVE DISCOID LESIONS – localized

Resolution at Week 52, n (%)

BEL (n=187)	89 (48)
PBO (n=156)	57 (37)

Tx difference
BEL-PBO

11%; p=0.0483



SELENA-SLEDAI

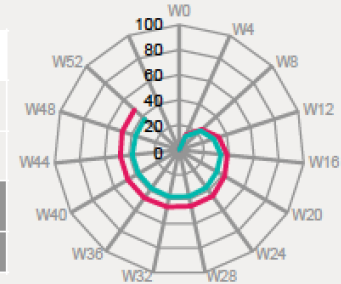
RASH

Resolution at Week 52, n (%)

BEL (n=1157)	558 (48)
PBO (n=794)	294 (37)

Tx difference
BEL-PBO:

11%; p<0.0001



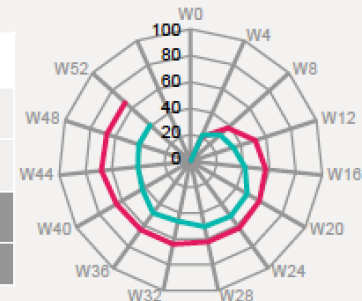
VASCULITIS

Resolution at Week 52, n (%)

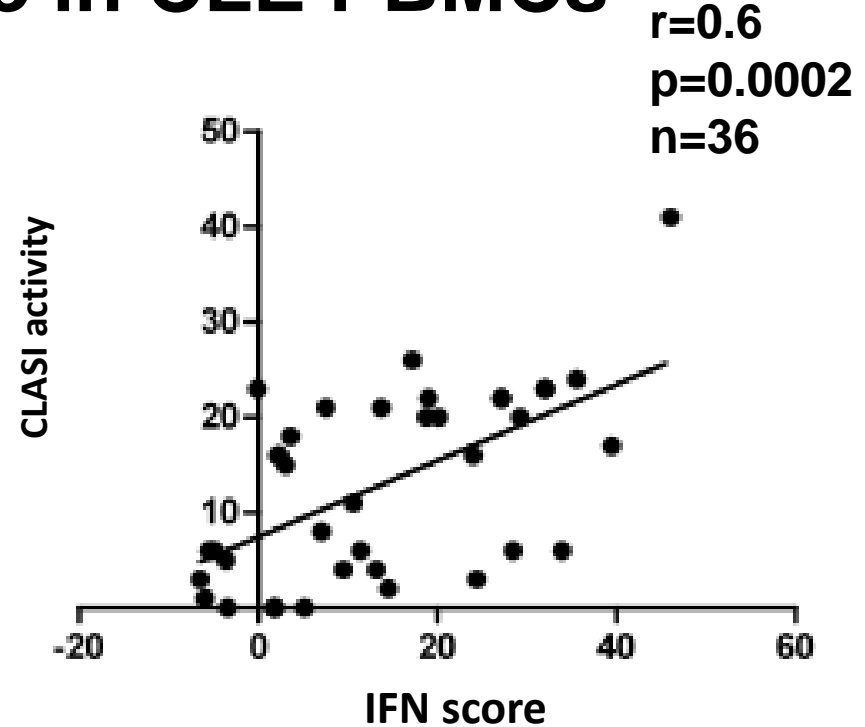
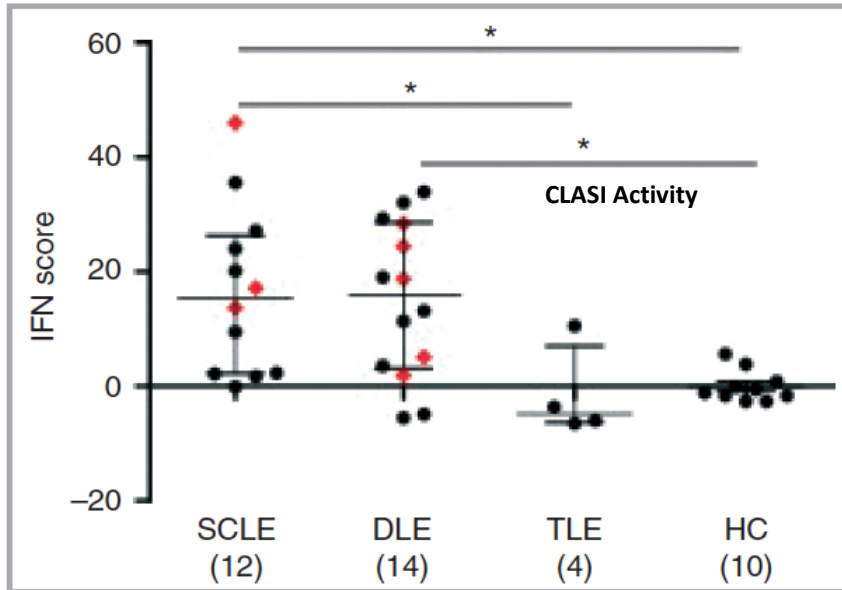
BEL (n=165)	110 (67)
PBO (n=97)	40 (41)

Tx difference
BEL-PBO

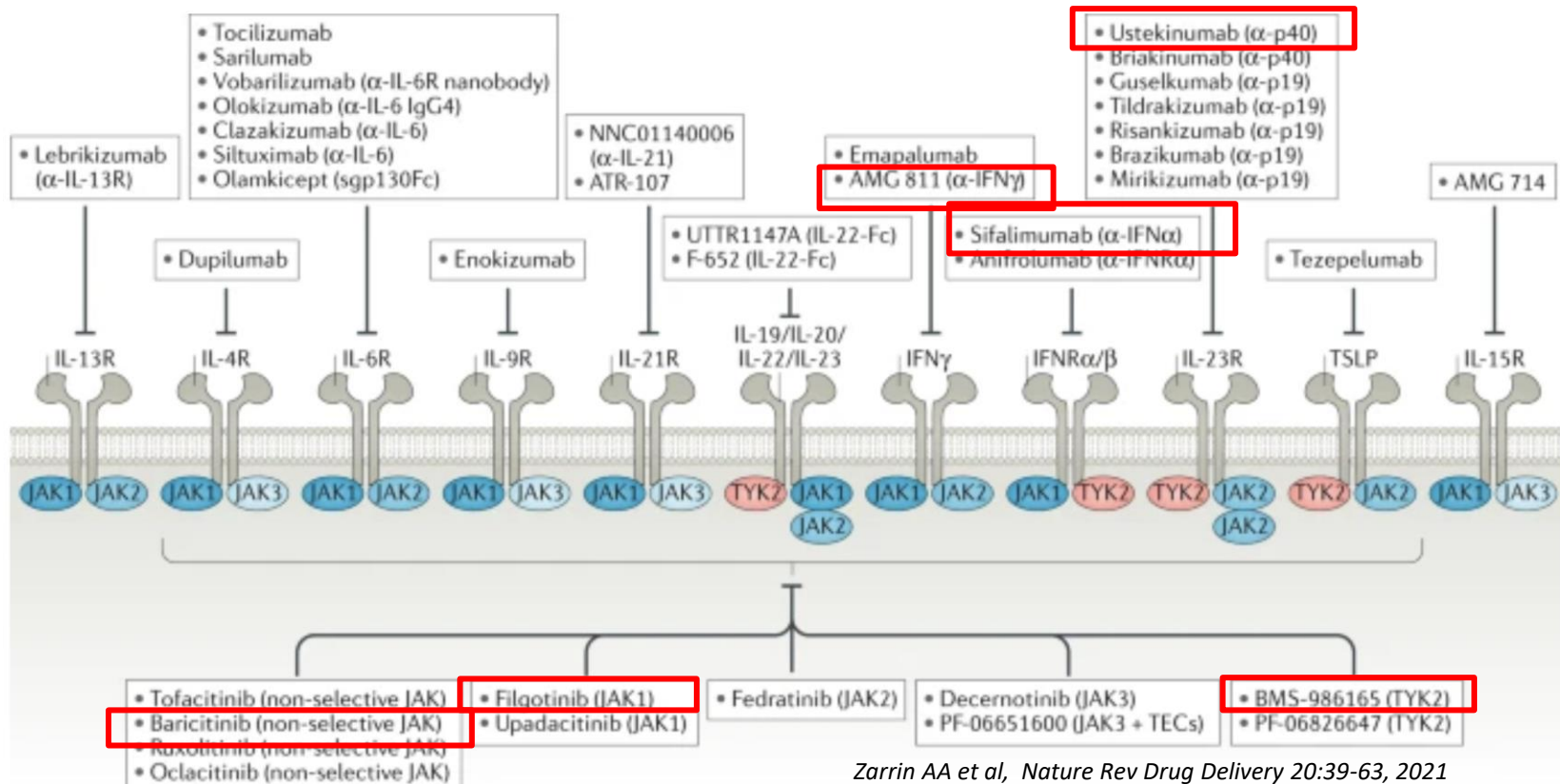
25%; p<0.0001



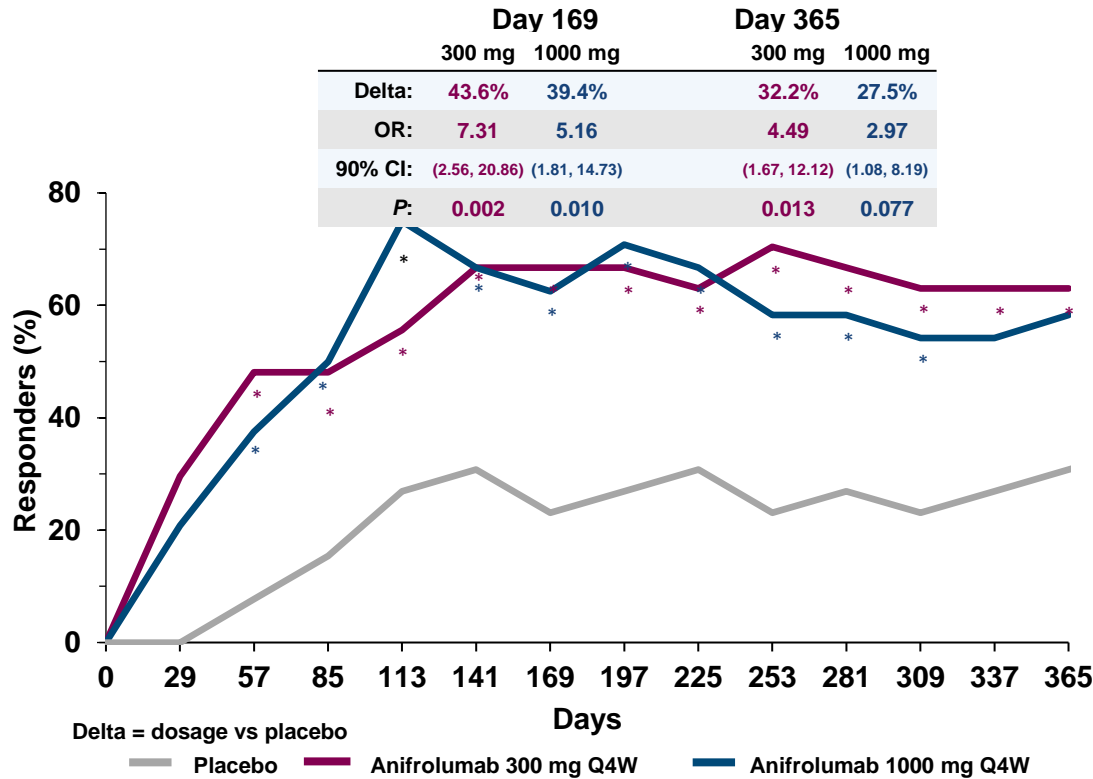
Interferon Signature in CLE PBMCs



Major druggable inflammatory receptors and corresponding kinases implicated in human



At Least 50% Improvement in CLASI in Patients with CLASI Activity Score ≥ 10 at Baseline (N=77 [25%])



Day 1



Day 281



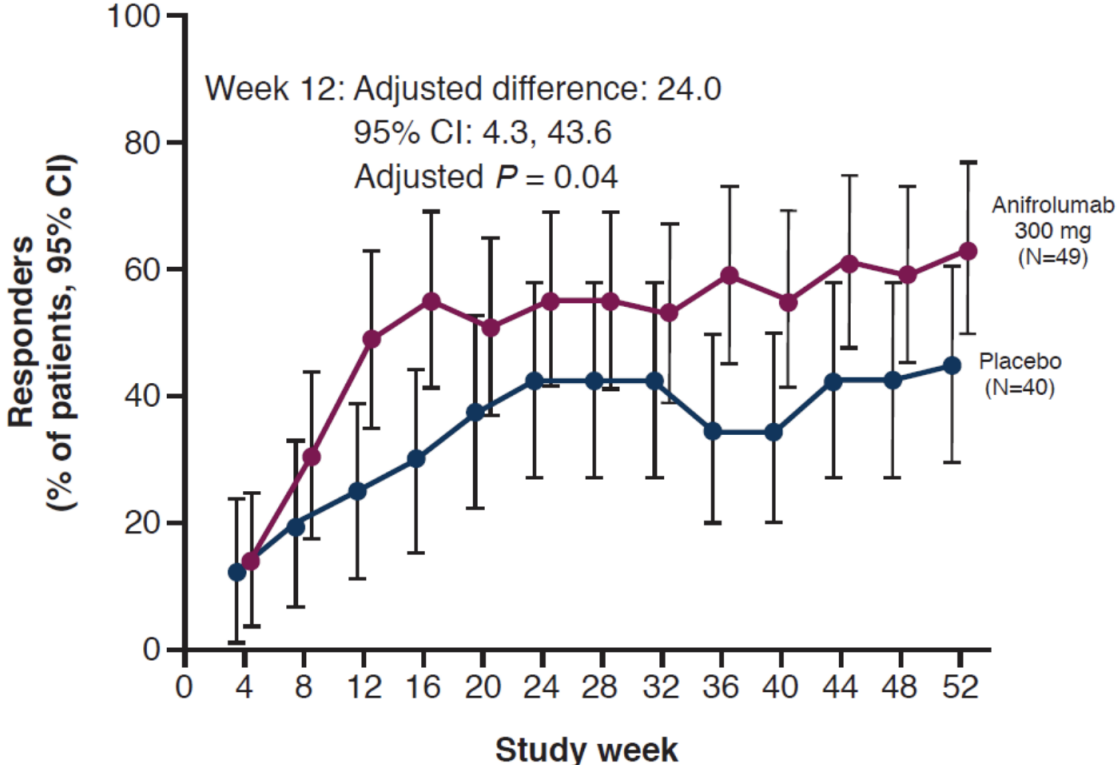
Patient was receiving 300 mg/day anifrolumab

* $P \leq 0.05$ compared with placebo.

OR = odds ratio; CI = confidence interval.

Furie R, et al. *Arthritis Rheumatol.* 2017;69(2):376-386.

Phase 3 Trial: Twice as Many Responders in Treatment Arm ($\geq 50\%$ Reduction in CLASI-A from Baseline)



Morand EF, et al. *N Engl J Med.* 2020;382(3):211-221.

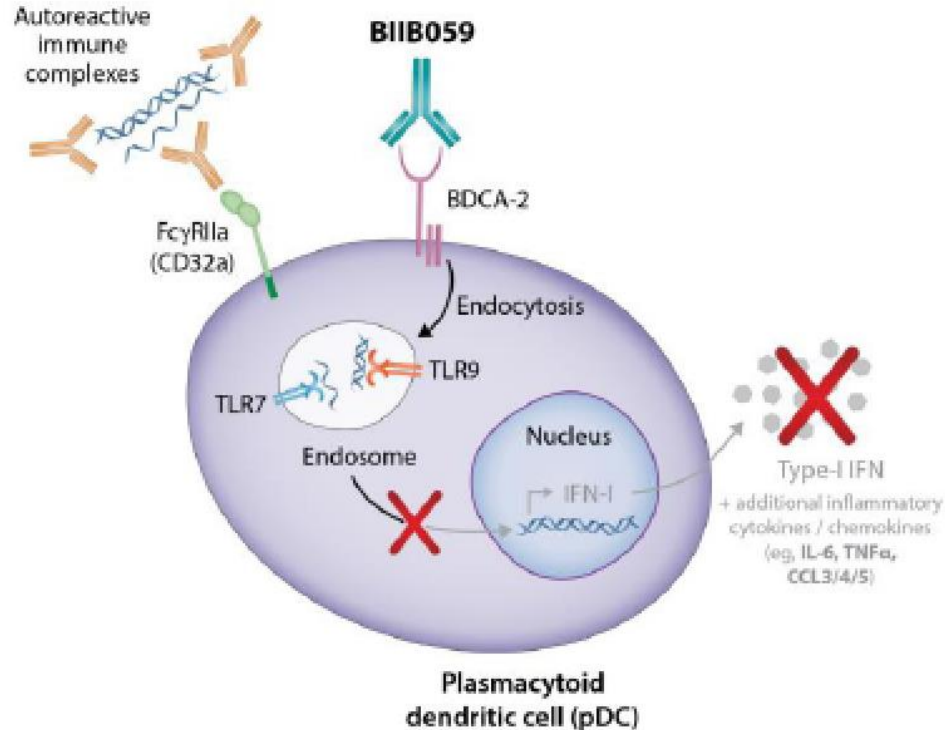
Overview

- Classification criteria
 - SLE
 - DLE
- Treatment of CLE
- **New developments**

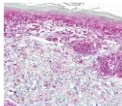
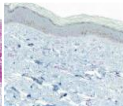
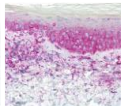
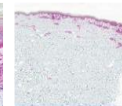
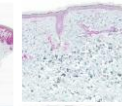
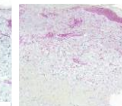
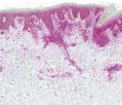
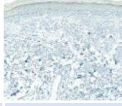
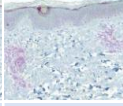




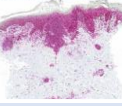
New Treatments for CLE

- Inhibit or deplete plasmacytoid dendritic cells
 - Anti-BDCA2 (Litifilimab)
 - Anti-ILT7
- Anti-Tyk2
- Anti-TLR7/8
- Many more approaches in the pipeline

Litifilimab: A Humanized IgG1 Anti-BDCA2 mAb Specifically Targets pDCs

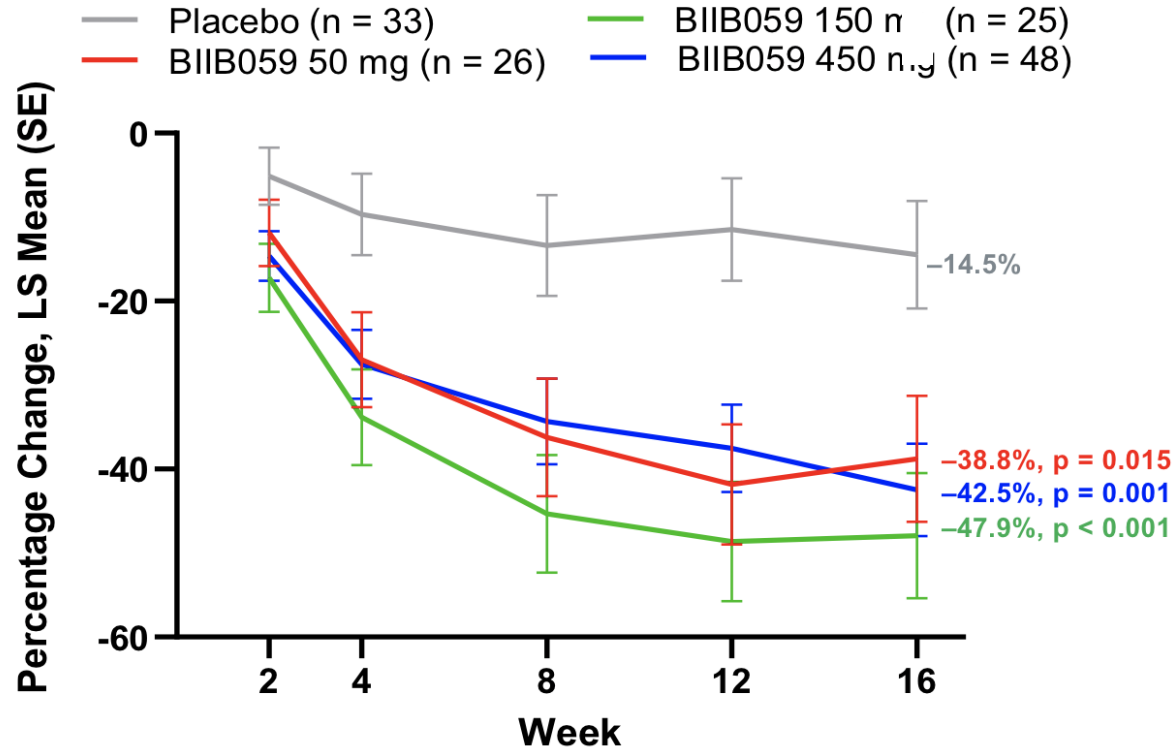


Litifilimab-Treated Subjects Have Reductions in CLASI-A and Skin IFN-Induced MxA Expression

		Subject / CLE Subtype							
		191 SCLE	196 ACLE	274 ACLE	001 DLE	002 ACLE	007 ACLE	185 DLE	310 DLE
MxA area Epidermis	D -1	58.4%	1.2%	21.0%	34.3%	23.1%	26.4%	ND	57.5%
	Week 4	0.1%	0.4%	2.2%	1.0%	2.4%	3.6%	ND	78.4%
MxA histology	Day -1							ND	
	Week 4							ND	
CLASI-A score	D -1	9	5	6	10	14	18	4	17
	Week 4	0	0	2	6	8	8	5	15
	Week 12	0	0	4	6	2	7	4	18
CLASI response [†]		R	R	R	R	R	R	NR	NR

[†]Response defined as a ≥ 4 -point reduction from baseline in CLASI-A at either week 4 or week 12; MxA is calculated by measuring the percent area of immunoreactivity as a ratio of total epidermal area. Furie R, et al. *J Clin Invest.* 2019;129(3):1359-1371.

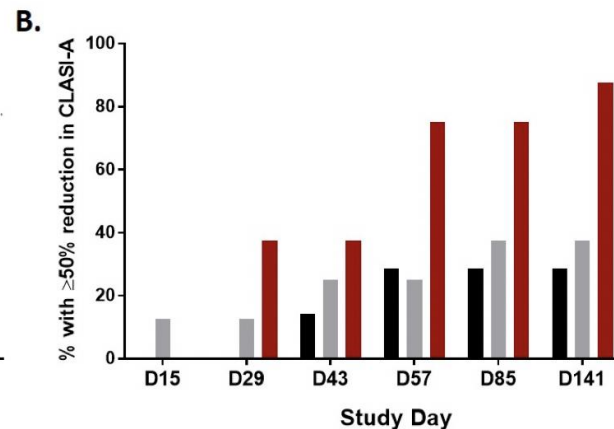
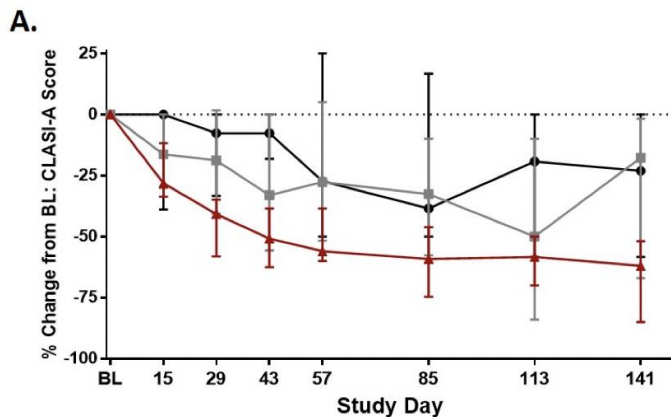
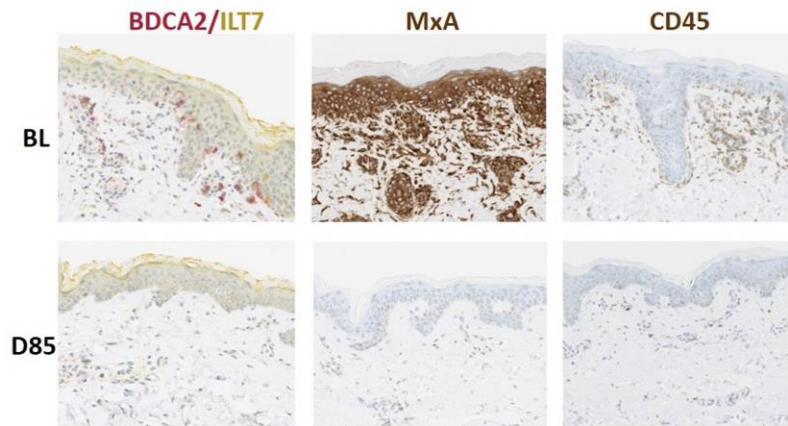
Litifilimab: Change in CLASI-A Score from Baseline



LS = least squares.

Werth VP et al, N Engl J Med 387:321-331, 2022

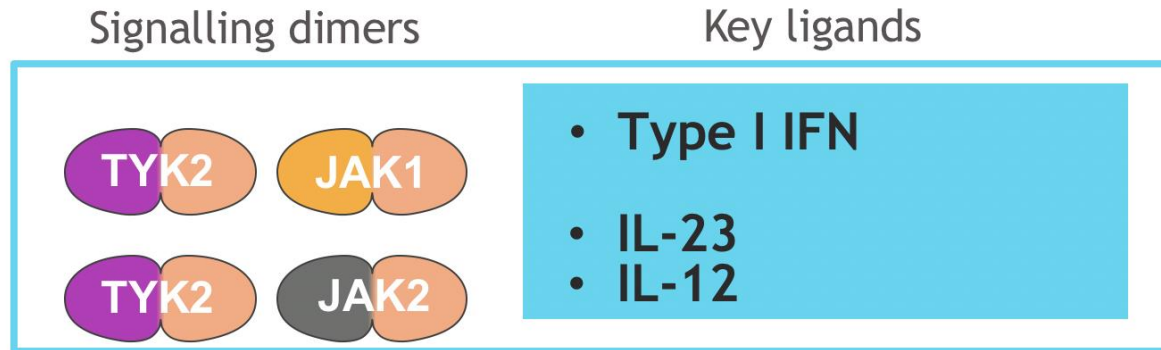
Phase 1 Anti-pDC (ILT7)



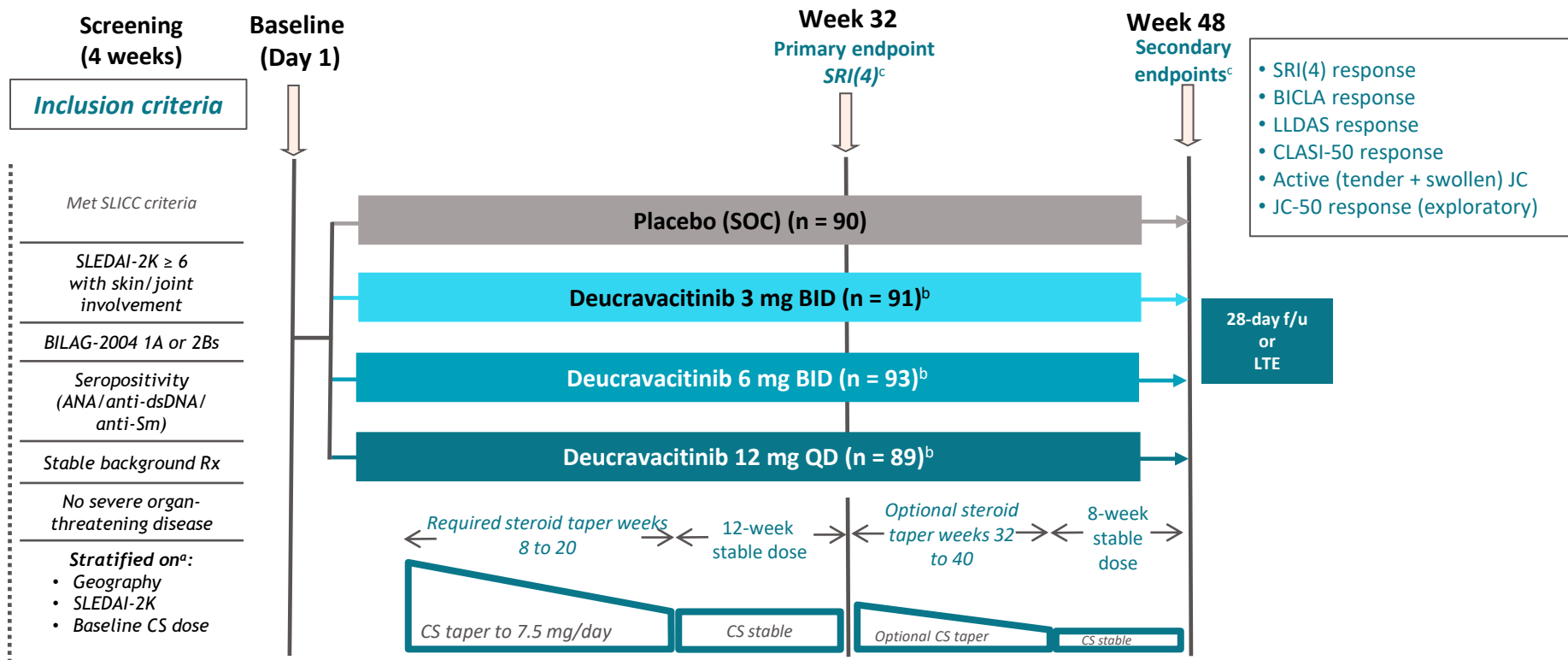
Karnell JL, et al, *Science Translational Medicine*, on line first. doi: 10.1126/scitranslmed.abf8442

Phase 2 Deucravacitinib (Tyk2) Inhibitor

- Oral, selective, allosteric TYK2 inhibitor
- Deucravacitinib, a selective tyrosine kinase 2 (TYK2) inhibitor
 - Blocks IL-23, IL-12, and type I IFN signaling in cell assays.
- Well tolerated in two phase 3 trials in psoriasis, leading to FDA approval 9/9/2022 for psoriasis

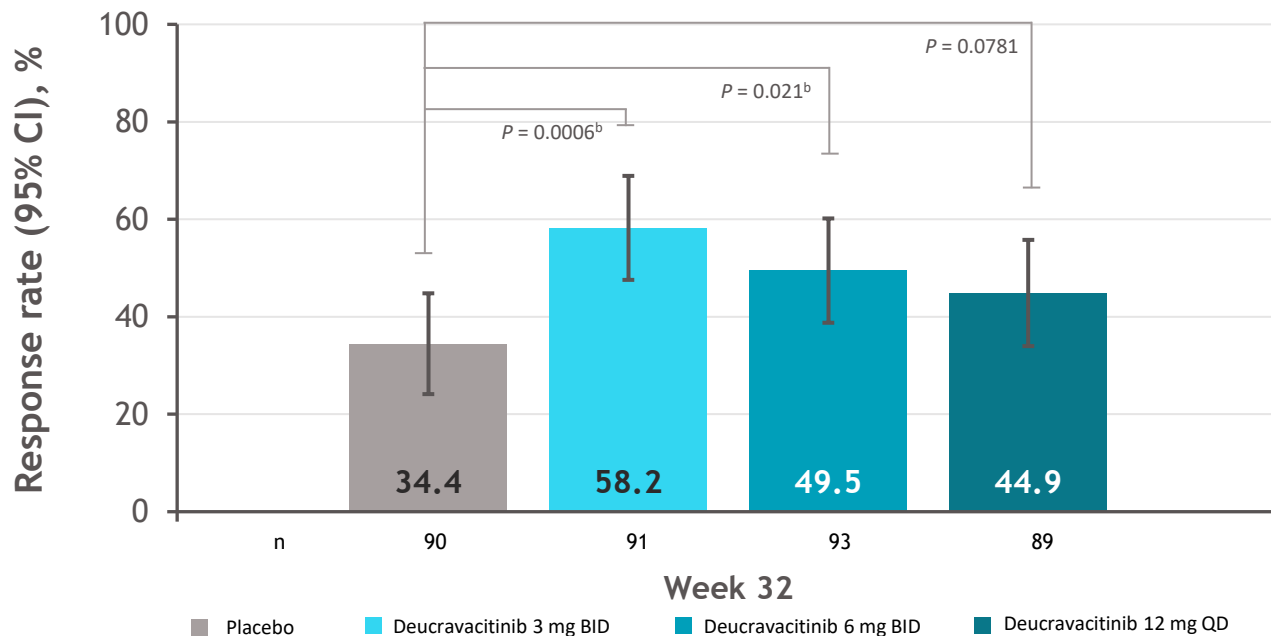


PAISLEY: Phase 2 study of deucravacitinib in active SLE



^aStratification factors included CS dose (≥ 10 mg/day or < 10 mg/day), SLEDAI-2K score (≥ 10 or < 10), and region (United States of America, Latin America, rest of world, and Japan [other stratification factors were not applied in Japan]). ^bType 1 error (alpha value) rate was allocated unequally between the 3 mg BID dose (alpha = 0.015), 6 mg BID dose (alpha = 0.025), and 12 mg QD dose (alpha = 0.01). ^cAssessed by nonresponder imputation, adjusted for multiplicity. ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA; anti-Sm, anti-Smith; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BID, twice daily; BILAG-2004, British Isles Lupus Assessment Group 2004 index; CLASI-50 (CLASI-A-50), decrease of $\geq 50\%$ from baseline Cutaneous Lupus Erythematosus Disease Area and Severity Index; CS, corticosteroid; f/u, follow-up; JC, joint count; JC-50, $\geq 50\%$ improvement from baseline active joint counts; LLDAS, Lupus Low Disease Activity State; LTE, long-term extension; QD, once daily; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics; SOC, standard of care; SRI, Systemic Lupus Erythematosus Responder Index.

Primary endpoint: SRI(4) response rates at week 32^a



Median time to first onset of SRI(4) response, days (95% CI)	Placebo	Deucravacitinib 3 mg BID	Deucravacitinib 6 mg BID	Deucravacitinib 12 mg QD
	116 (112–144)	85 (85–113)	92 (85–138)	111 (85–115)

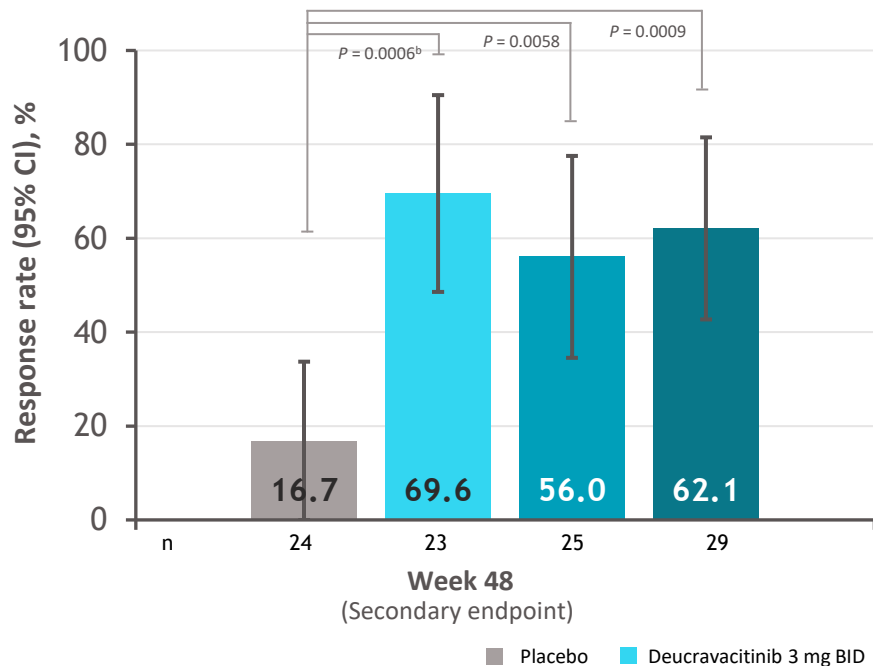
^aAssessed by nonresponder imputation. All randomised patients assessed; missing data, prohibited medication use, or early discontinuation analysed as a nonresponse. ^bP value was significant vs placebo in multiplicity-controlled prespecified analysis.

BID, twice daily; CI, confidence interval; DEUC, deucravacitinib; QD, once daily; SRI, Systemic Lupus Erythematosus Responder Index.

CLASI-50 and Joint Count-50 at week 48

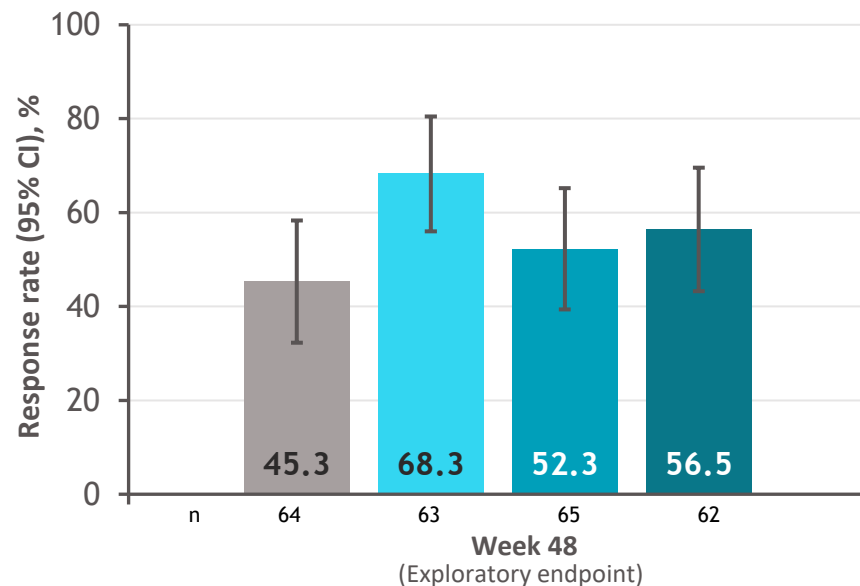
CLASI-50^a

Patients with a baseline CLASI-A score ≥ 10 who have $\geq 50\%$ decrease from baseline



Joint Count-50^c

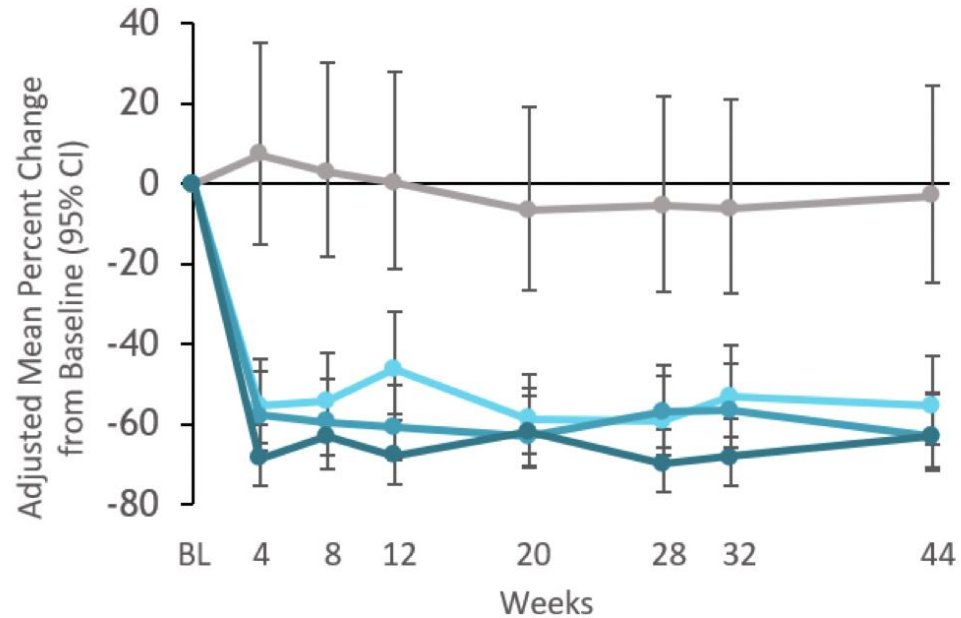
Patients with ≥ 6 active (tender + swollen) joints at baseline, who have $\geq 50\%$ decrease from baseline



^aAssessed by nonresponder imputation. All randomised patients assessed; missing data, prohibited medication use, or early discontinuation analysed as a nonresponse. ^bP value was significant vs placebo in multiplicity-controlled prespecified analysis. ^cNo P values calculated for this exploratory endpoint.

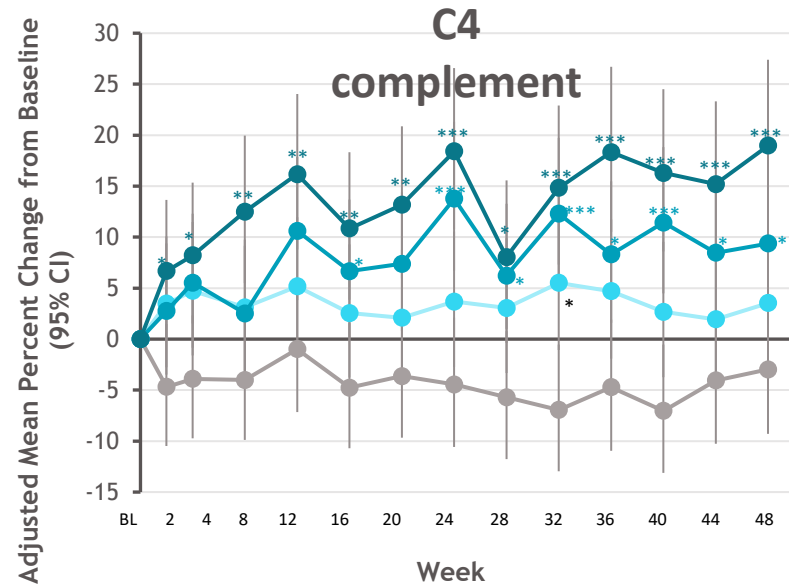
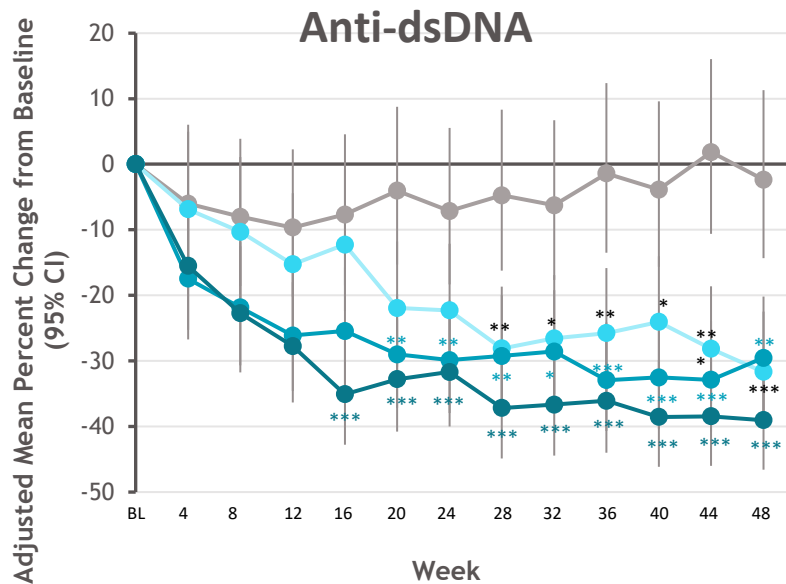
BID, twice daily; CI, confidence interval; CLASI-50, decrease of $\geq 50\%$ from baseline in CLASI-A; CLASI-A, Cutaneous Lupus Area and Severity Index Activity; QD, once daily.

IFN Gene Signature



■ Placebo ■ Deucravacitinib 3 mg BID ■ Deucravacitinib 6 mg BID ■ Deucravacitinib 12 mg QD

Percentage change in anti-dsDNA and complement through week 48



■ Placebo
 ■ Deucravacitinib 3 mg BID
 ■ Deucravacitinib 6 mg BID
 ■ Deucravacitinib 12 mg QD

P < 0.05; ***P* < 0.01; ****P* < 0.001. Adjusted *P* values vs placebo. Imputation done using a mixed-effects model.
 BID, twice daily; BL, baseline; C4, complement component 4; CI, confidence interval; dsDNA, double-stranded DNA; QD, once daily.

Summary

- Lupus as a spectrum disease.
 - Skin frequently associated with systemic findings
 - Need to follow CLE patients for development of systemic findings
- Think about drugs as a frequent cause of SCLE
- Several new drugs not available for CLE
- Many new therapies in development