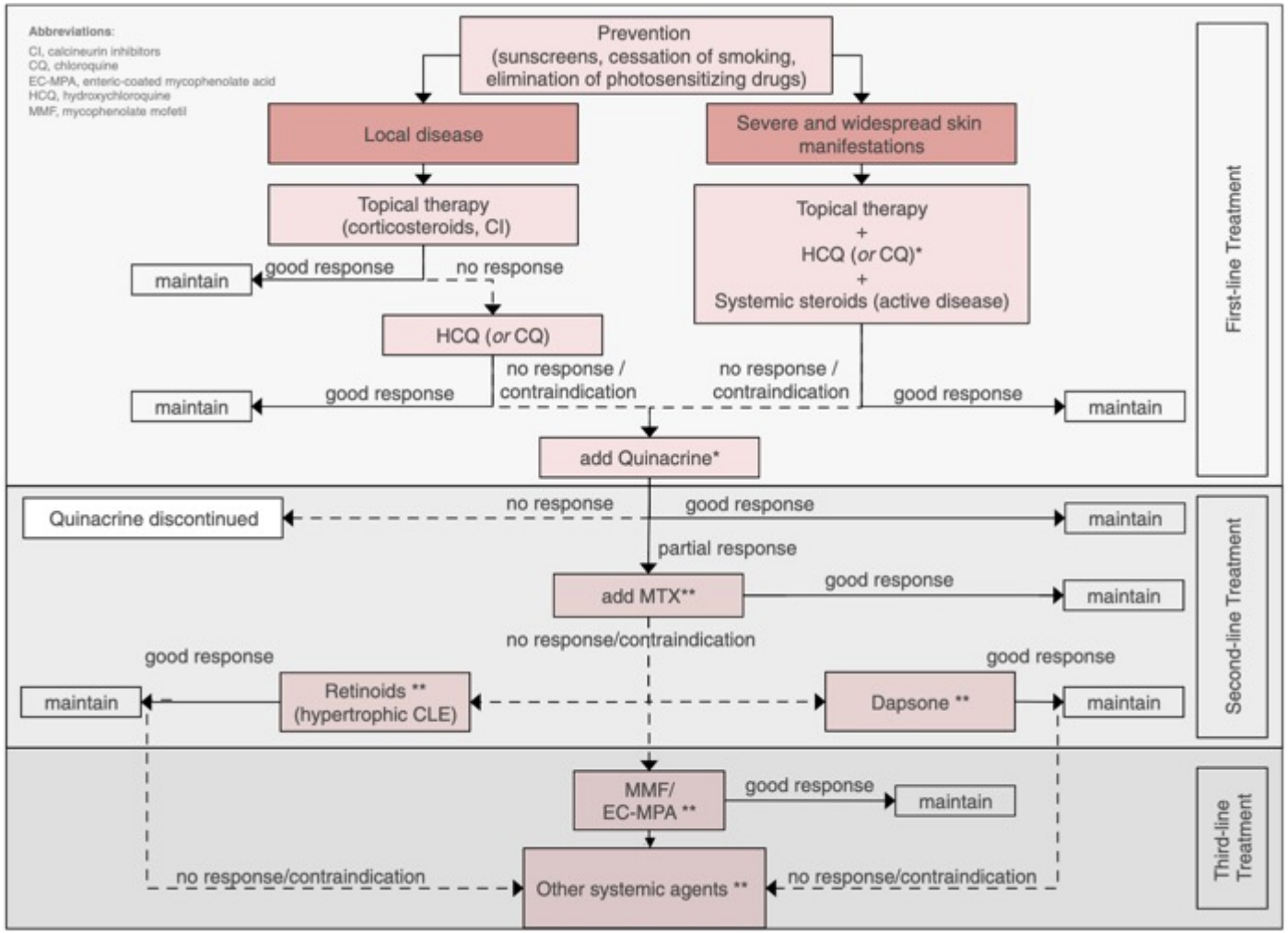
ORIGINAL ARTICLE

Trial of Anti-BDCA2 Antibody Litifilimab for Cutaneous Lupus Erythematosus

V.P. Werth, R.A. Furie, J. Romero-Diaz, S. Navarra, K. Kalunian, R.F. van Vollenhoven, F. Nyberg, B.H. Kaffenberger, S.Z. Sheikh, G. Radunovic, X. Huang, G. Clark, H. Carroll, H. Naik, F. Gaudreault, A. Meyers, C. Barbey, C. Musselli, and N. Franchimont, for the LILAC Trial Investigators*

膠原病 Journal club 2022/9/6　田口　宏和

CLEの治療

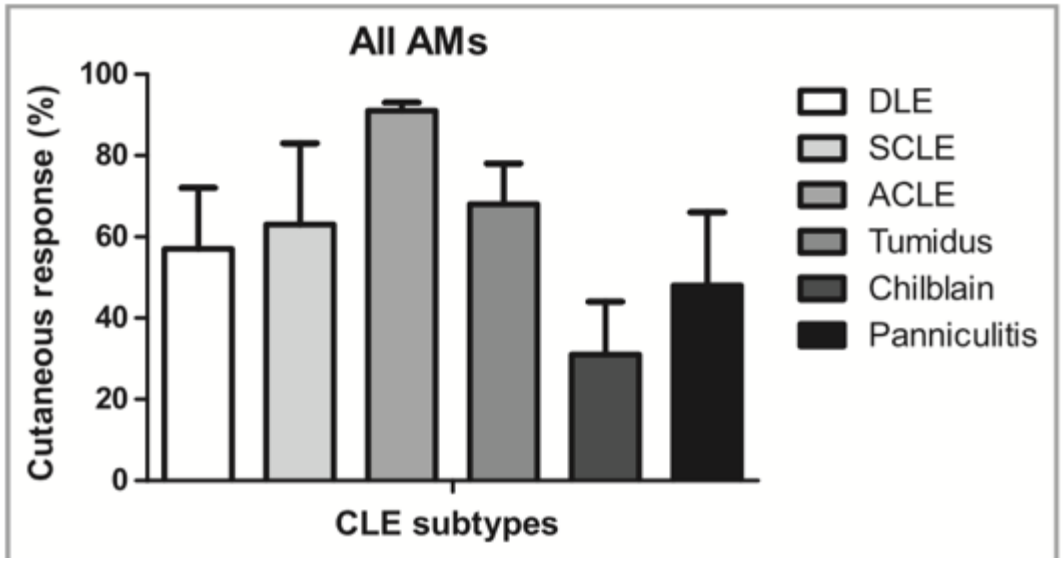


○GC外用薬

- 第1選択薬.
- 副作用の懸念, エビデンスが不足.

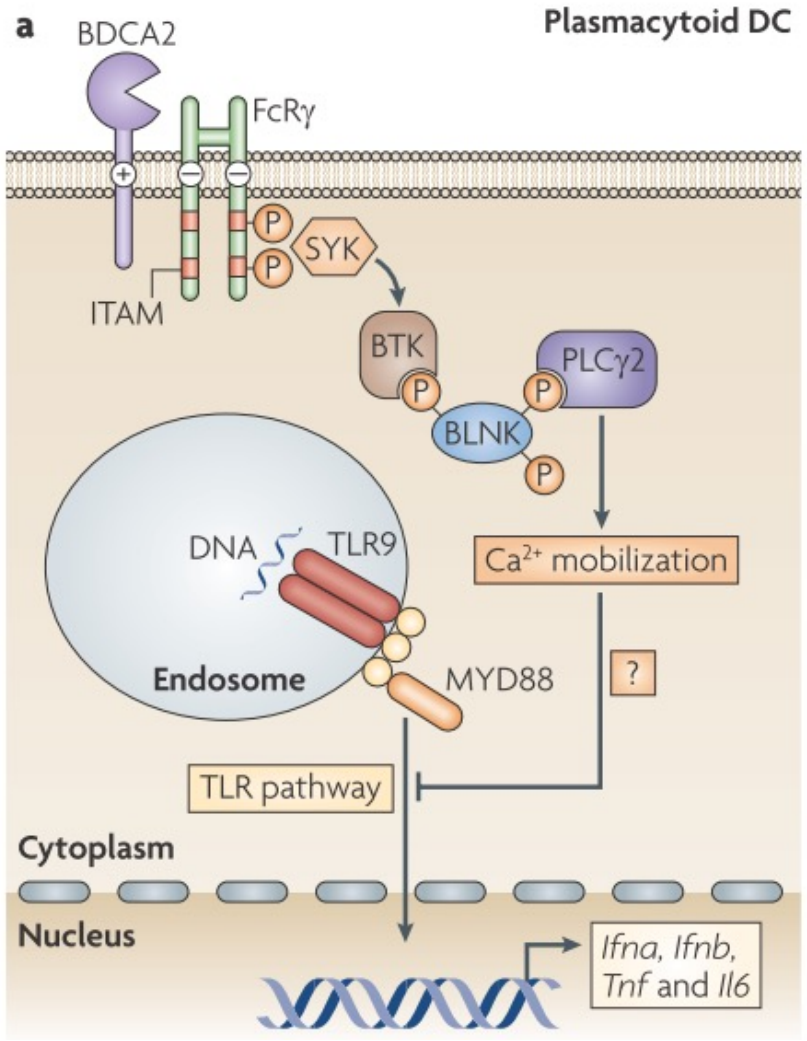
○HCQ

- 病変が広い場合, 瘢痕化のリスクがある場合などで第1選択薬として使用.
- サブタイプによって効果にばらつきがある.



Kuhn A, et al. ***J Eur Acad Dermatol Venereol.*** 2017 Mar;31(3):389-404
Chasset F, et al. ***Br J Dermatol.*** 2017 Jul;177(1):188-196

plasmacytoid dendritic cells (pDC)とBDCA-2



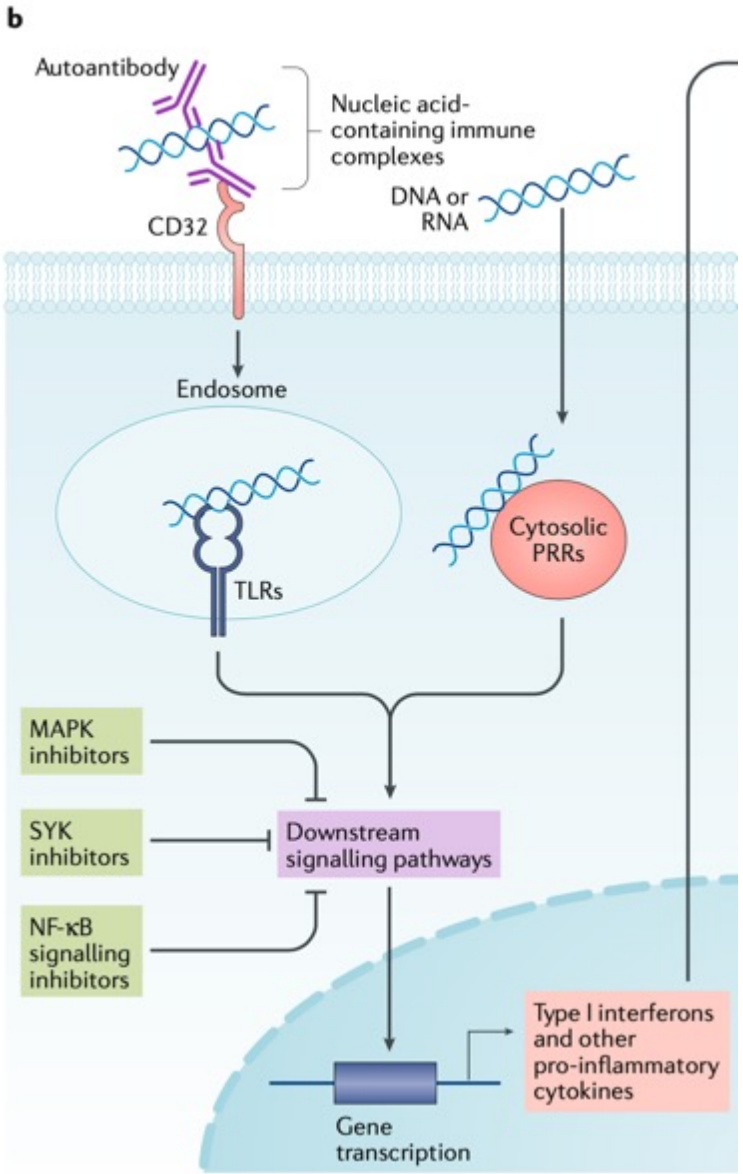
BDCA-2(CD303)

- pDC上にのみ発現するC型レクチンファミリーの膜貫通型蛋白.
- Natural ligandはまだわかっていない.
- BDCA-2が活性化されると, SYKが活性化され, その後, BTK, BLNK, PLCγ2複合体が活性化されCaが動員される.
- 最終的に, pDCからの**IFN-1, TNF, IL-6などの産生が抑制.**

CLR*	Expression	Glycan PAMPs	Pathogenic (exogenous) ligands	Signalling motif or adaptor	Signalling proteins involved	Immunological outcome
BDCA2 (CLEC4C, CD303)	pDCs, monocytes, macrophages and neutrophils	ND	ND	FcRγ	SYK, BTK, BLNK and PLCγ2	• Inhibition of TLR9-induced type I IFN, TNF and IL-6 production • Upregulation of TLR9-induced IL-10 production

Geijtenbeek T, et al. ***Nat Rev Immunol***. 2009 Jul;9(7):465-79.

IFN-1とLitifilimab

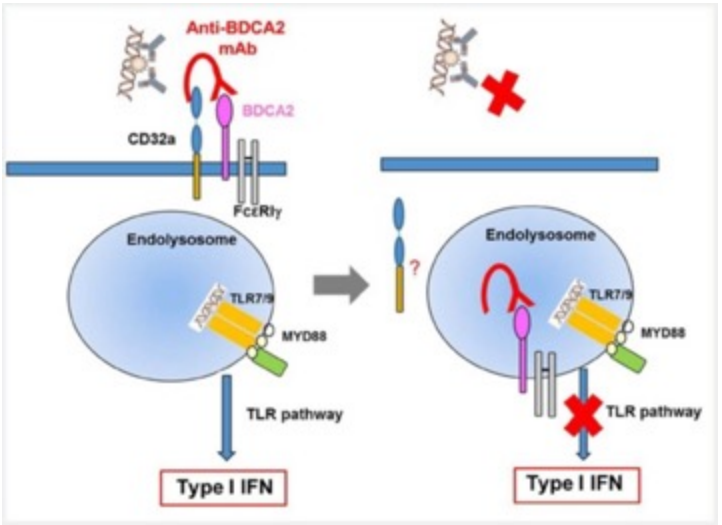


SLEにおけるpDCのIFN-1産生

- 免疫複合体(IC)が pDC 上の CD32a Fc領域に結合する.
- ICとCD32aが複合体を形成し, 細胞内に移動する.
- この複合体がTLR7およびTLR9をそれぞれ刺激してIFN-Iが産生.

Litifilimab(ヒト化抗IgG monoclonal antibody)

- Fc領域でCD32aと結合し, 共に細胞内に取り込まれる
  →ICが結合できずTLR経路が活性化されないので, **IFN産生が抑制.**
- BDCA-2がLitifilimabとのLigationにより細胞内に取り込まれる.
  →BDCA-2が取り込まれることが具体的にどう影響するかは不明.



Pellerin A, et al. ***EMBO Moll Med.*** 2015 Apr;7(4):464-76
Joerg W. ***Nat Rev Rheumatol.*** 2019 Sep;15(9):519-32
Rock J, et al. ***Eur J Immunol.*** 2007 Dec;37(12):3564-75

The Journal of Clinical Investigation CLINICAL MEDICINE

phase1

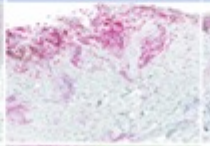
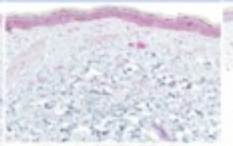
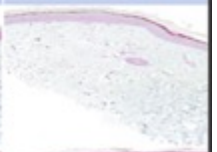
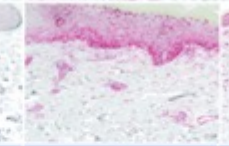
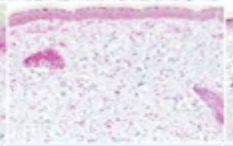
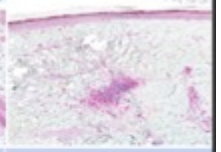
Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus

Richard Furie,[1] Victoria P. Werth,[2] Joseph F. Merola,[3] Lauren Stevenson,[4] Taylor L. Reynolds,[4] Himanshu Naik,[4] Wenting Wang,[4] Romy Christmann,[4] Agnes Gardet,[4] Alex Pellerin,[4] Stefan Hamann,[4] Pavan Auluck,[4] Catherine Barbey,[4] Parul Gulati,[4] Dania Rabah,[4] and Nathalie Franchimont[4]

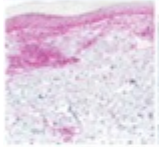
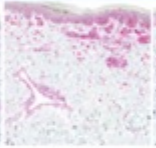
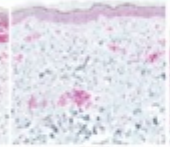
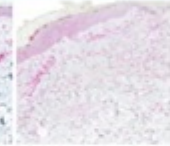
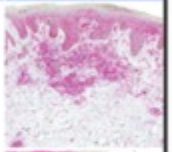
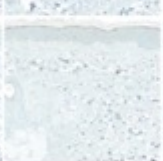
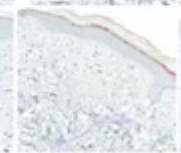
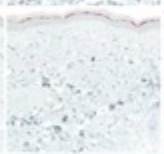
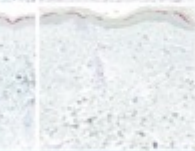
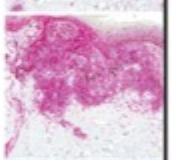
[1]Division of Rheumatology, Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York, USA. [2]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania and Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA. [3]Department of Dermatology and Department of Medicine, Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. [4]Biogen, Cambridge, Massachusetts, USA.

- 活動性の皮膚病変を持つSLE患者
- litifilimab 20mg/kg 単回投与
- IFN-1関連蛋白の発現の減少を認めた

プラセボ

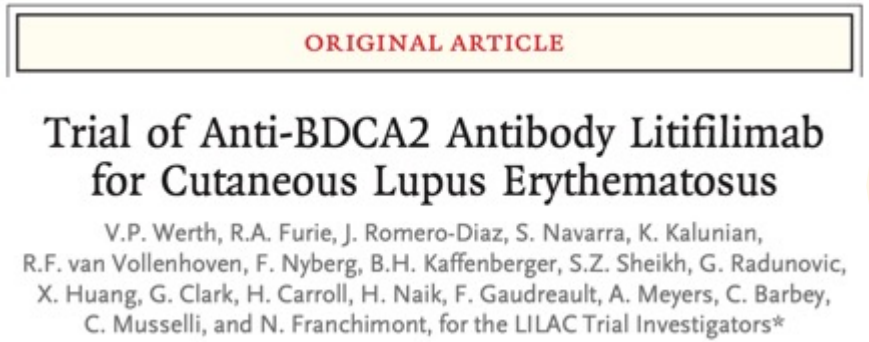
		Subject / CLE Subtype			
	Timepoint	1* SCLE	2 DLE	3 SCLE/DLE	4 DLE
MxA area Epidermis	Day –1 Week 4	9.1% 0.1%	54.3% 29.4%	41.6% 54.7%	17.3% 45.1%
MxA histology	Day –1				
	Week 4				
CLASI-A score	Day –1 Week 4 Week 12	45 26 4	7 7 ND	5 4 8	8 9 7
CLASI response		R	NR	NR	NR

BIIB059(Litifilimab)

Subject / CLE Subtype							
5 SCLE	6 ACLE	7 ACLE	8 DLE	9 ACLE	10 ACLE	11 DLE	12 DLE
58.4% 0.1%	1.2% 0.4%	21.0% 2.2%	34.3% 1.0%	23.1% 2.4%	26.4% 3.6%	ND ND	57.5% 78.4%
						ND	
						ND	
9 0 0	5 0 0	6 2 4	10 6 6	14 8 2	18 8 7	4 5 4	17 15 18
R	R	R	R	R	R	NR	NR

Richard F. et al. ***J Clin Invest.*** 2019;129(3):1359-71

今回の論文



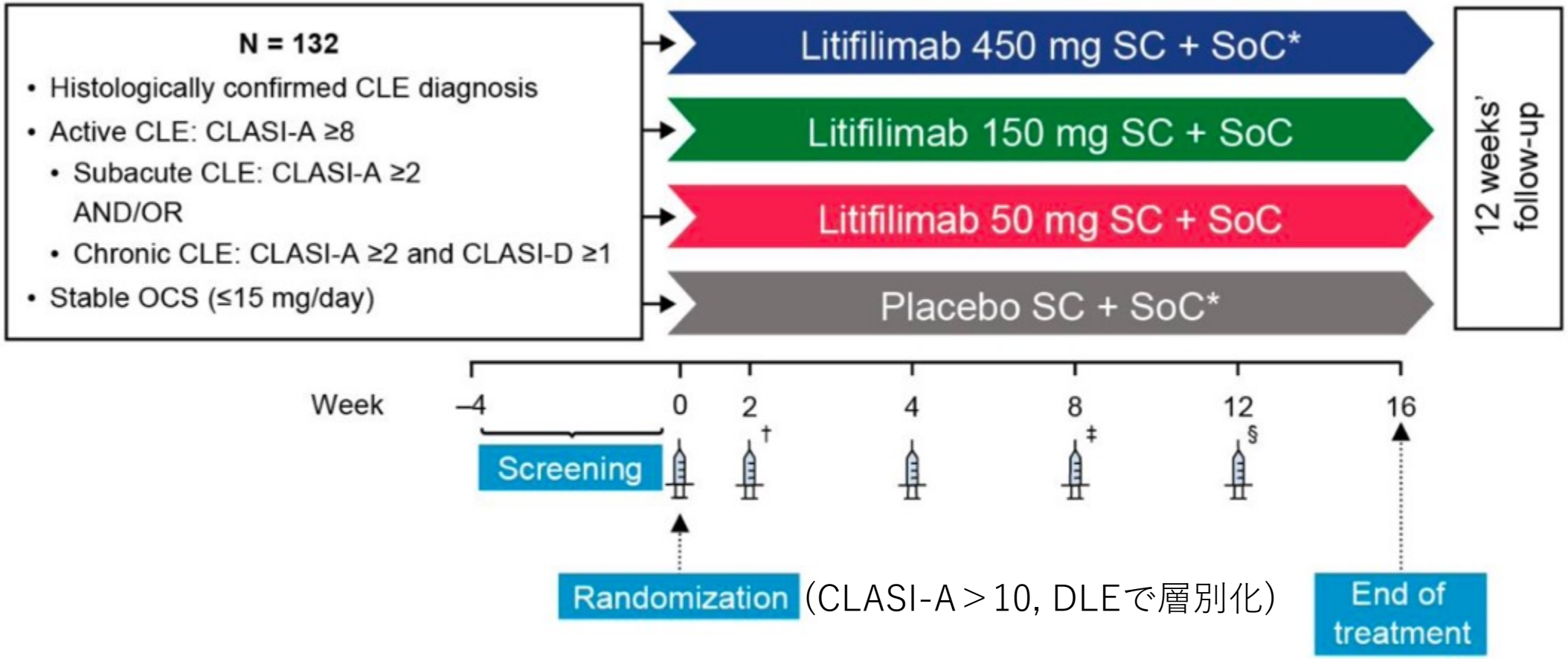
ORIGINAL ARTICLE

Trial of Anti-BDCA2 Antibody Litifilimab for Cutaneous Lupus Erythematosus

V.P. Werth, R.A. Furie, J. Romero-Diaz, S. Navarra, K. Kalunian, R.F. van Vollenhoven, F. Nyberg, B.H. Kaffenberger, S.Z. Sheikh, G. Radunovic, X. Huang, G. Clark, H. Carroll, H. Naik, F. Gaudreault, A. Meyers, C. Barbey, C. Musselli, and N. Franchimont, for the LILAC Trial Investigators*

- **P** 組織学的に診断されたCLE
- **I** Litifilimab 皮下注
- **C** プラセボ 皮下注
- **O** 16週におけるCLASI-Aの変化率

研究デザインと方法



・2016/10/20~2019/11-18. アジア, 欧州, ラテンアメリカ, 米国が参加.
・プラセボ対照2重盲検ランダム化比較試験.
・300人のうちスクリーニングで132人が登録され, 120人が完遂

Protocol

○当初のデザイン(Version.1)

・本試験はPart AとBがあるうちのPart B.
  A） SLEの皮膚症状におけるLitifilimabの効果
  B） CLEにおけるLitifilimabの効果

・450mg群とプラセボの比較で2：1にランダムに配分.

・サンプルサイズは31人.

・Primary end point
  ：12週でのCLASI-Aの変化率

○Protocolの変更(Version.2-5)

・Part Aの募集が遅れた影響で用量設定試験に変更.

・50mg群と150mg群が追加され、4群となった.

・サンプルサイズは130人.

・ Primary end point
  ：16週でのCLASI-Aの変化率

CLASI, Cutaneous LE Area and Severity Index

○Lupusの皮膚症状の評価項目

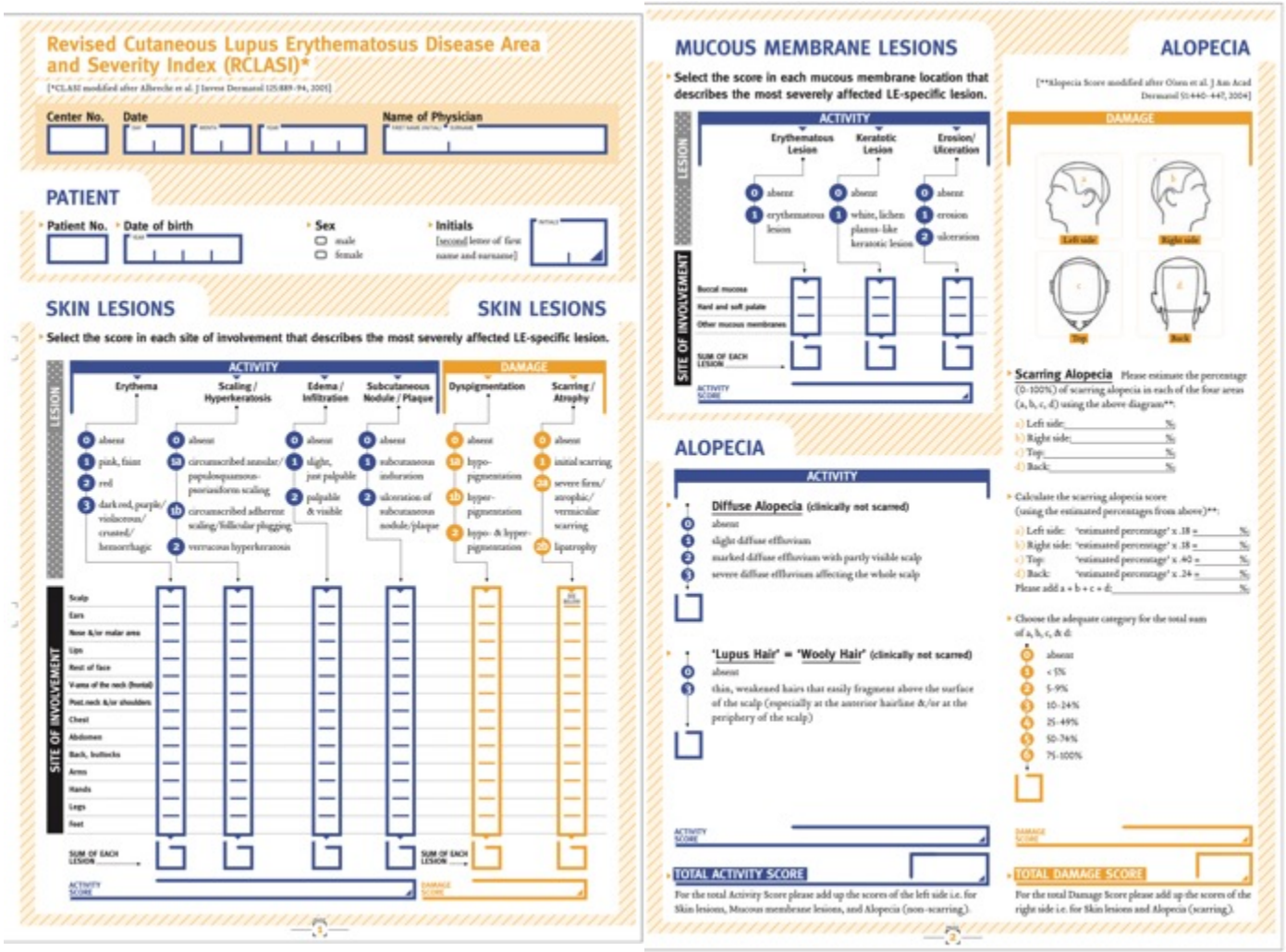
・活動性(CLASI-A)と障害度(CLASI-D)
　をそれぞれ部位別に評価する.

*表面積や病変の数は関係ない。
*色素沈着のみ1年以上の経過なら得点2倍

A
紅斑、鱗屑、浮腫、皮下結節
粘膜病変、非瘢痕性脱毛、
Lupus hair

○重症度(CLASI-A)

・軽症　：0-9点
・中等症：10-20点
・重症　：21-70点



Kuhn A, et al. ***Br J Dermatol.*** 2010 Jul;163(1):83-92

主な適格基準

- 組織学的に診断された18-75歳の活動性(CLASI-A≧8)のCLE.
- 少なくとも3ヶ月間HCQ/GC外用しているが活動性あり.
- 3ヶ月以内に開始した薬剤の用量変更が1ヶ月以内に無い.

主な除外基準

- 活動性LN, 活動性NP-SLE, CLE以外の活動性皮膚疾患.
- PSL≧15mg
- 3ヶ月以内の使用：CyA, Tac, sirolimus, CY, IVIg, PE, BEL, ABT, TCZ, TNF阻害薬.
- 6ヶ月以内の使用：IFNα阻害薬, RTX(12ヶ月以内の使用でも$CD19^{+}$Bcell<25).

研究期間中の他剤使用

○SLEの治療薬として使用可能な薬剤.

AZA(≦200mg/日), MMF(≦2g/日),
MTX(≦20mg/週), HCQ(≦6.5mg/kg/日),
GC(PSL換算≦15mg, 局注は不可)

○GCの減量基準

・試験開始29日目から漸減可能.
・71日目までに10mg/日以下にする.
・漸減計画から外れても、研究者の判断でそのまま治験に残留できる.

○再燃時の対応

・治療期間：GC増量可能(条件あり)

Timing	Corticosteroid Starting Dose Prior to Tapering (mg/day)[1]							
	20	17.5	15	12.5	10	7.5	5	2.5 - < 5
Week 1-4	Stable 1 OCS rescue for SLE activity allowed up to maximum 10 mg/day above Day1 dosage, but must return to Day 1 level within 7 days.							
Week 5[2]	17.5	15.0	12.5	10	7.5	7.5	5	2.5 - < 5
Week 6[2]	17.5	15.0	12.5	10	7.5	7.5	5	2.5 - < 5
Week 7[2]	15.0	12.5	10	10 or 7.5	7.5	7.5 or 5	5 or 2.5	2.5 - < 5
Week 8	12.5	12.5	10	10 or 7.5	7.5	7.5 or 5	5 or 2.5	0 or 2.5 - < 5
Week 9	12.5	10	10 or 7.5	7.5	7.5 or 5	7.5 or 5*	5 or 2.5	0 or 2.5 - < 5
Week 10	10	10	10 or 7.5	7.5 or 5	7.5 or 5	7.5 or 5	5 or 2.5	0 or 2.5 - < 5
Week 11-12	Stable at Week 10 dose							
Week 13-16	Stable or Decrease by 2.5 mg as tolerated. 1 OCS rescue for SLE activity allowed up to Day 1 corticosteroid dose (maximum 20 mg/day), however must be returned to week 12 level within 7 days.							
Week 17-24	Stable at Week 16 dose							

主要評価項目

16週におけるCLASI-Aの変化率

副次評価項目

12週・16週におけるCLASI-Aの50%以上の低下

12週におけるCLASI-Aの変化率

12週・16週におけるCLASI-Aの4点・7点以上の低下

統計解析

- プラセボ群とLitifilimab群でCLASI-Aの変化がないという帰無仮説を棄却するための研究(オムニバス傾向検定).
- 2群間での用量比較やプラセボと各群間での効果の比較はできない.
- modified Intention-to-treat
- 各評価項目の検出力
  - 主要評価項目：100人の参加者で検出力が90%になるように募集人数の設定.
    (SD 30%, 最大絶対偏差 27.5%, 脱落率20%と仮定)
  - 副次評価項目：評価できるほどの検出力はこの研究にはない.

結果

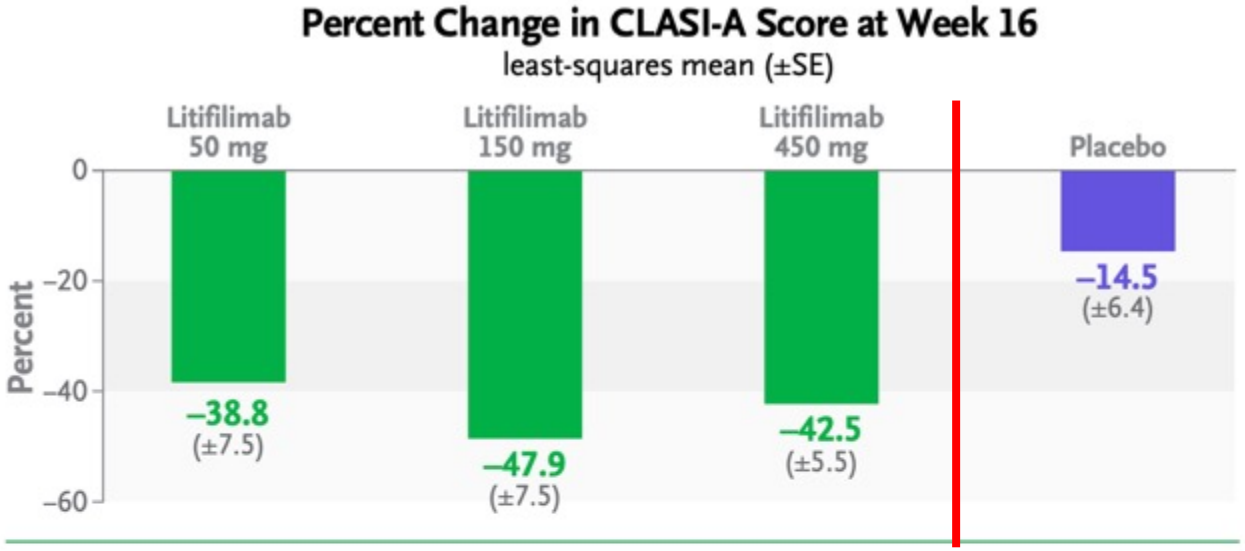
患者背景

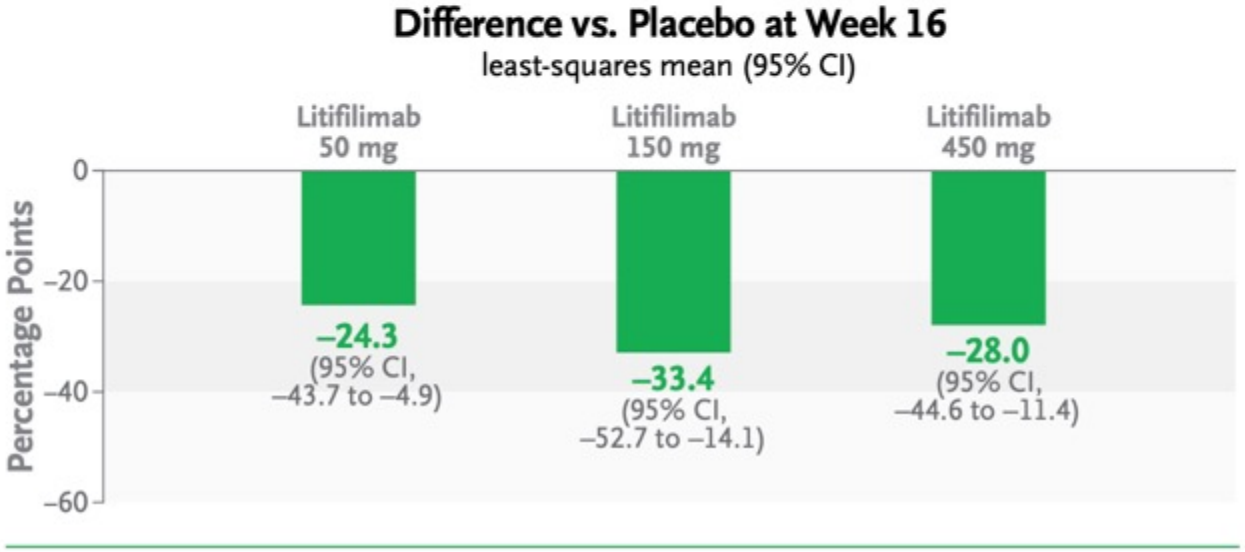
ほとんどがSubacuteかChronic
(HCQは有効性が低いSubtype)

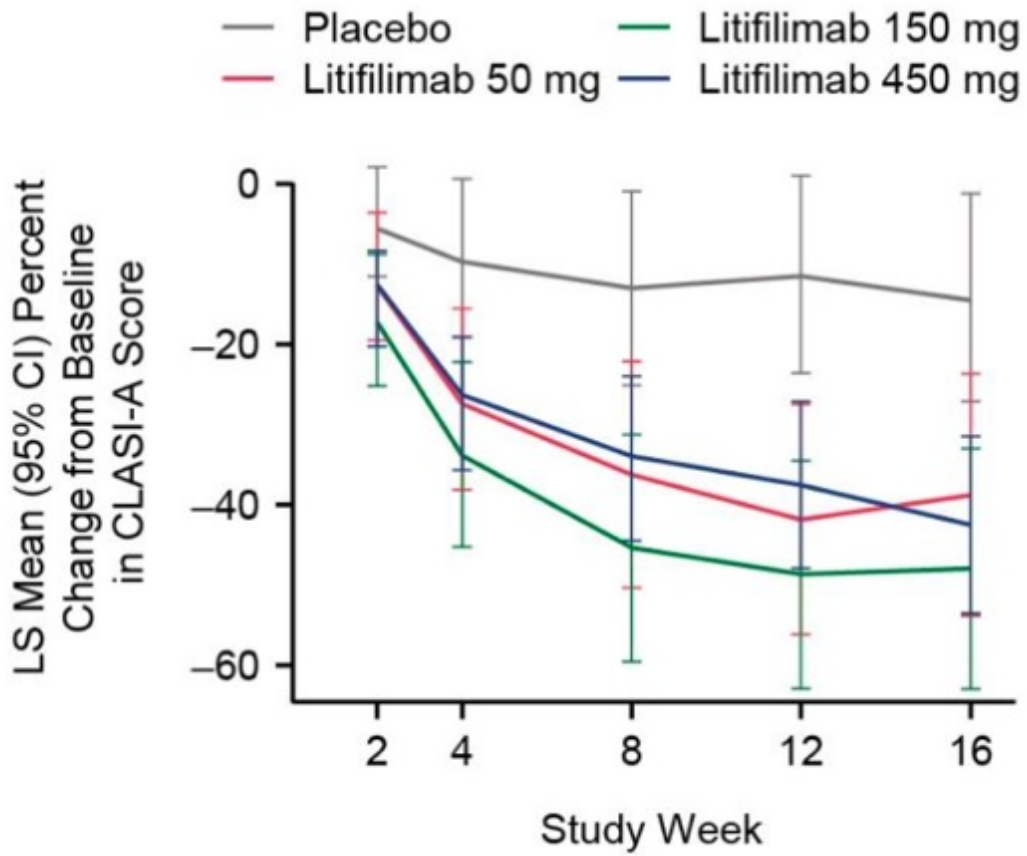
Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Litifilimab, 50 mg (N=26)	Litifilimab, 150 mg (N=25)	Litifilimab, 450 mg (N=48)	Placebo (N=33)
Age — yr	43.3±15.3	43.6±12.1	44.0±12.6	43.4±11.6
Female sex — no. (%)	20 (77)	20 (80)	36 (75)	30 (91)
Disease duration — yr	6.9±10.9	8.4±7.6	10.2±8.9	8.8±7.7
Race and ethnic group — no. (%)†				
Asian	7 (27)	6 (24)	17 (35)	14 (42)
White	4 (15)	6 (24)	13 (27)	9 (27)
Black or African American	5 (19)	2 (8)	5 (10)	2 (6)
Not reported	7 (27)	11 (44)	10 (21)	8 (24)
Other	3 (12)	0	3 (6)	0
Hispanic or Latino	5 (19)	1 (4)	4 (8)	3 (9)
CLASI-A score‡	15.2±8.8	18.4±8.7	16.5±8.8	16.5±8.5
CLASI-A score >10 — no. (%)‡	18 (69)	20 (80)	34 (71)	22 (67)
Cutaneous lupus erythematosus subtype — no. (%)§				
Acute	1 (4)	1 (4)	0	1 (3)
Subacute	8 (31)	11 (44)	15 (31)	11 (33)
Chronic	19 (73)	17 (68)	33 (69)	23 (70)
SLE — no. (%)	11 (42)	12 (48)	20 (42)	14 (42)
SLEDAI-2K score¶	6.5±3.1	6.7±3.4	6.2±2.6	7.3±2.6
Receiving oral glucocorticoid — no. (%)	10 (38)	10 (40)	24 (50)	19 (58)
Daily oral glucocorticoid dose — mg‖	10.9±4.0	8.2±2.8	7.3±3.7	7.0±3.2
Receiving medication for cutaneous lupus erythematosus, SLE, or both — no. (%)	23 (88)	21 (84)	45 (94)	29 (88)
Antimalarial agent — no./total no. (%)**††	18/23 (78)	18/21 (86)	37/45 (82)	20/29 (69)
Antimalarial agent and glucocorticoid — no./total no. (%)††	11/23 (48)	11/21 (52)	23/45 (51)	16/29 (55)
Azathioprine — no./total no. (%)	2/23 (9)	2/21 (10)	2/45 (4)	2/29 (7)
Methotrexate — no./total no. (%)	2/23 (9)	1/21 (5)	2/45 (4)	1/29 (3)
Mycophenolate — no./total no. (%)	0	2/21 (10)	4/45 (9)	0

16週におけるCLASI-Aの変化率（主要評価項目）







副次評価項目

Secondary				
CLASI-50 response: decrease of ≥50% from baseline in CLASI-A score				
At wk 12				
No. of participants (%)	10 (38)	12 (48)	18 (38)	4 (12)
LSM — %	42.3±9.5	51.2±10.6	39.4±7.6	16.6±5.9
LSM difference vs. placebo (95% CI) — percentage points	25.7 (5.1 to 46.2)	34.6 (12.0 to 57.1)	22.8 (5.2 to 40.4)	
At wk 16				
No. of participants/total no. (%)	10/26 (38)	11/25 (44)	20/43 (47)	7/32 (22)
LSM — %	41.4±9.9	46.8±10.5	48.9±8.1	25.6±7.6
LSM difference vs. placebo (95% CI) — percentage points	15.8 (–7.2 to 38.8)	21.2 (–2.8 to 45.2)	23.3 (2.9 to 43.6)	
Percent change from baseline in CLASI-A score at wk 12				
LSM change — %	–41.8±7.1	–48.6±7.1	–37.5±5.2	–11.5±6.1
LSM difference vs. placebo (95% CI) — percentage points	–30.4 (–48.8 to –12.0)	–37.2 (–55.5 to –18.9)	–26.1 (–41.7 to –10.4)	
Decrease of ≥4 points from baseline in CLASI-A score				
At wk 12				
No. of participants (%)	13 (50)	19 (76)	23 (48)	11 (33)
LSM — %	50.0±9.3	73.3±8.2	46.9±8.2	32.8±8.0
LSM difference vs. placebo (95% CI) — percentage points	17.2 (–6.0 to 40.3)	40.5 (19.0 to 62.0)	14.1 (–7.2 to 35.4)	
At wk 16				
No. of participants/total no. (%)	12/26 (46)	18/25 (72)	24/43 (56)	12/32 (38)
LSM — %	47.9±9.6	70.2±8.7	58.3±8.5	38.1±8.4
LSM difference vs. placebo (95% CI) — percentage points	9.8 (–14.3 to 33.9)	32.1 (9.2 to 54.9)	20.2 (–2.2 to 42.7)	
Decrease of ≥7 points from baseline in CLASI-A score				
At wk 12				
No. of participants (%)	10 (38)	10 (40)	16 (33)	6 (18)
LSM — %	35.1±9.7	35.7±8.9	28.5±7.7	16.7±10.2
LSM difference vs. placebo (95% CI) — percentage points	18.3 (–8.0 to 44.7)	18.9 (–6.9 to 44.8)	11.7 (–11.7 to 35.1)	
At wk 16				
No. of participants/total no. (%)	8/26 (31)	12/25 (48)	18/43 (42)	7/32 (22)
LSM — %	31.2±8.0	43.9±9.2	38.4±8.9	21.1±8.3
LSM difference vs. placebo (95% CI) — percentage points	10.1 (–13.0 to 33.2)	22.8 (–1.5 to 47.0)	17.3 (–6.2 to 40.9)	

安全性

○主な副作用(頻度>5%)

鼻咽頭炎、頭痛、注射部位反応
関節痛、上気道感染症
インフルエンザ、掻痒、咳嗽

○投与中止に至る重篤なAE

・Litifilimabで8例、Placebo無し
・実際の副作用(重複あり)
過敏症(3)、髄膜炎(3)
注射部位反応(＊)、過多月経、
脱力、めまい、嘔吐、胸痛、動悸

○死亡：無し

○SLE flare

・Placeboで1例
・Litifilimab 150mgで2例

Table 3. Adverse Events.*

Event	Litifilimab, 50 mg (N=26)	Litifilimab, 150 mg (N=25)	Litifilimab, 450 mg (N=48)	Pooled Litifilimab (N=99)	Placebo (N=33)
	number of patients (percent)				
Any adverse event†	18 (69)	15 (60)	38 (79)	71 (72)	22 (67)
Adverse events according to severity‡					
Mild	7 (27)	7 (28)	21 (44)	35 (35)	12 (36)
Moderate	11 (42)	7 (28)	14 (29)	32 (32)	6 (18)
Severe	0	1 (4)	3 (6)	4 (4)	4 (12)
Serious adverse event	1 (4)	3 (12)	3 (6)	7 (7)	3 (9)
Serious adverse event occurring in >1 participant: SLE§	0	2 (8)	0	2 (2)	1 (3)
Fatal adverse event	0	0	0	0	0
Adverse event leading to discontinuation of litifilimab or placebo¶	3 (12)	1 (4)	4 (8)	8 (8)	0
Adverse event leading to trial withdrawal	0	0	1 (2)	1 (1)	0
Viral infections and infestations					
Influenza	2 (8)	1 (4)	2 (4)	5 (5)	0
Oral herpes infection	1 (4)	1 (4)	1 (2)	3 (3)	0
Viral upper respiratory tract infection	1 (4)	1 (4)	0	2 (2)	0
Herpes zoster infection	1 (4)	0	0	1 (1)	0
Systemic viral infection	1 (4)	0	0	1 (1)	2 (6)
Viral rash	0	1 (4)	0	1 (1)	0
Herpes simplex infection	0	0	0	0	1 (3)
Herpes zoster meningitis‖	1 (4)	0	0	1 (1)	0
Adverse events that occurred in ≥5% of participants in the pooled litifilimab group					
Nasopharyngitis	2 (8)	5 (20)	3 (6)	10 (10)	2 (6)
Headache	7 (27)	0	2 (4)	9 (9)	3 (9)
Injection-site erythema	3 (12)	2 (8)	4 (8)	9 (9)	1 (3)
SLE	2 (8)	3 (12)	2 (4)	7 (7)	4 (12)
Arthralgia	1 (4)	2 (8)	3 (6)	6 (6)	2 (6)
Upper respiratory tract infection	2 (8)	2 (8)	2 (4)	6 (6)	1 (3)
Cough	2 (8)	1 (4)	2 (4)	5 (5)	1 (3)
Influenza	2 (8)	1 (4)	2 (4)	5 (5)	0
Pruritus	1 (4)	3 (12)	1 (2)	5 (5)	1 (3)

Discussion

◎プラセボに比較してCLASI-Aが低下することが示された.

・HCQ投与(全体の80%)してもCLEの活動性が中等症以上あった症例で効果を示した.

・HCQの効果が低いDLEやSubacute CLEが多く含まれている中で効果を示した.

・HCQとLitifinimabはともにIFNを抑制するが, HCQ併用でも効果が減じない.

○Limitation

・途中で研究デザインを変更.

・Biogen社から資金提供あり.

・副次評価項目に関しては検出力が足りない.

・投与量が違うと効果が違うかは不明.

・サブタイプごとに比較しているわけではない.