Cibler l'interféron dans le Lupus Systémique

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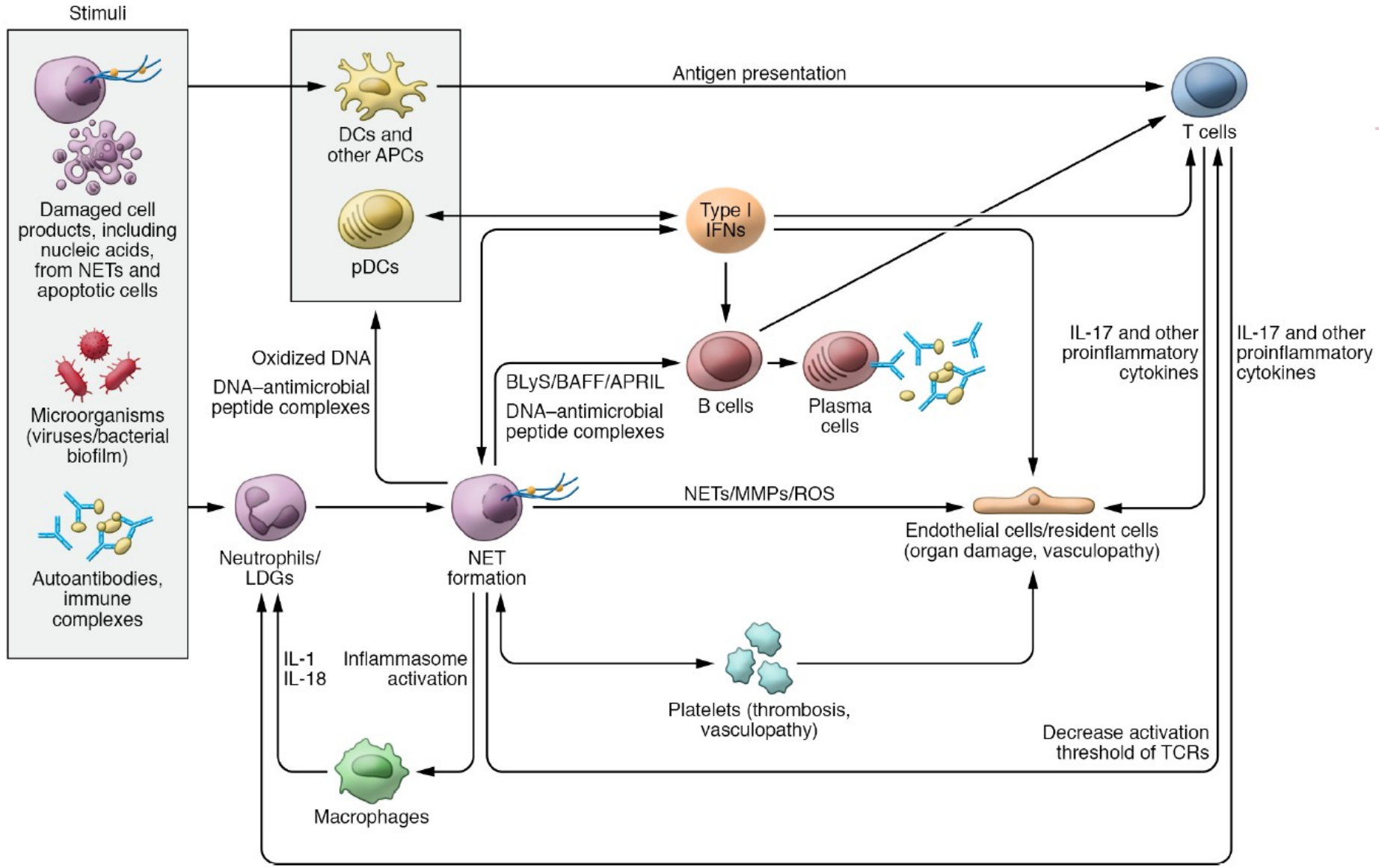
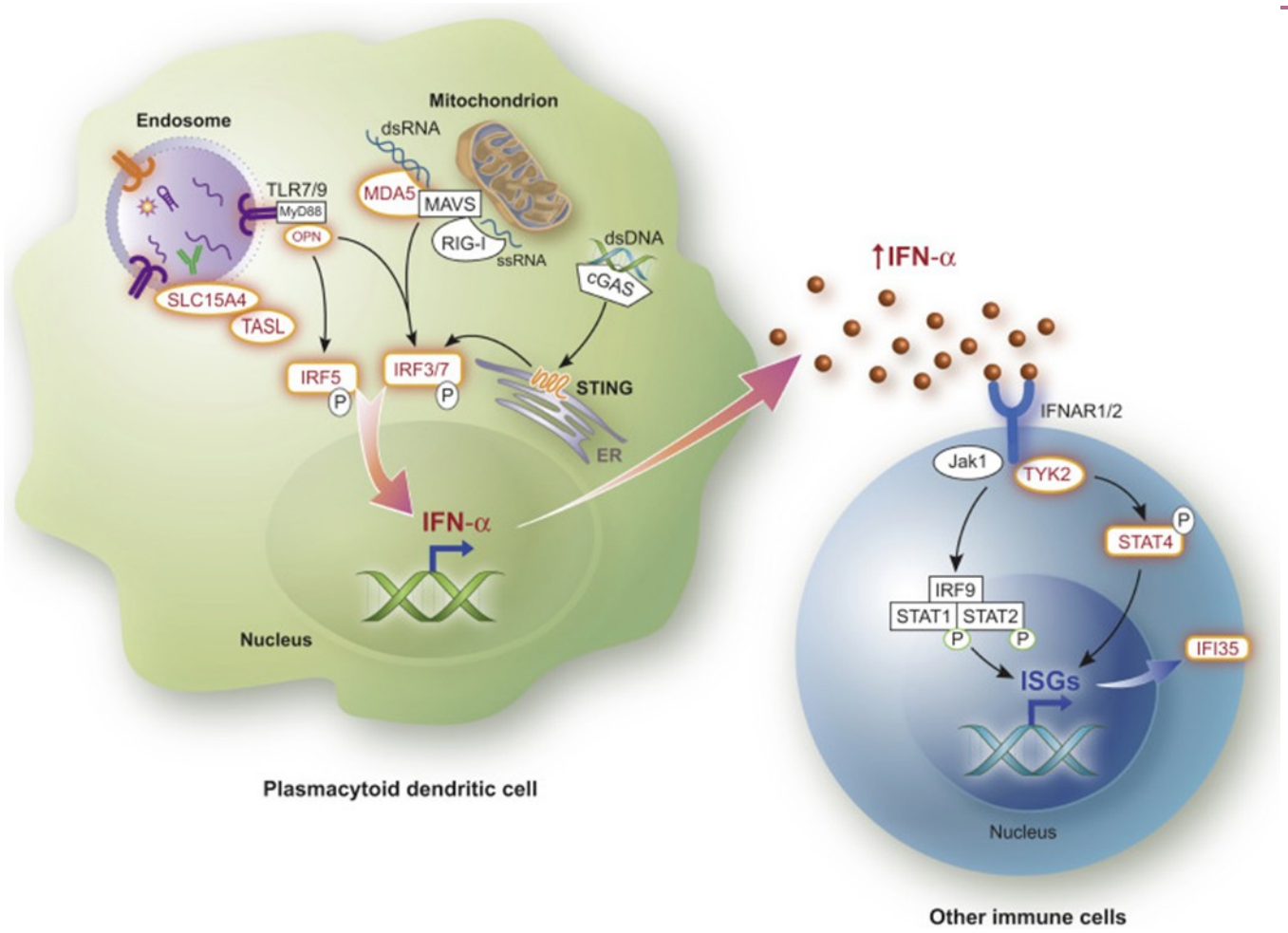
Disclosures of interest Pr Zahir Amoura

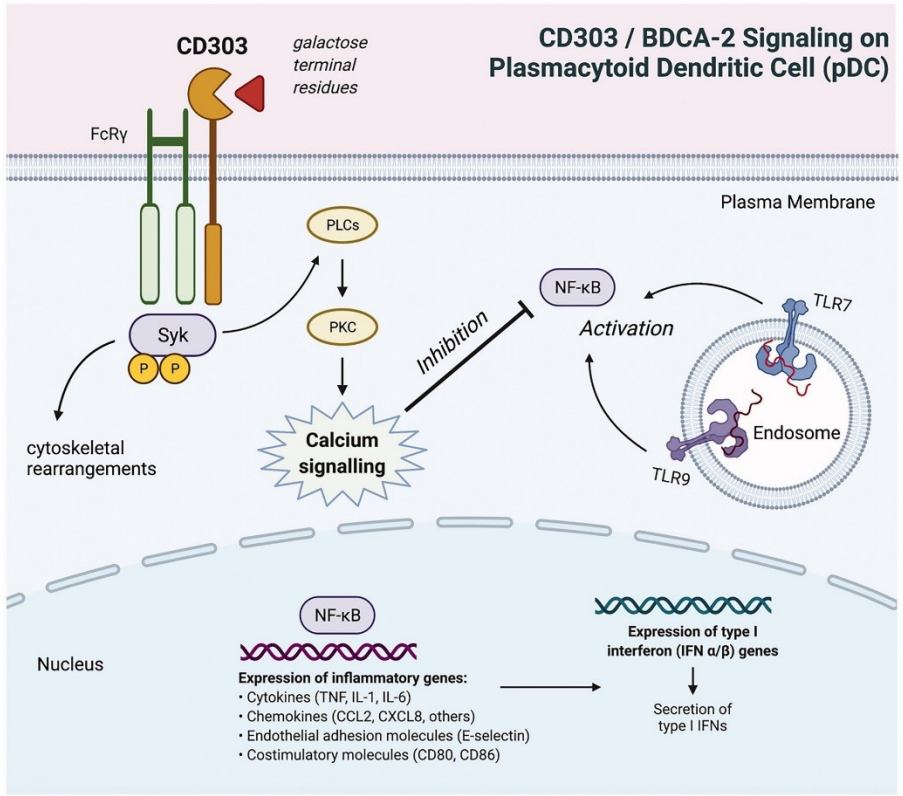
- **Roche: Research recipient**
- **GSK: grants, research recipients, advisor.**
- **Astra Zeneca: advisor, research recipient**
- **Amgen: advisor, research recipients**
- **Novartis: advisor, research recipients**
- **Kezar: advisor**



J Clin Invest. 2021;131(3):e144918 https://doi.org/10.1172/JCI144918

Cibler BDCA2 (CD303)





J Clin Invest. 2019;129(3):1359–1371.

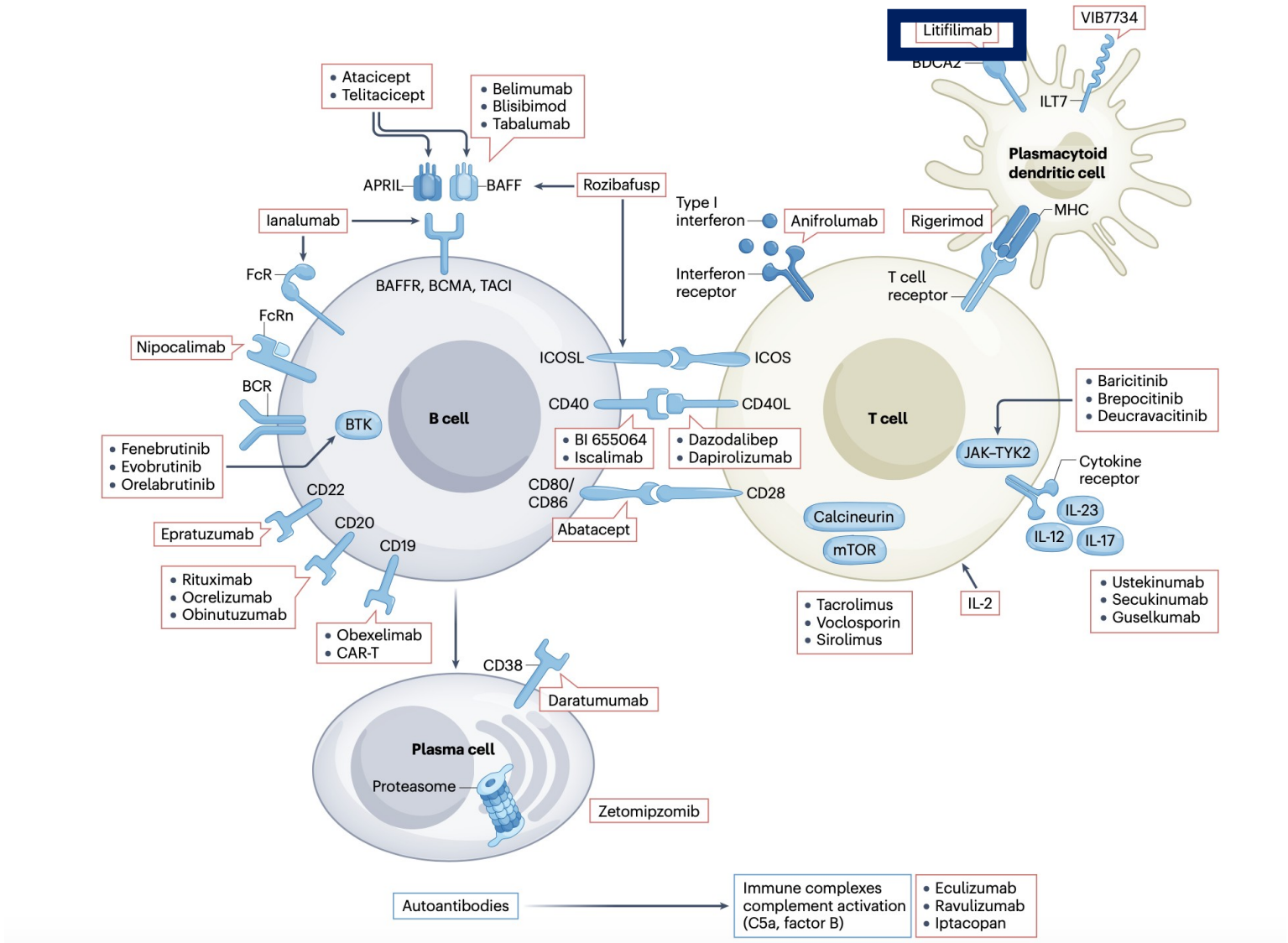
Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus

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.

J Clin Invest. 2019;129(3):1359–1371.

Litifilimab

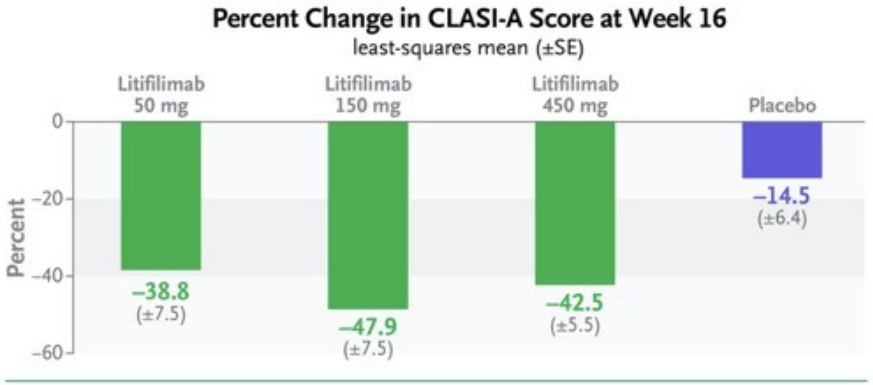


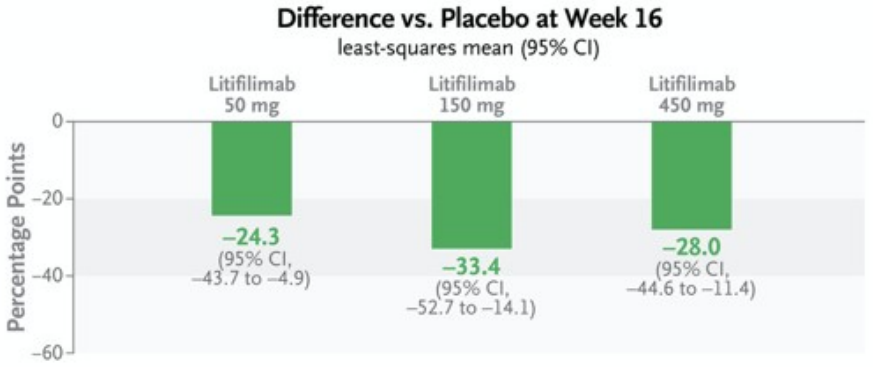
Anticorps monoclonal bloquant le récepteur BDCA-2

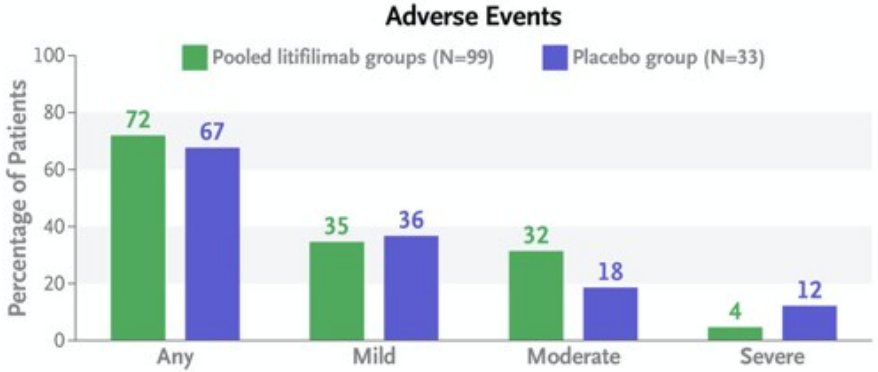
Exprimé uniquement sur les pDC

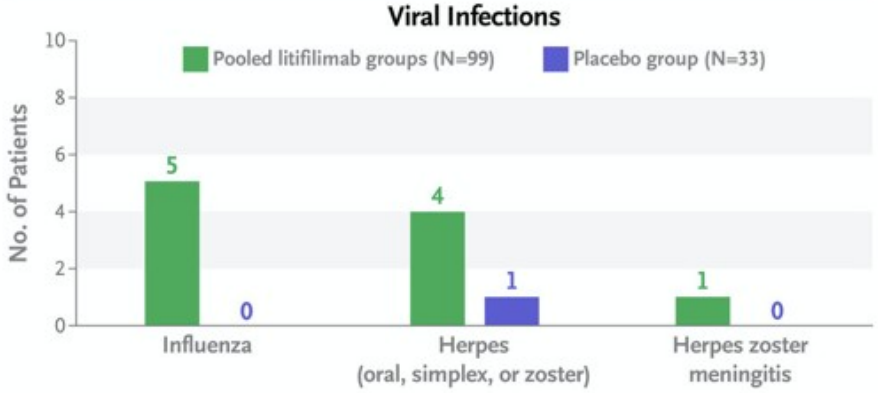
À l'origine de la production des interférons de type I

Litifilimab phase II





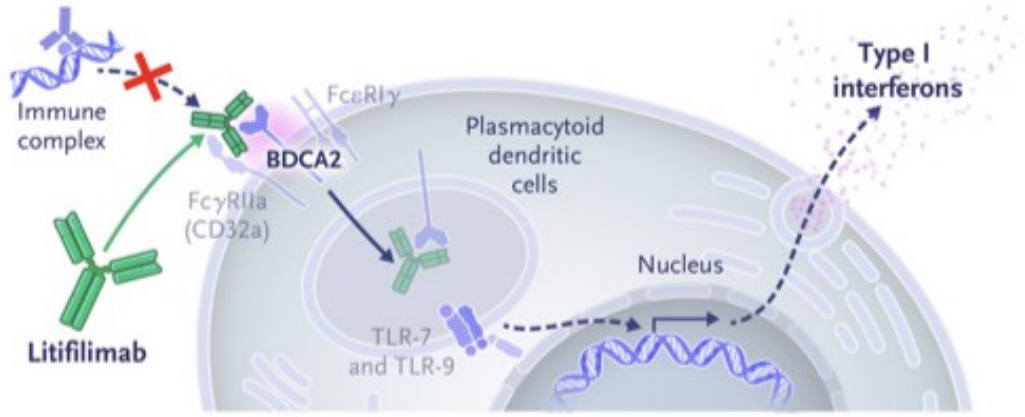




Etude pilote phase II – 12 semaines – placebo et 3 doses de litifilimab (50-150-450)
132 participants
Efficacité sur la peau : score CLASI significatifs
MAIS critères II négatifs et effets secondaires++

Werth VP. N Engl J Med. 2022 Jul 28;387(4):321-331.

Litifilimab



ORIGINAL ARTICLE

Trial of Anti-BDCA2 Antibody Litifilimab for Systemic Lupus Erythematosus

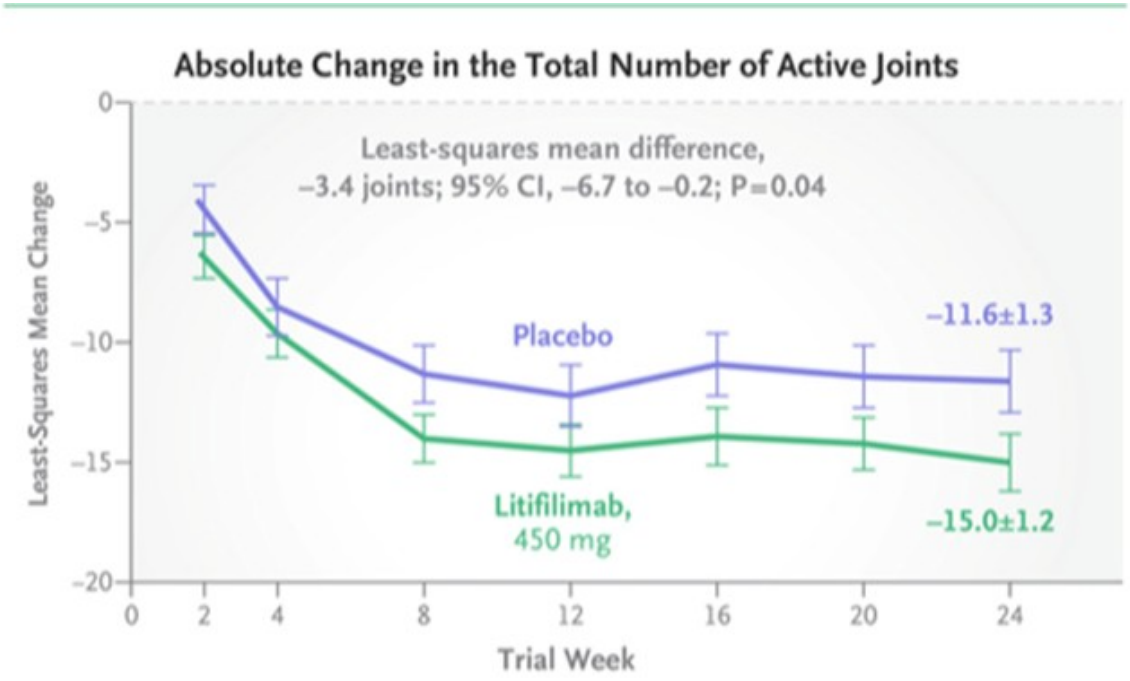
Richard A. Furie, M.D., Ronald F. van Vollenhoven, M.D., Kenneth Kalunian, M.D., Sandra Navarra, M.D., Juanita Romero-Diaz, M.D., Victoria P. Werth, M.D., Xiaobi Huang, Ph.D., George Clark, B.S., Hua Carroll, M.D., Adam Meyers, M.S., Cristina Musselli, M.D., Catherine Barbey, Ph.D., and Nathalie Franchimont, M.D., Ph.D., for the LILAC Trial Investigators*

Litifilimab is a subcutaneously administered, humanized IgG1 monoclonal antibody that binds BDCA2, resulting in the down-regulation of type I interferon, cytokine, and chemokine production.

litifilimab at a dose of 450 mg

Furie RA. LILAC Trial Investigators.N Engl J Med. 2022 Sep 8;387(10):894-904.

Litifilimab



Effet sur les articulations (changement en cours d'étude, initialement sur la peau…)

Furie RA. LILAC Trial Investigators.N Engl J Med. 2022 Sep 8;387(10):894-904.

Litifilimab

Secondary: SLE disease activity§¶		
SRI-4 response‖		
Participants — no./total no. (%)	36/64 (56)	16/56 (29)
LSM — %	56.8±7.4	30.4±7.4
LSM difference vs. placebo (95% CI) — percentage points	26.4 (9.5 to 43.2)	
Absolute change in SLEDAI-2K score at wk 24		
LSM — percentage points	–4.4±0.5	–2.6±0.5
LSM difference vs. placebo (95% CI) — percentage points	–1.7 (–3.0 to –0.5)	
No new A score and ≤1 new B score on the BILAG-2004 index		
Participants — no./total no. (%)	55/64 (86)	46/56 (82)
LSM change — %	86.5±6.2	78.8±6.9
LSM difference vs. placebo (95% CI) — percentage points	7.7 (–7.6 to 23.0)	

Effet positif sur le SRI-4 et SLEDAI

Pas d'effet sur les poussées ni PGA

Furie RA. LILAC Trial Investigators.N Engl J Med. 2022 Sep 8;387(10):894-904.

Litifilimab

Concomitant receipt of medications for SLE — no./total no. (%)	62/64 (97)	55/56 (98)
Antimalarial agent**	55/62 (89)	49/55 (89)
Glucocorticoids†††‡‡	56/62 (90)	53/55 (96)
Antimalarial agent and glucocorticoid††	51/62 (82)	47/55 (85)
Azathioprine	10/62 (16)	9/55 (16)
Methotrexate	8/62 (13)	9/55 (16)
Mycophenolate	3/62 (5)	7/55 (13)
Other allowed medications	29/62 (47)	16/55 (29)

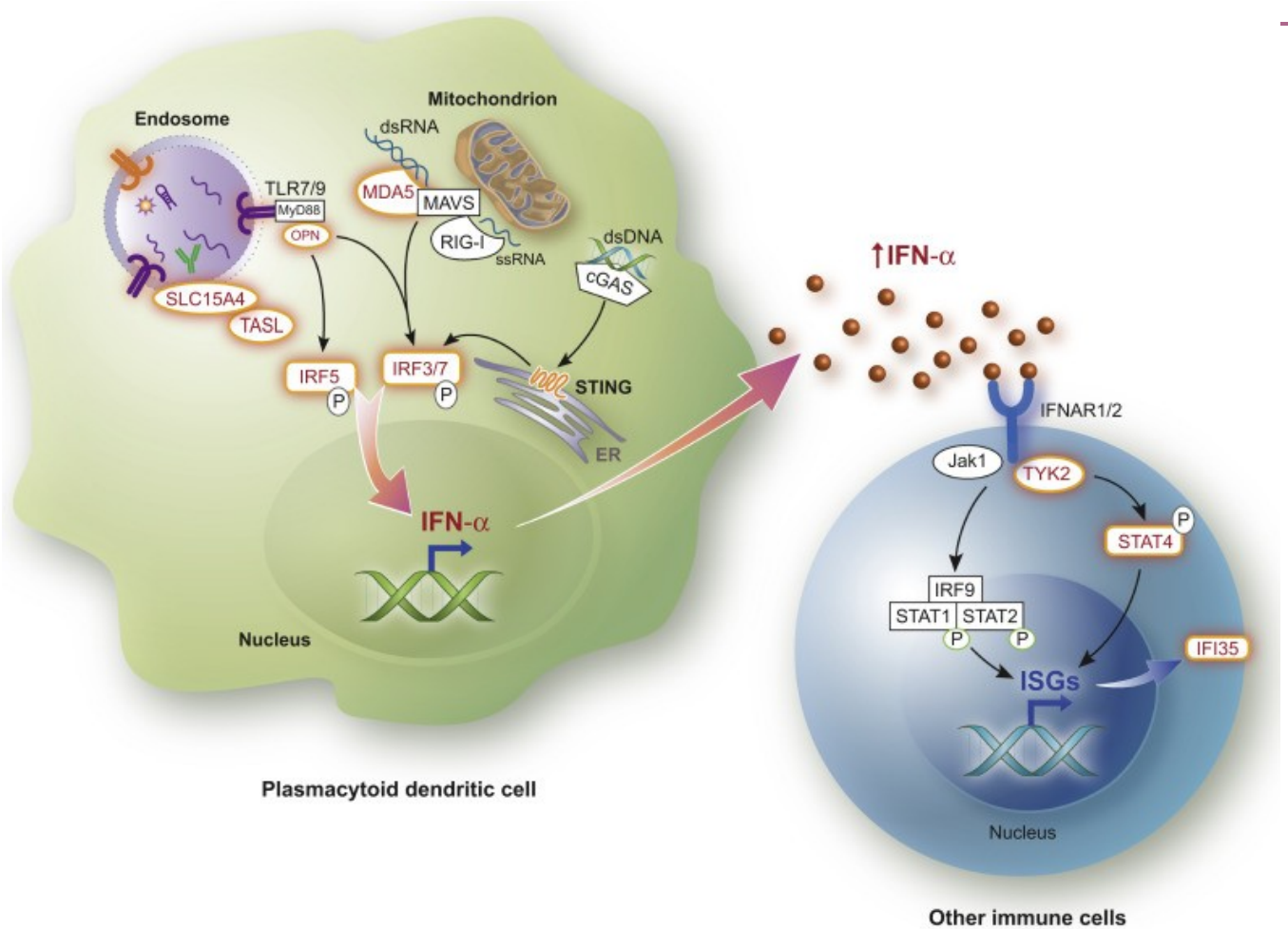
End Point	Litifilimab, 450 mg (N=64)	Placebo (N=56)
Primary		
No. of participants	56	46
Absolute change from baseline to wk 24 in total no. of active joints (28-joint assessment)†		
LSM no. of joints	−15.0±1.2	−11.6±1.3
LSM difference vs. placebo (95% CI)‡	−3.4 (−6.7 to −0.2)	
Secondary: skin-related disease activity§		
Participants	39	38
CLASI-50 response: decrease of ≥50% from baseline in CLASI-A score		
Participants — no./total no. (%)	25/39 (64)	16/38 (42)
LSM — %	69.1±8.8	49.1±9.6
LSM difference vs. placebo (95% CI) — percentage points	20.0 (−1.3 to 41.3)	

Patients sous CT et HCQ
Peu d'immunosuppresseurs

Réponse élevée dans le bras placebo (42%)
Signification clinique sur les articulations ?

Furie RA. LILAC Trial Investigators.N Engl J Med. 2022 Sep 8;387(10):894-904.

Cibler CD11b



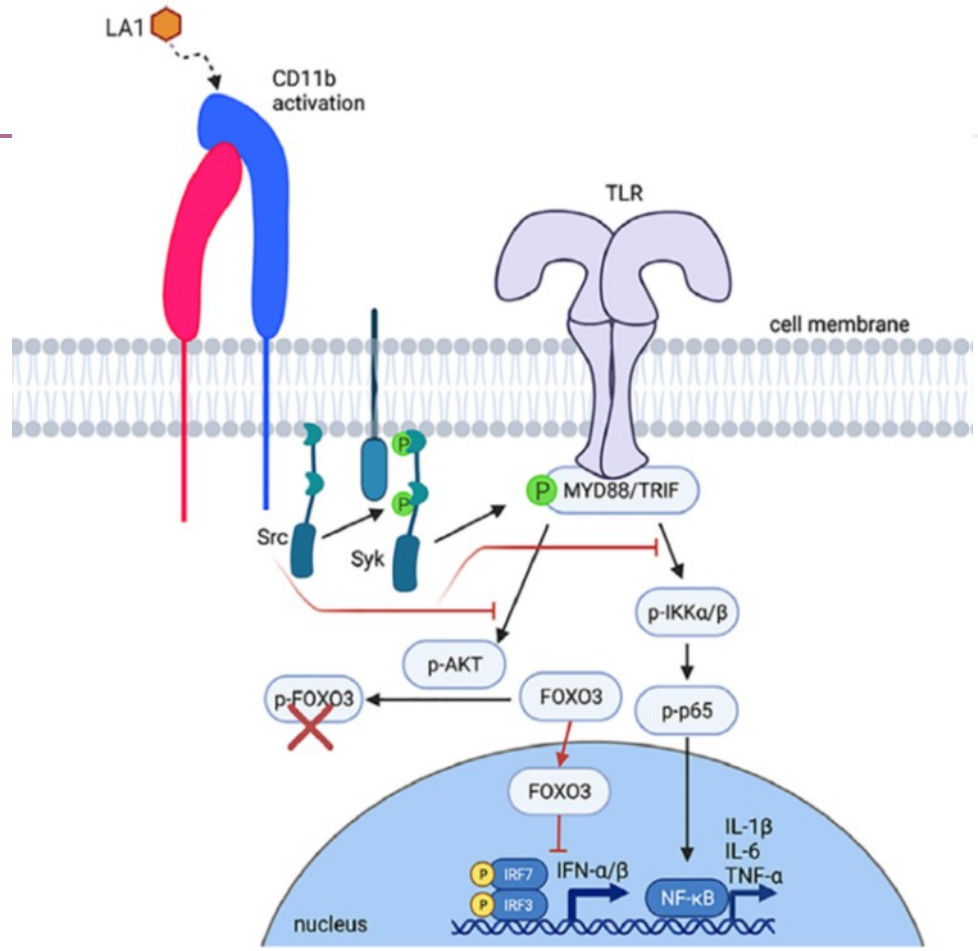


Fig 3. TLR-dependent signaling pathways are modulated by allosteric activation of CD11b. The conventional TLR-dependent signaling is mediated via membrane recruited MyD88/TRIF proteins, that result in phosphorylation and nuclear import for NFκB complex, thereby transcriptionally upregulating pro-inflammatory molecules, such as IL-6, IL-1β and TNFα. A second arm of TLR-dependent signaling results in AKT-dependent phosphorylation and degradation of FOXO3, that results in de-repression of IFN I pathway, resulting in transcriptional upregulation of IFN I. Novel small molecule allosteric agonists, such as LA1, activate CD11b that results in recruitment of kinases Src and Syk, leading to phosphorylation and subsequent degradation of MyD88/TRIF downstream of TLRs. This leads to suppression of p65 phosphorylation and reduced nuclear translocation of NFκB, suppressing generation of pro-inflammatory cytokines IL-6, IL-1β and TNFα. Allosteric activation of CD11b also suppresses AKT phosphorylation, decreasing pFOXO3 levels, that allows import of FOXO3 to repress IRF3/IRF7 mediated expression of IFNα/β. TLR, Toll-like receptor. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.) (Color version of figure is available online.)

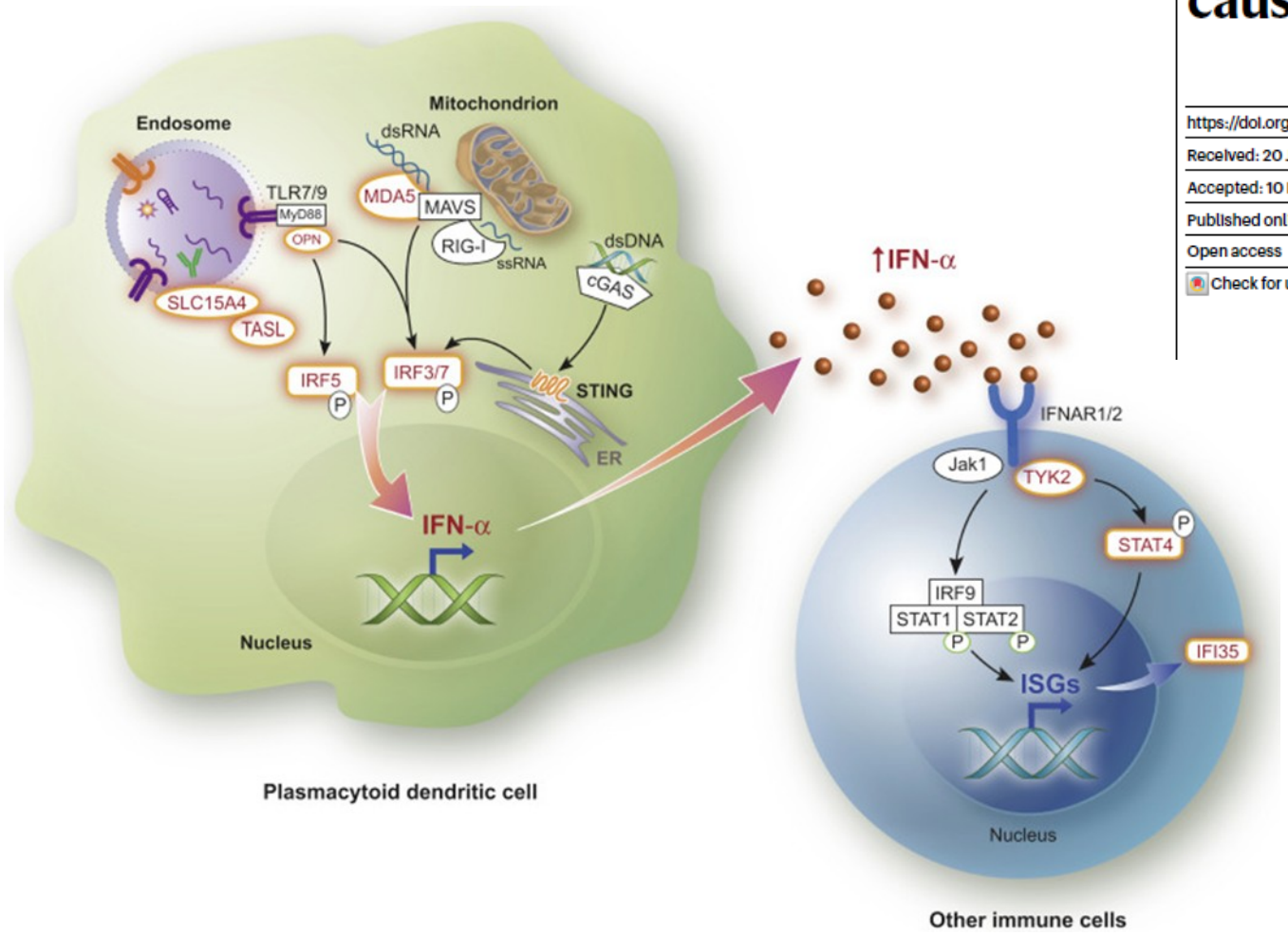
CD11b agonists offer a novel approach for treating lupus nephritis

VERONICA VILLANUEVA, XIAOBO LI, VIVIANA JIMENEZ, HAFEEZ M. FARIDI, and VINEET GUPTA

CHICAGO, ILLINOIS

Translational Research
July 2022

Cibler TLR7



Article

TLR7 gain-of-function genetic variation causes human lupus

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Grant J. Brown[1], Pablo F. Cañete[1,28], Hao Wang[1,28], Arti Medhavy[1], Josiah Bones[2], Jonathan A. Roco[1], Yuke He[3], Yuting Qin[3], Jean Cappello[1], Julia I. Ellyard[1], Katharine Bassett[1], Qian Shen[1], Gaetan Burgio[1], Yaoyuan Zhang[1], Cynthia Turnbull[1], Xiangpeng Meng[1], Phil Wu[1], Eun Cho[1], Lisa A. Miosge[1], T. Daniel Andrews[1], Matt A. Field[1,4], Denis Tvorogov[5], Angel F. Lopez[5], Jeffrey J. Babon[6], Cristina Aparicio López[7], África Gónzalez-Murillo[8,9], Daniel Clemente Garulo[10], Virginia Pascual[11], Tess Levy[12,13], Eric J. Mallack[14], Daniel G. Calame[15,16,17], Timothy Lotze[15,16], James R. Lupski[16,17,18,19], Huihua Ding[3,20], Tomalika R. Ullah[21,22], Giles D. Walters[23], Mark E. Koina[24], Matthew C. Cook[1], Nan Shen[3,20,25], Carmen de Lucas Collantes[7,26], Ben Corry[2], Michael P. Gantier[20,21], Vicki Athanasopoulos[1,29] & Carola G. Vinuesa[1,5,27,29]

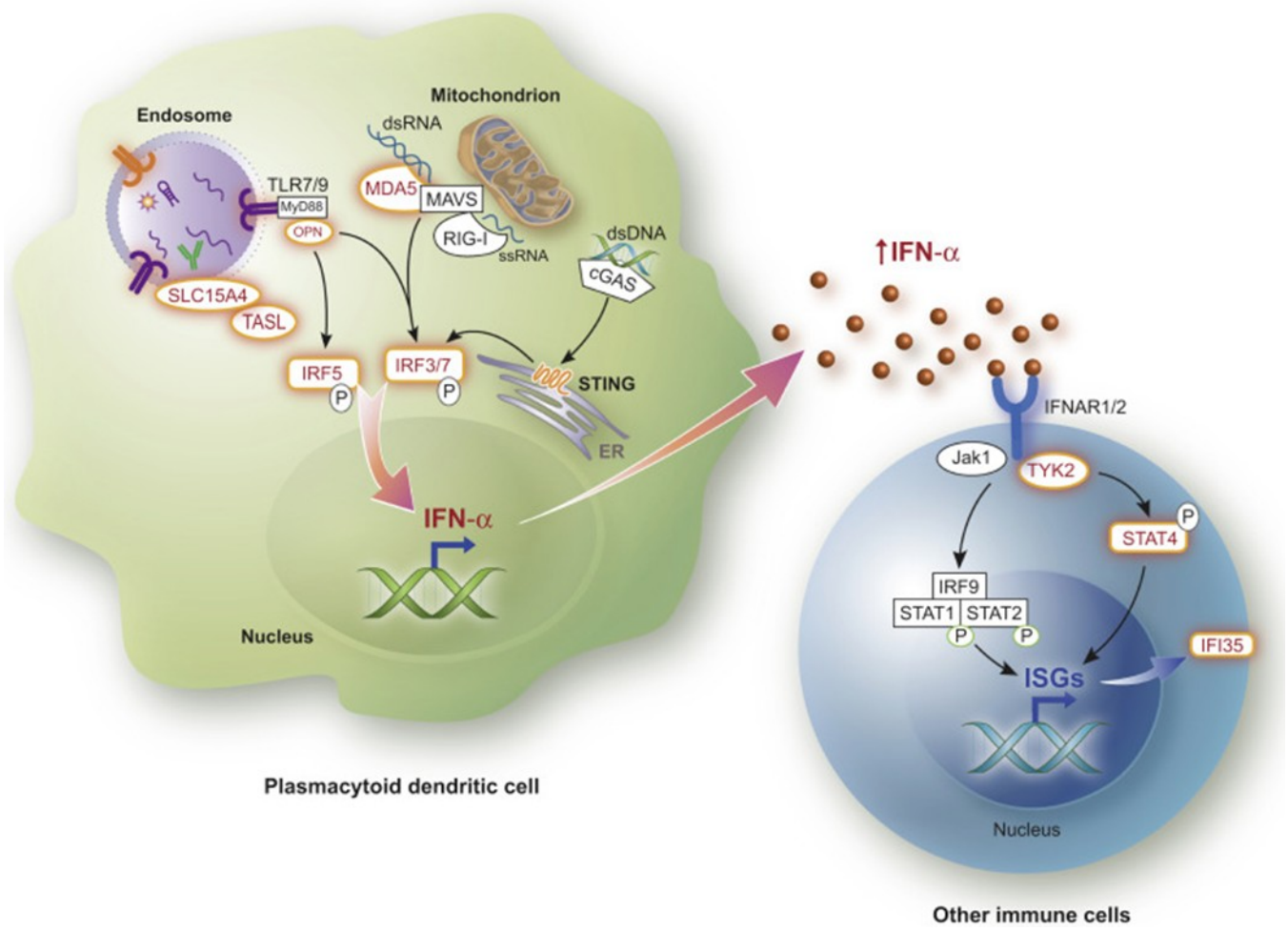
Cibler TLR

Table 1 | **TLR modulators in clinical development for inflammatory diseases**

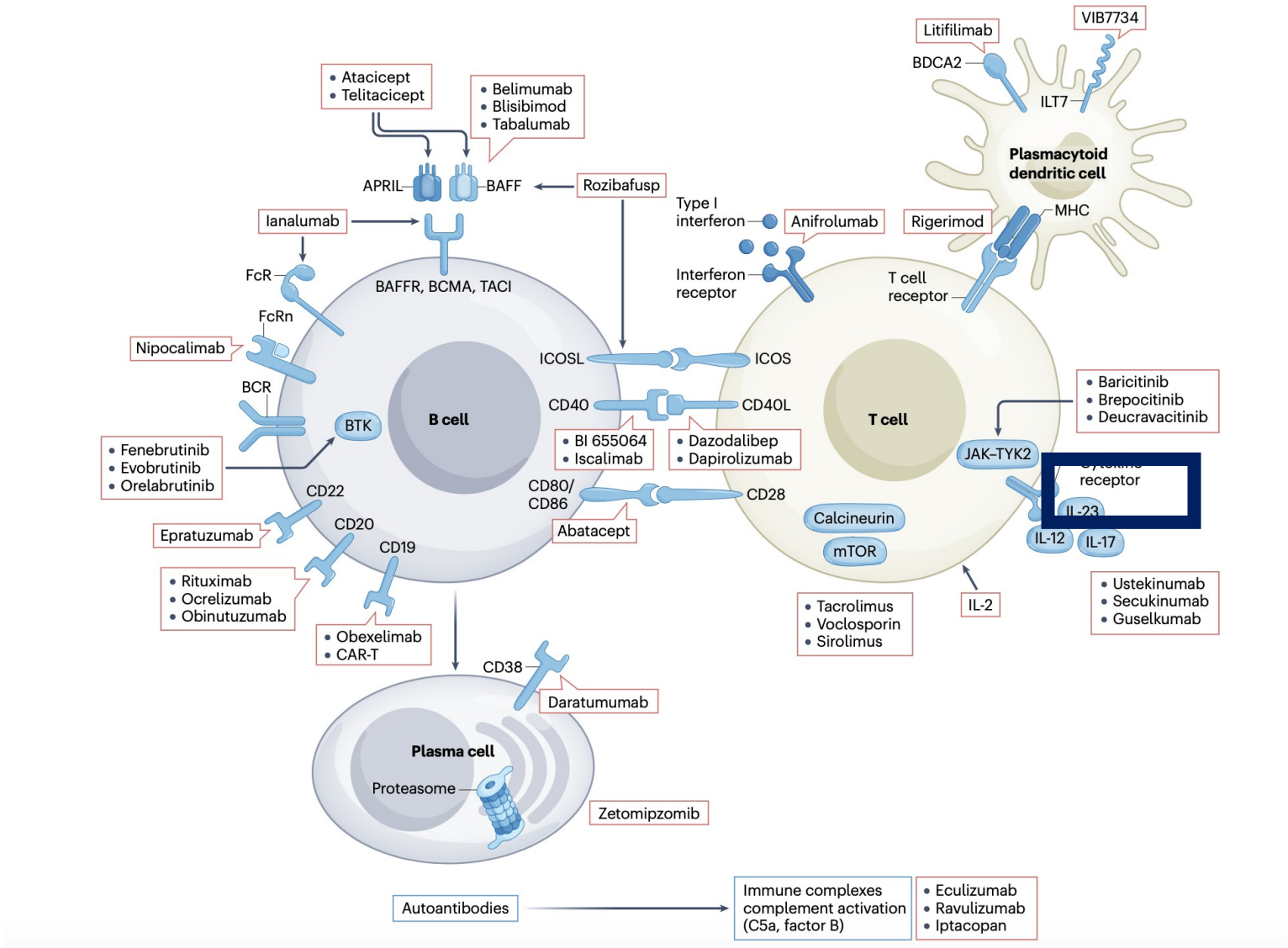
TLR target	Compound	Target disease	Mechanism of action	Development phase (NCT number)	Refs
TLR7	Imiquimod	Actinic keratosis	Immune-stimulator	Phase I (NCT01151956); phase IV (NCT00777127, NCT01453179)	108–112
	GSK2245035	Rhinitis	Induces type I IFN; immune-stimulator	Phase II (NCT01788813, NCT02446613, NCT01607372); phase I (NCT01480271)	113, 114
		Asthma	Induces type I IFN; immune-stimulator	Phase II (NCT03707678); phase I/II (NCT02833974)	115
TLR9	CYT003-QbG10	Asthma	Induces a T_H1 cell-mediated immune response	Phase II (NCT02087644, NCT00890734)	116, 117
	AZD1419	Asthma	Induces T_H1-type IFN response	Phase II (NCT02898662)	118, 119
	Hydroxychloroquine	Sjögren's syndrome	Immune modulator	Phase III (NCT00632866, NCT01601028)	120, 121
IRAK4	ND-2158	Rodent models of: lipopolysaccharide-induced TNF production; collagen-induced arthritis; gout; activated B cell like-diffuse large B cell lymphoma; chronic lymphocytic leukaemia	Small molecule inhibitors of inflammatory pathways	Preclinical	122, 123
	BMS-986126	Systemic lupus erythematosus	Inhibitor	Preclinical	124
	PF-06650833	Rheumatic autoimmune diseases	Inhibitor	Phase I (NCT02224651, NCT02485769); phase II (NCT02996500)	98
	BAY1834845	Psoriasis; pelvic inflammatory disease	Small-molecule inhibitor	Phase I (NCT03493269, NCT03054402)	125
IRAK1, IRAK4 and TAK1	HS-243	Autoimmune diseases	Inhibitor	Preclinical	99

IRAK-, IL-1 receptor-associated kinase; TAK1, transforming growth factor-β-activated kinase 1; T_H1, T helper 1; TLR, Toll-like receptor.

Cibler JAK


Endosome
Mitochondrion
dsRNA
TLR7/9
MyD88
OPN
MDA5
MAVS
RIG-I
ssRNA
dsDNA
cGAS
SLC15A4
TASL
IRF5
P
IRF3/7
P
STING
ER
IFN-α
Nucleus
Plasmacytoid dendritic cell
↑IFN-α
IFNAR1/2
Jak1
TYK2
P
STAT4
IRF9
STAT1
STAT2
P
P
IFI35
ISGs
Nucleus
Other immune cells

Inhibiteurs de JAK



Baricitinib

Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I)

Eric F Morand, Edward M Vital, Michelle Petri, Ronald van Vollenhoven, Daniel J Wallace, Marta Mosca, Richard A Furie, Maria E Silk, Christina L Dickson, Gabriella Meszaros, Bochao Jia, Brenda Crowe, Inmaculada de la Torre, Thomas Dörner

www.thelancet.com **Vol 401 March 25, 2023**

Participants

Eligible participants were aged 18 years or older; had a clinical diagnosis of SLE at least 24 weeks before screening; met at least four of 11 revised American College of Rheumatology 1997 criteria for classification of SLE;[16] were positive at screening for at least one of anti-nuclear antibody (titre ≥1:80), anti-dsDNA, or anti-Smith; and had active disease evidenced by a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of at least 6 at screening; and had at least one British Isles Lupus Assessment Group (BILAG) A score or two BILAG B scores at screening despite SOC medications.

Patients were excluded if they had severe active lupus nephritis, severe active CNS lupus, or had been treated for, or had an active occurrence of a systemic inflammatory condition other than SLE. Full inclusion and exclusion criteria are provided in the trial protocol (appendix pp 10–15).

All participants provided written informed consent.

Baricitinib

	Placebo (n=253)	Baricitinib 2 mg (n=255)	Baricitinib 2 mg odds ratio (95% CI); difference with placebo (95% CI); p value	Baricitinib 4 mg (n=252)	Baricitinib 4 mg odds ratio (95% CI); difference with placebo (95% CI); p value
Primary outcome					
SRI-4*†	116 (46%)	126 (50%)	1·14 (0·79 to 1·65); 3·9 (−4·9 to 12·6); 0·47	142 (57%)	1·57 (1·09 to 2·27); 10·8 (2·0 to 19·6); 0·016
Reduction of ≥4 points from baseline in SLEDAI-2K score*†	117 (47%)	128 (50%)	1·14 (0·80 to 1·64); 0·47	146 (58%)	1·62 (1·12 to 2·34); 0·010
No new BILAG A and no more than one new BILAB B disease activity score*†	182 (72%)	196 (77%)	1·25 (0·83 to 1·88); 0·29	200 (80%)	1·49 (0·98 to 2·29); 0·065
No worsening (defined as an increase of ≥0·3 points [10 mm] from baseline) in the PGA*†	183 (73%)	197 (77%)	1·25 (0·83 to 1·89); 0·29	197 (79%)	1·37 (0·90 to 2·09); 0·14

Baricitinib

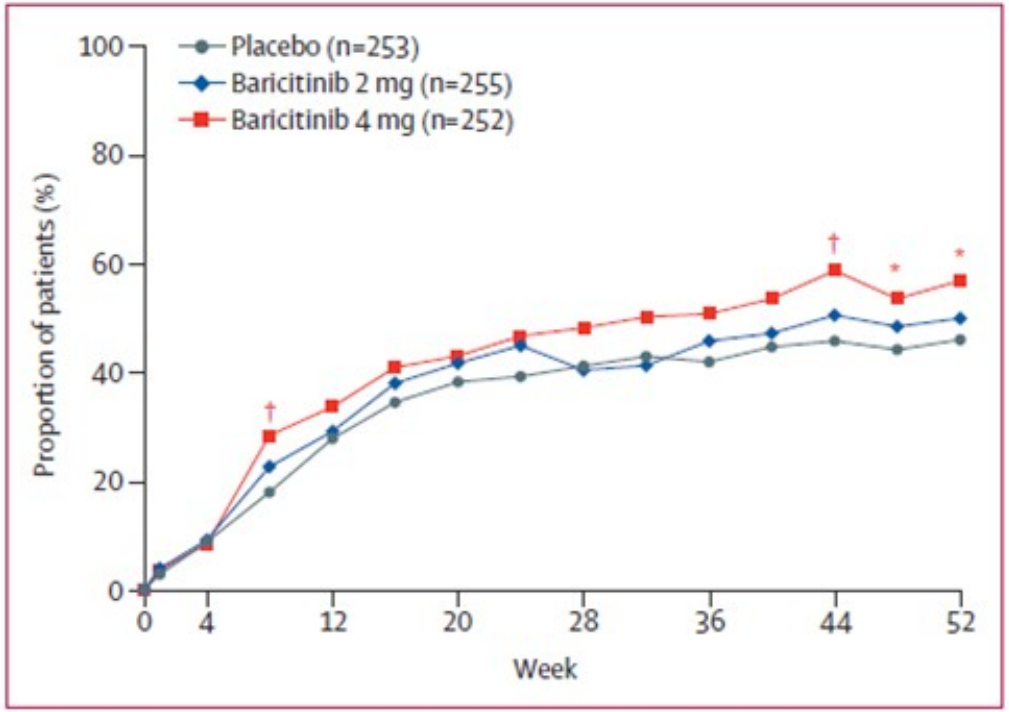


Figure 2: **SRI-4 response through 52 weeks in overall study population**
Proportion of patients reaching SRI-4 response over the 52-week study period. SRI-4=Systemic Lupus Erythematosus Responder Index-4. *p≤0·05. †p≤0·01

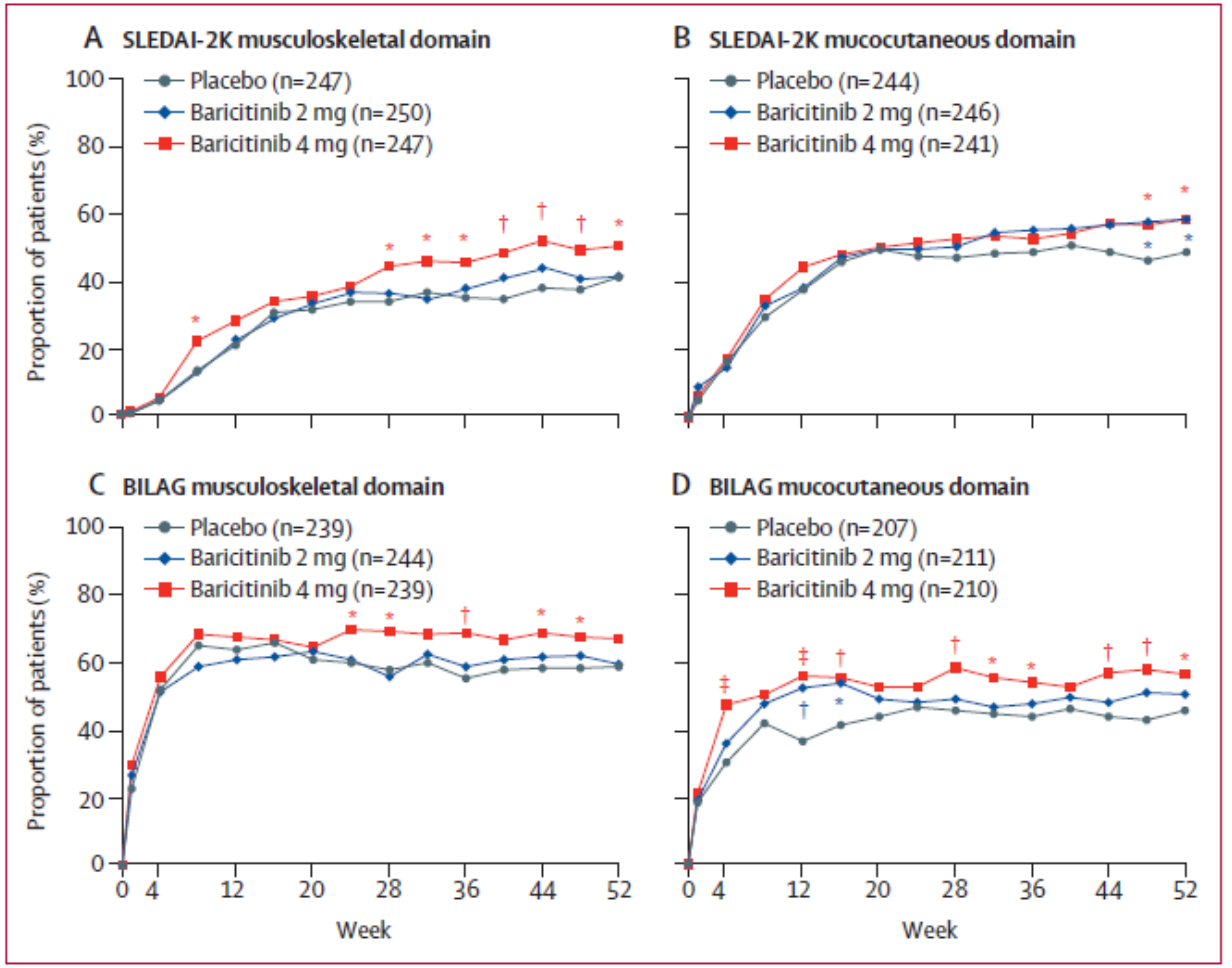


Figure 3: **Improvement from baseline in SLEDAI-2K and BILAG organ systems through 52 weeks**
Improvement from baseline in the SLEDAI-2K organ system for the musculoskeletal domain (A) and mucocutaneous domain (B). Improvement from baseline in the BILAG organ system for the musculoskeletal domain (C) and

Petri M, Bruce IN, Dörner T, Tanaka Y, Morand EF, Kalunian KC, Cardiel MH, Silk ME, Dickson CL, Meszaros G, Zhang L, Jia B, Zhao Y, McVeigh CJ, Mosca M. **Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II).** Lancet. 2023 Mar 25;401(10381):1011-1019. doi: 10.1016/S0140-6736(22)02546-6. Epub 2023 Feb 24. PMID: 36848919.

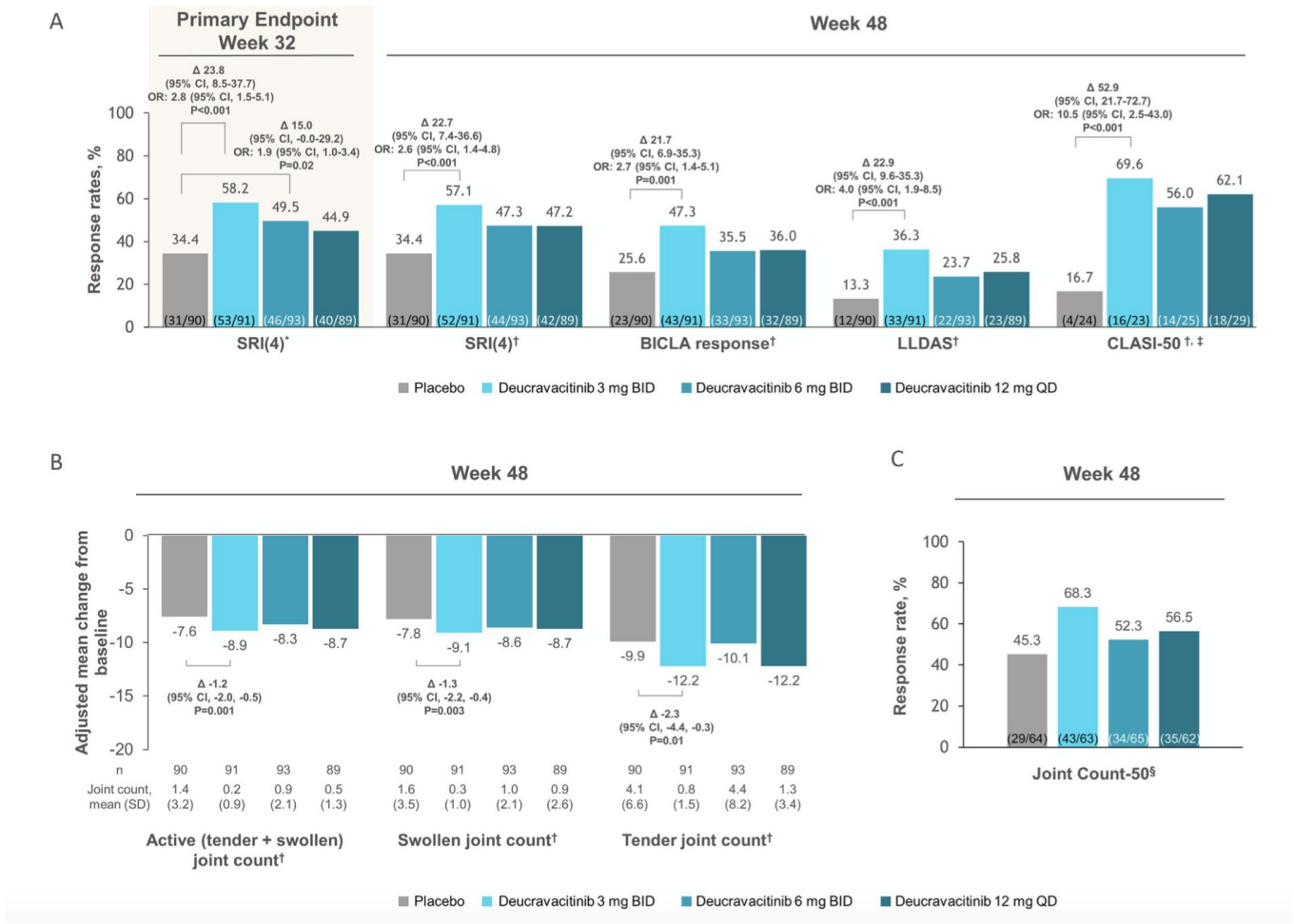
BRAVE-II: phase 3, essai réalisé en double aveugle, randomisé et contrôlé contre placebo, en 3 bras parallèles (identiques BRAVE-I) : Baricitinib 4 mg, Baricitinib 2 mg, ou placebo une fois par jour pendant 52 semaines.

Critère d'évaluation principal = proportion de patients présentant une réponse SRI-4 à 52 semaines. Réduction progressive des glucocorticoïdes était encouragée mais non requise par le protocole.

Aucune différence dans la réponse SRI-4 à 52 semaines : 47 % dans le bras Baricitinib 4 mg odds ratio à 1,07 (IC à 95 % de 0,75 à 1,53], vs 46 % dans le bras placebo.

Aucun des principaux critères secondaires, y compris la diminution progressive des glucocorticoïdes et le délai jusqu'à la première poussée sévère, n'a été atteint.

Deucravacinitib



Essai de phase II

4 bras

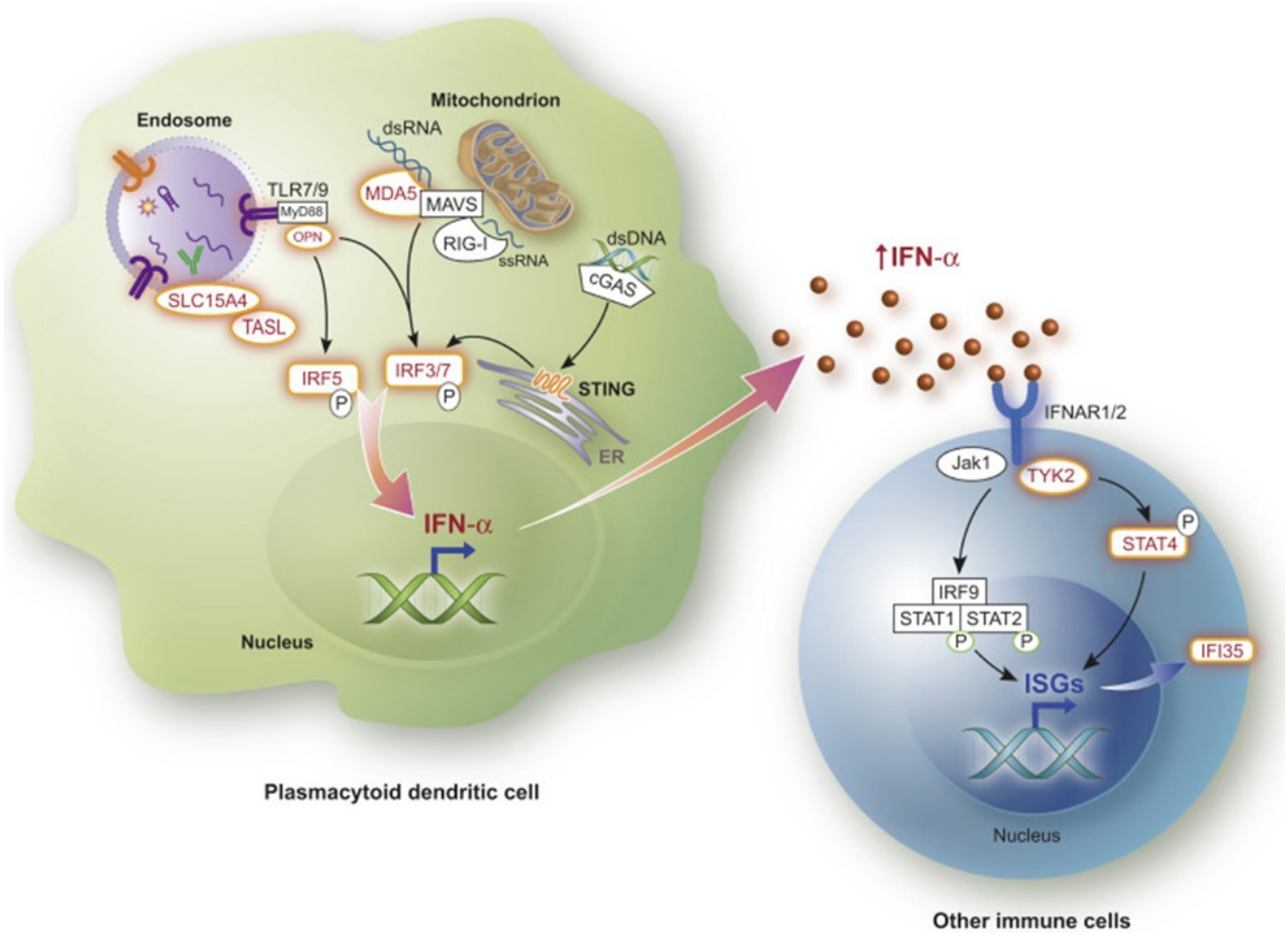
Critère I atteint (SRI4)

MAIS

- Pas d'effet dose
- Pas de réduction sur les articulations
- Acné+++

Morand E. Arthritis Rheumatol. 2023 Feb;75(2):242-252.

Cibler IFN


Endosome
Mitochondrion
dsRNA
TLR7/9
MyD88
OPN
MDA5
MAVS
RIG-I
ssRNA
dsDNA
cGAS
SLC15A4
TASL
IRF5
P
IRF3/7
P
STING
ER
IFN-α
Nucleus
Plasmacytoid dendritic cell
↑IFN-α
IFNAR1/2
Jak1
TYK2
P
STAT4
IRF9
STAT1
STAT2
P
P
ISGs
IFI35
Nucleus
Other immune cells

Cibler l'Interferon

Table 3. Potential therapeutics that target the IFN/neutrophil pathogenic crosstalk in SLE

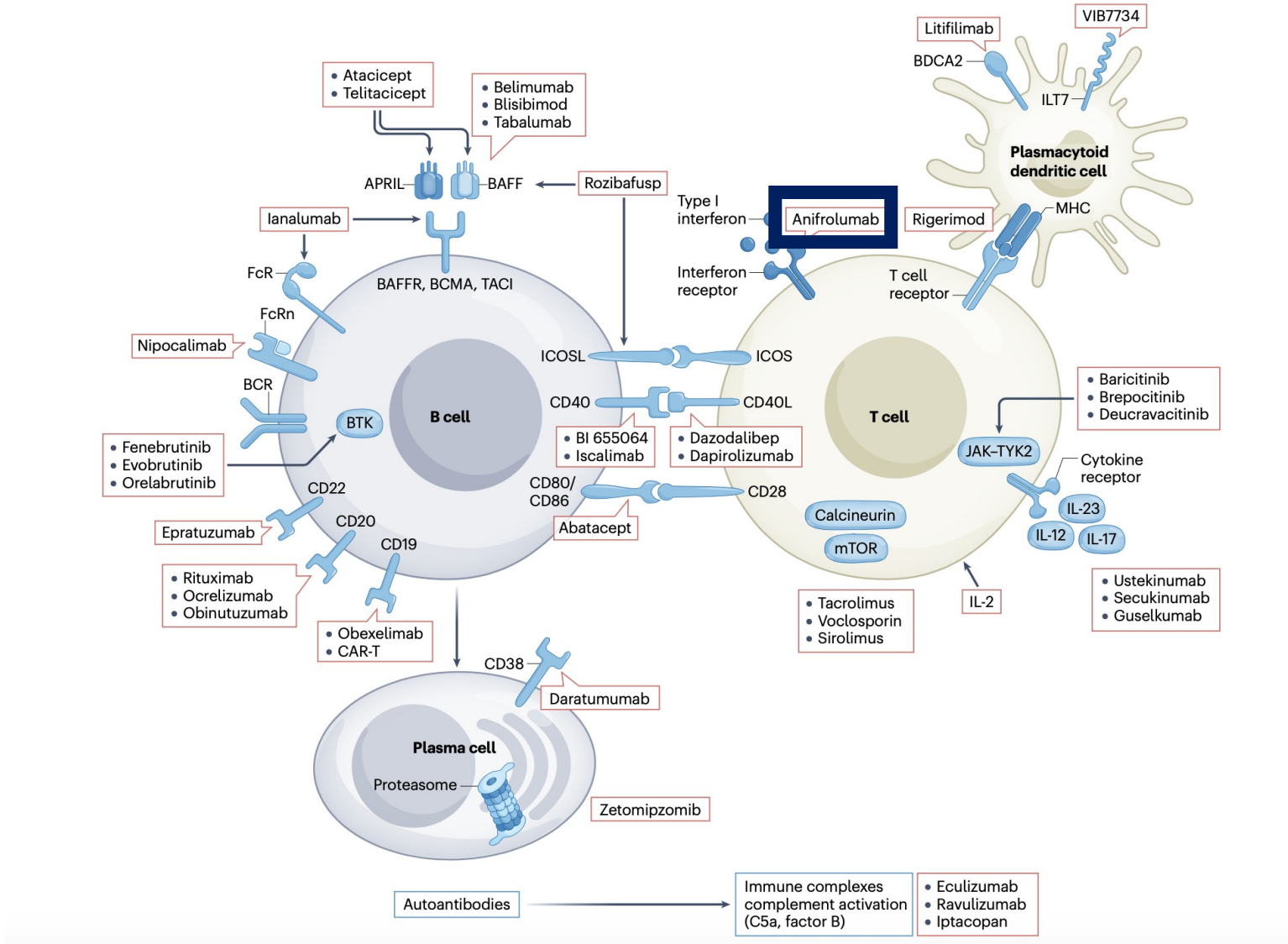
Target/function (molecules)	Effects on neutrophils/type I IFNs	References
ROS scavenger (NAC)	Decreased NET release/decreased IFN responses	173–175
Mitochondrial ROS scavengers and modulators of mitochondrial function (MitoTEMPO, idebenone, MitoQ, inhibitor of VDAC-1 oligomerization)	Decreased NET release; decreased intracellular and extracellular oxidation of nucleic acids with decreased immunogenicity and IFN responses; improvement in mitochondrial function	55, 112–114
MPO inhibitors	Decreased neutrophil recruitment, NET formation, and release of inflammatory cytokines	176
PAD inhibitors	Reduced NET formation	124, 126, 127
Calcineurin inhibitors (cyclosporin A, tacrolimus)	Modulation of calcium pools; reduced NET release	200
DNases	Enzymatic degradation of NETs	181–183
Kindlin-3/integrin inhibitors	Inhibition of neutrophil recruitment and NET release	188
C5a (eculizumab)	Reduced NET formation and neutrophil activation	190, 191
B cells (rituximab, belimumab)	Reduced NET formation and neutrophil activation	192
IFNAR blockade (anifrolumab)	Decreased IFN signaling; reduced NET formation	138, 139, 194
JAK/STAT blockade (tofacitinib, baricitinib, filgotinib, upadacitinib, etc.)	Blockade of signaling of IFN and other proinflammatory cytokines; reduced NET formation	106, 135, 198
IL-17 (secukinumab, ixekizumab, etc.)	Modulation of NET formation and neutrophil migration	186, 187
Antimalarials (hydroxychloroquine, chloroquine)	Decreased NET formation; weak type I IFN inhibition through modulation of endosomal TLRs and cGAS/STING	129

Cibler l'Interferon

Clinical-stage drugs targeting IFN-α or IFNR.

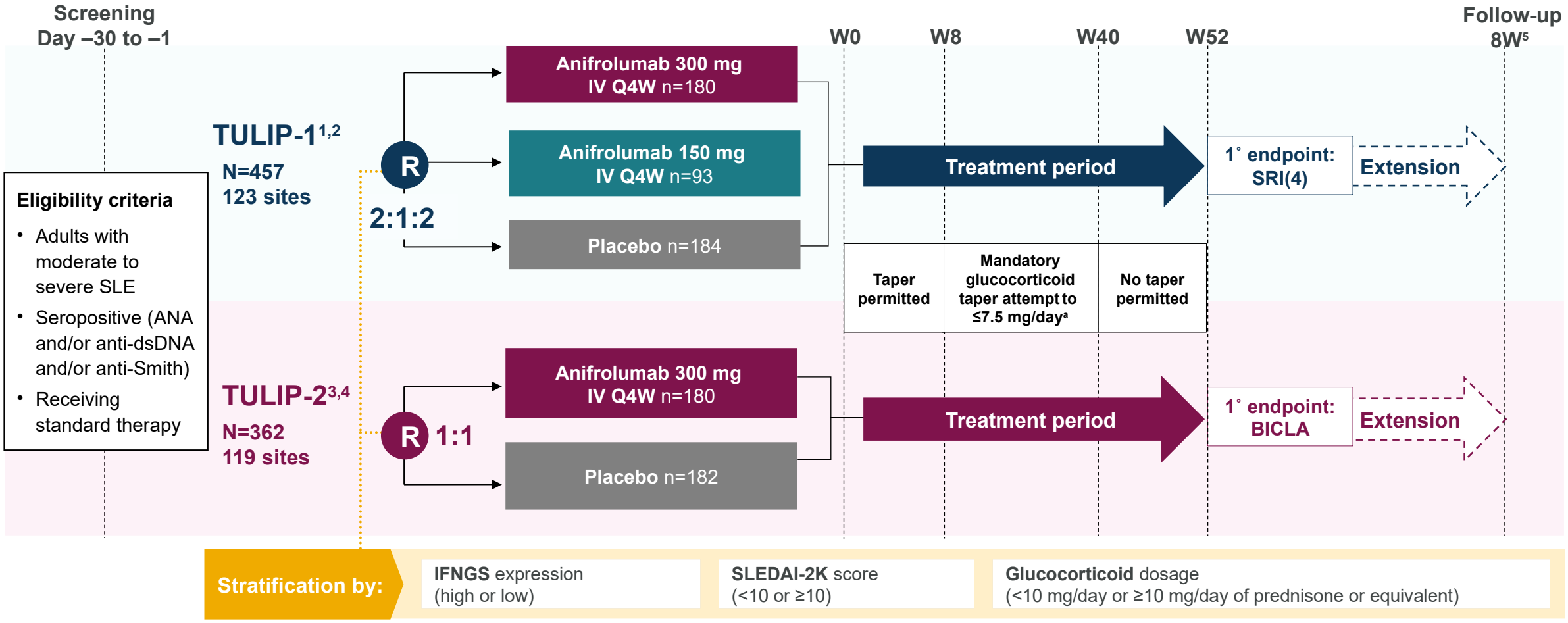
Drug	Characteristics	Disease	Study	Patient number (% with high basal IGS)	Doses and administration regimen	Main biological and clinical results	Current status	Refs
Targeting IFN-α								
AGS-009; Argos Therapeutics	Humanized IgG4 mAb. Binds a broad range of IFN-α subtypes	SLE	Phase Ia; NCT-00960362	*N* = 25 (80%)	0.01–30 mg/kg IV	27-gene IGS score: significant neutralization at doses > 0.6 mg/kg; no quantitative data available; no clinical evaluation reported	Terminated by sponsor	33
Sifalimumab; MedImmune-AstraZeneca	Fully human IgG1 mAb. Binds most IFN-α subtypes	SLE	Phase I; NCT-00299819	*N* = 69 (58%)	0.3–30 mg/kg IV	21-gene IGS score: dose-dependent inhibition (36–78%) in blood; trend for improvement in disease activity (flare occurrence) versus placebo	Discontinued for strategic refocusing to anifrolumab	34–37
		SLE	Phase I; NCT-00482989	*N* = 161 (75%)	0.3–10 mg/kg IV	21-gene IGS score: sustained and dose-dependent inhibition (15–38%) in blood; trend for improvement in disease activity (SELENA-SLEDAI) in patients with high IGS neutralization		
		SLE	Phase IIb; NCT-01283139	*N* = 431 (81%)	200–1200 mg IV	No evaluation of IGS neutralization; primary endpoint met (SRI-4 at W52); disease activity improved (CLASI, BICLA composite score, SLEDAI-2 K); no effect in patients with low baseline IGS		
		DM/PM	Phase Ib; NCT-00533091	*N* = 72 (75%)	0.3–10 mg/kg IV	13-gene IGS score: sustained inhibition in blood (20–98%) and muscle (25–98%); muscle strength improved in patients with high IGS neutralization; disappearance of muscle lymphocyte infiltrates		
Rontalizumab; Genentech	Humanized IgG1 mAb; binds most IFN-α subtypes	SLE	Phase I; NCT00541749	*N* = 60 (50%)	0.3–10 mg/kg IV	7-gene IGS score: dose-dependent inhibition in blood (2.1–55.5%); no change in expression of correlated proteins, no effect on autoantibodies levels	Discontinued (lack of efficacy)	38,39
			Phase II; NCT00962832	*N* = 238 (76%)	300 mg SC or 750 mg IV	No evaluation of IGS; primary clinical endpoint not met		
JNJ-59920839; Janssen	Fully human IgG1 mAb; binds 11 out of 13 IFN-α subtypes, and IFN-ω	SLE	Phase Ib; NCT02609789	*N* = 28 (100%)	10 mg/kg IV	IGS: rapid inhibition in blood (50–74%); trend for efficacy at day 100 on SRI-4, SLEDAI-2 K, PGA, and SRI-50	Ongoing; no recent reports of development	42
S95021; Servier	Fully human IgG1 mAb; binds all IFN-α subtypes	SLE, pSS	Phase I in preparation	NA	NA	Pan IFN-α neutralization in picomolar range; inhibition of STAT-1 phosphorylation and IGS neutralization in human PBMCs treated with IFN-α subtypes or plasmas from patients with SLE/pSS	Ongoing	41
IFN-α-kinoid; Neovacs	Vaccination with recombinant IFN-α2b-kinoid leading to induction of endogenous anti-IFN-α antibodies	SLE	Phase I; NCT01058343	*N* = 28 (64%)	30–240 μg IM	21-gene IGS score: mean neutralization ~ 20%; trend to normalize complement C3 level; no difference in disease activity	Ongoing; Phase III announced	43–44
		SLE	Phase II; NCT02665364	*N* = 185 (100%)	240 μg (D0, 7, 28) and 120 μg at W12 and W24 IM	21-gene IGS score: mean neutralization ~ 30%; no difference in proportion of responders defined by BICLA; trend to difference in patients with neutralizing antibodies		

Anifrolumab



Anticorps monoclonal ciblant le récepteur des interférons de type I

Cibler IFN: Anifrolumab
TULIP-1 and TULIP-2 Had Similar Trial Designs



[a]For patients with baseline glucocorticoid dosage ≥10 mg/day prednisone or equivalent.

1. Furie RA, et al. Supplementary Appendix. *Lancet Rheumatol*. 2019;1:e208–19. 2. Furie RA, et al. *Lancet Rheumatol*. 2019;1:e208–19.
3. Morand EF, et al. *N Engl J Med*. 2020;382:211–21. 4. Morand EF, et al. Supplementary Appendix. *N Engl J Med*. 2020;382:211–21.
5. Tanaka Y, Tummala R. *Mod Rhematol*. 2020;1–12;doi:10.1080/14397595.2020.1812201.

TULIP-1 and TULIP-2 Had Different Primary Endpoints

	TULIP-1[1]	TULIP-2[2]
Primary Endpoint	**SRI(4) response at Week 52** • SRI(4) response is driven primarily by the SLEDAI-2K index[3,4]	**BICLA response at W52** • BICLA response is driven primarily by the BILAG-2004 index[3,4]
Key secondary endpoints (unique)	• SRI(4) response in IFNGS-high patients at Week 52 • SRI(4) response at Week 24	• BICLA response in IFNGS-high patients at Week 52 • ≥50% reduction in both swollen and tender joints[a]
Key secondary endpoints (shared)	• Reduction in the glucocorticoid dosage to ≤7.5 mg/day sustained from Week 40 to 52[b] • ≥50% reduction in CLASI-activity score at Week 12[c] • Reduced annualized flare rate through Week 52[d]	

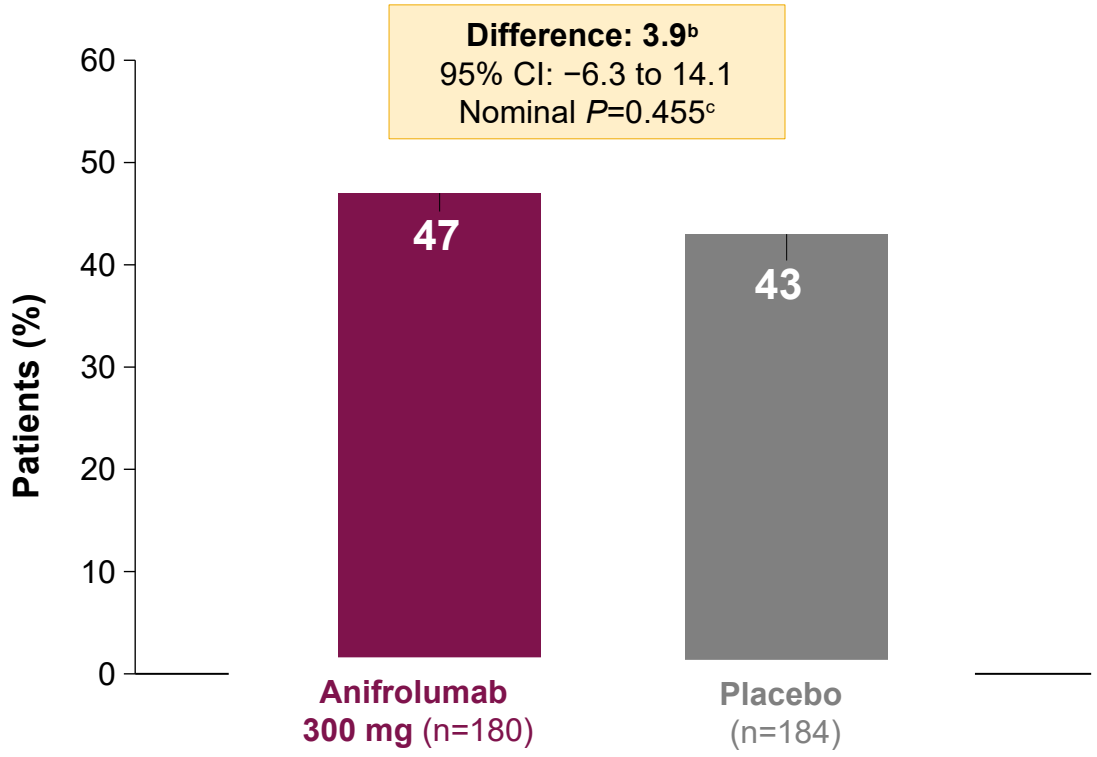
[a]Among patients with ≥6 swollen/tender joints at baseline. [b]Among patients with a baseline dosage of ≥10 mg/day. [c]Among patients with moderate to severe cutaneous activity (CLASI ≥10) at baseline. [d]A flare was defined as at least one new BILAG-2004 A or at least two new BILAG-2004 B organ domain scores vs the previous visit.

1. Furie RA, et al. *Lancet Rheumatol.* 2019;1:e208–19. 2. Morand EF, et al. *N Engl J Med.* 2020;382:211–21. 3. Ceccarelli F, et al. *Autoimmun Rev.* 2015;14(7):601-608. 4. Castrejón I, et al. *Clin Exp Rheumatol*. 2014;32(5 Suppl 85):S-85-95.

Reduction in Overall Disease Activity Across the Pivotal Trials

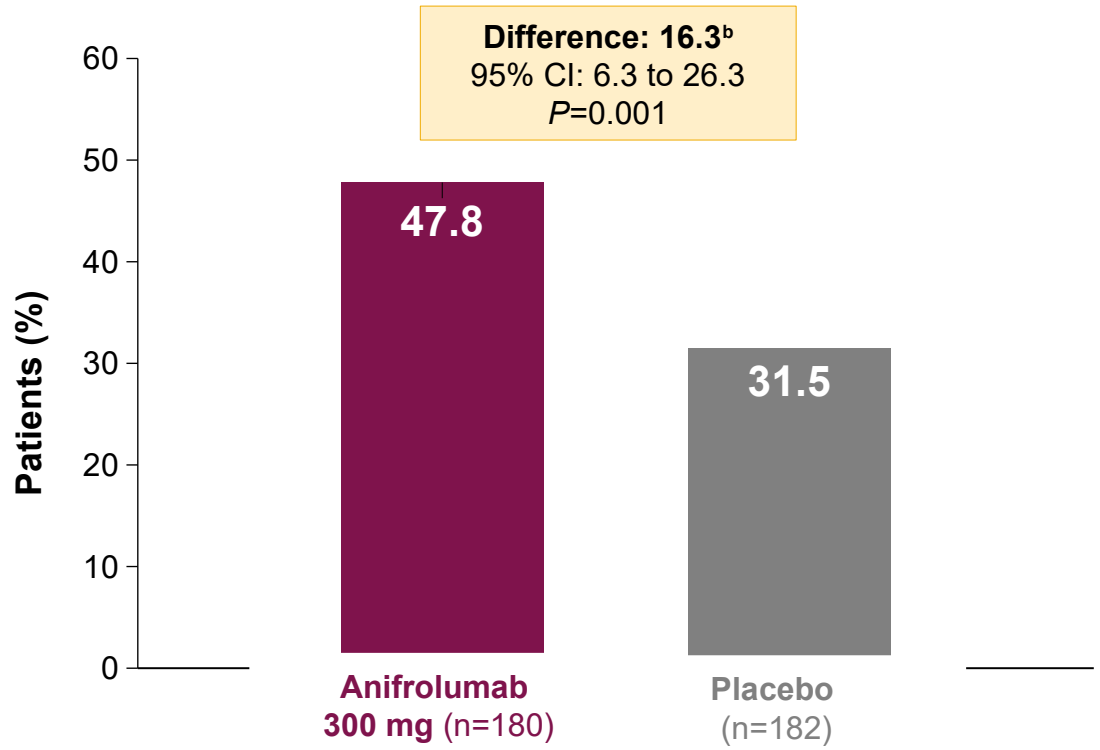
Primary Endpoint Results at Week 52

TULIP-1 Primary Endpoint: SRI(4) Response[1,a]



The primary endpoint of TULIP-1, SRI(4) response at Week 52, was not statistically significant[1]

TULIP-2 Primary Endpoint: BICLA Response[2]



The primary endpoint of TULIP-2, BICLA response at Week 52, was statistically significant[2]

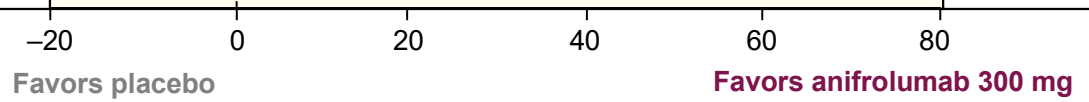
[a]Data shown are from the amended rules for restricted medications analysis, which corrected for inappropriately classified NSAID use early in the trial. [b]Responder rates, treatment differences, 95% CIs and *P*-values were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors of Systemic Lupus Erythematosus Disease Activity Index-2000 score at screening, glucocorticoid dosage at baseline, and type I interferon gene signature status at screening. [c]As the primary outcome was not significant per the prespecified analysis plan (unamended restricted medication rules), all other comparisons were not formally compared and are considered nonsignificant.

1. Furie RA, et al. *Lancet Rheumatol*. 2019;1:e208–219. 2. Morand EF, et al. *N Engl J Med*. 2020;382:211–221.

Anifrolumab Efficacy Across the Clinical Trial Program

Primary Endpoints

Endpoint		Anifrolumab 300 mg n/N (%)	Placebo n/N (%)	Treatment Difference (95% CI)	*P*-value
BICLA, Week 52 (primary endpoint of TULIP-2)[1]	MUSE[2]	53/99 (53.5)	26/101 (25.7)	15.1, **28.0**[b], 41.0	NR[c]
	TULIP-1[3,a]	83/180 (46.1)	54/184 (29.6)	6.7, **16.4**, 26.2	NR
	TULIP-2[4]	86/180 (47.8)	57/182 (31.5)	6.3, **16.3**, 26.3	0.001[4]
SRI(4), Week 52 (primary endpoint of TULIP-1)[1]	MUSE[2]	62/99 (62.6)	41/102 (40.2)	9.0, **22.4**[b], 35.9	NR[c]
	TULIP-1[3,a]	84/180 (46.9)	79/184 (43.0)	–6.3, **3.9**, 14.1	0.455[3,a]
	TULIP-2[4]	100/180 (55.5)	68/182 (37.3)	8.1, **18.2**, 28.3	<0.001[5,c]

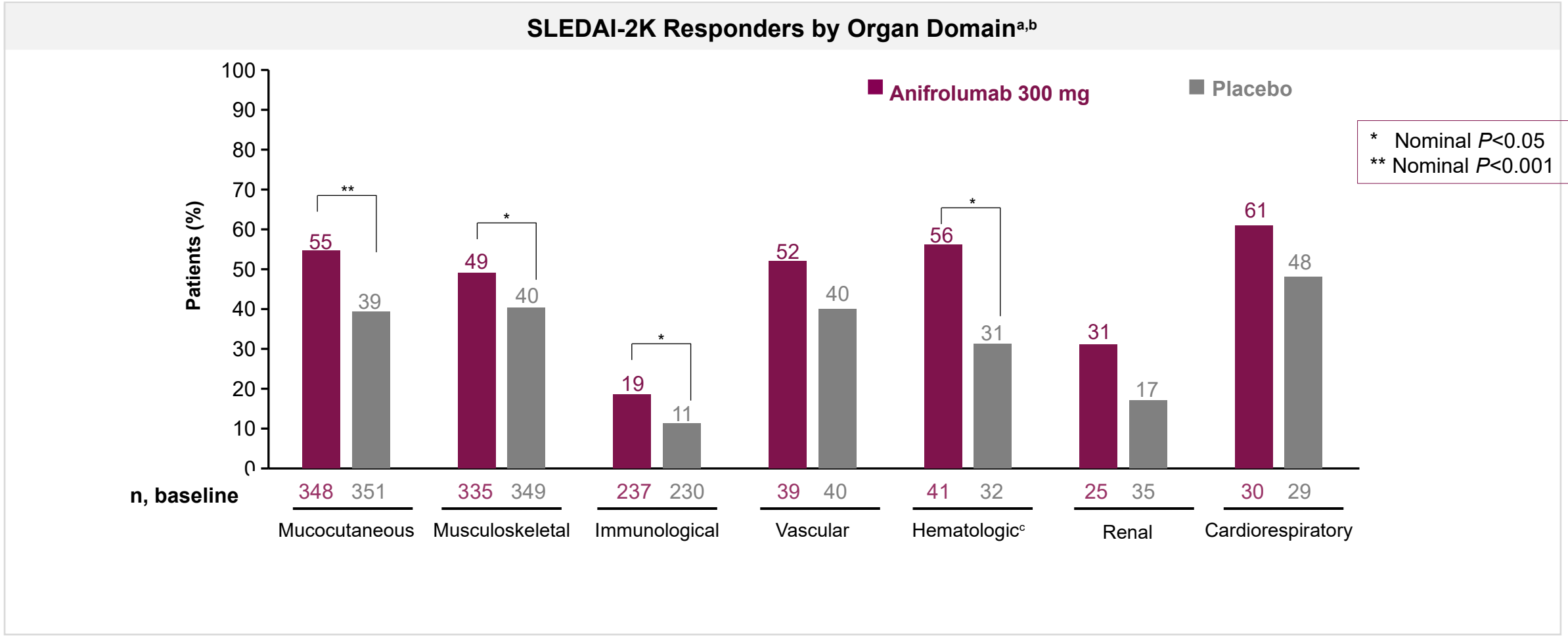


Analytic methods and definitions differ across trials.
[a]The primary endpoint of TULIP-1, SRI-4 response at Week 52, was not statistically significant. Data shown are from the amended rules for restricted medications analysis, which corrected for inappropriately classified NSAID use early in the trial. Therefore, the presented *P*-value is nominal. [b]The primary publication of MUSE[2] expressed these data as odds ratios rather than CIs.
[c]*P*-value not adjusted for multiplicity.

1. Tanaka Y, Tummala R. *Mod Rhematol.* 2020;1–12;doi:10.1080/14397595.2020.1812201. 2. Furie R, et al. *Arthritis Rheumatol.* 2017;69:376–386. 3. Furie RA, et al. *Lancet Rheumatol.* 2019;1:e208–219.
4. Morand EF, et al. *N Engl J Med.* 2020;382:211–221. 5. Morand EF, et al. Supplementary Appendix. *N Engl J Med.* 2020;382:211–221.

SLEDAI-2K Organ Domain Responses at Week 52

Pooled TULIP-1 and TULIP-2

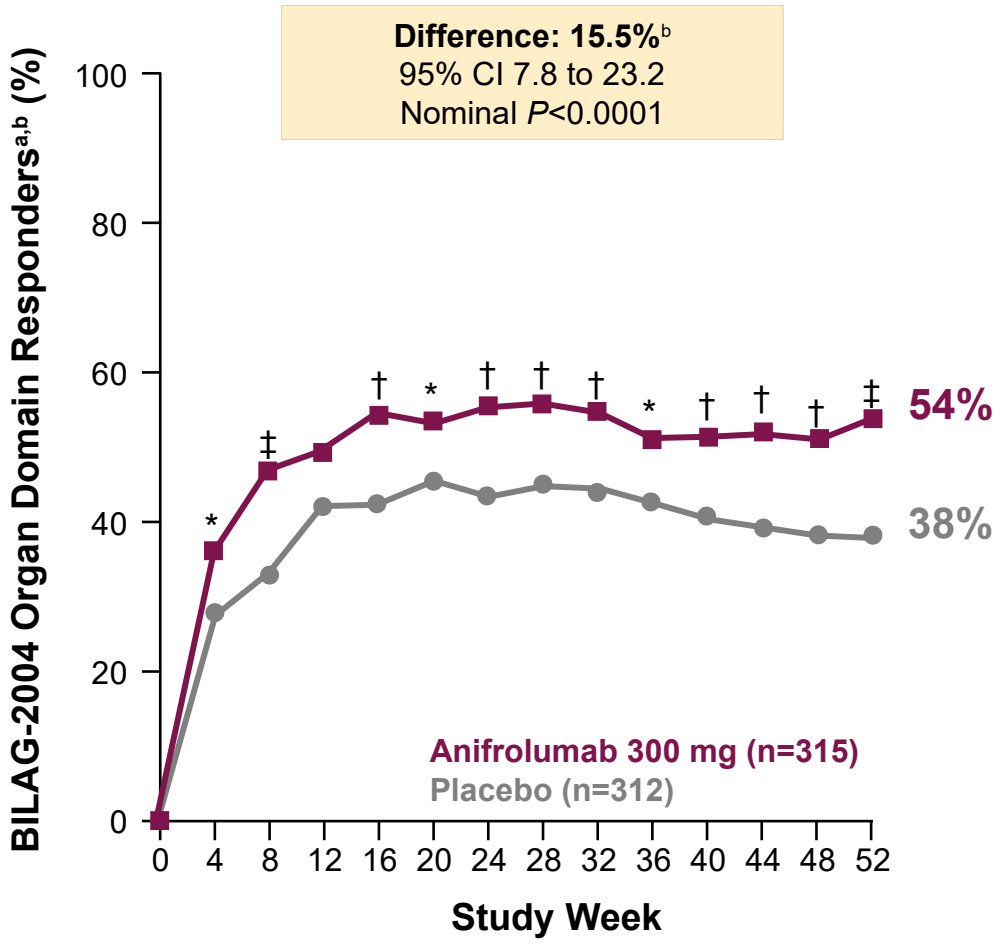


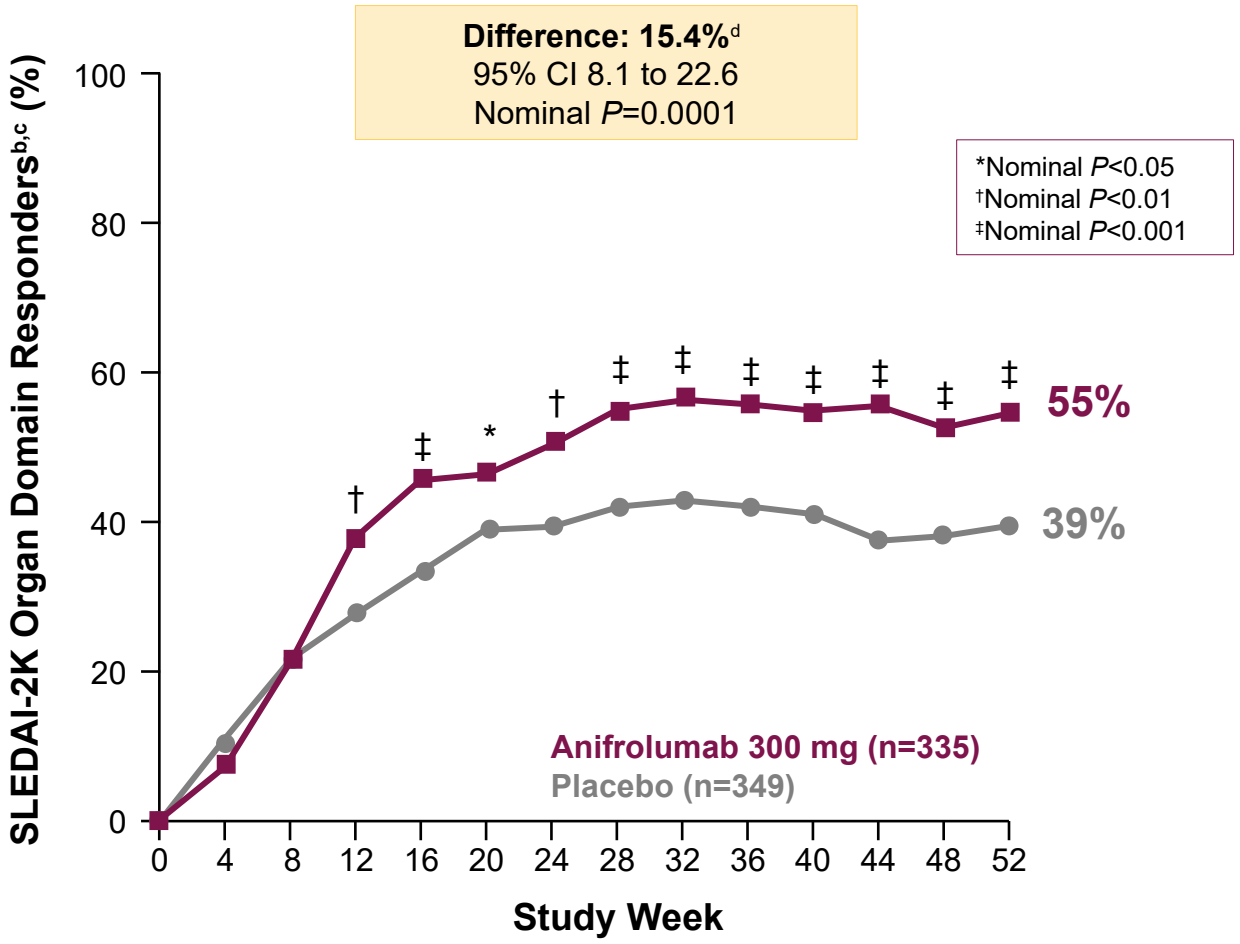
[a]SLEDAI-2K organ domain responder was defined as a reduction in baseline SLEDAI-2K organ domain score. SLEDAI-2K central nervous system domain was not included because there were too few patients in each treatment group. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]Excludes fever.

Morand EF, et al. Online ahead of print. *Lancet Rheumatol.* 2022.

Mucocutaneous Organ Domain Improvement at 52 Weeks

Pooled TULIP-1 and TULIP-2





[a]BILAG-2004 responders are defined as patients with a reduction in baseline BILAG-2004 organ domain A or B score at each timepoint. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score.

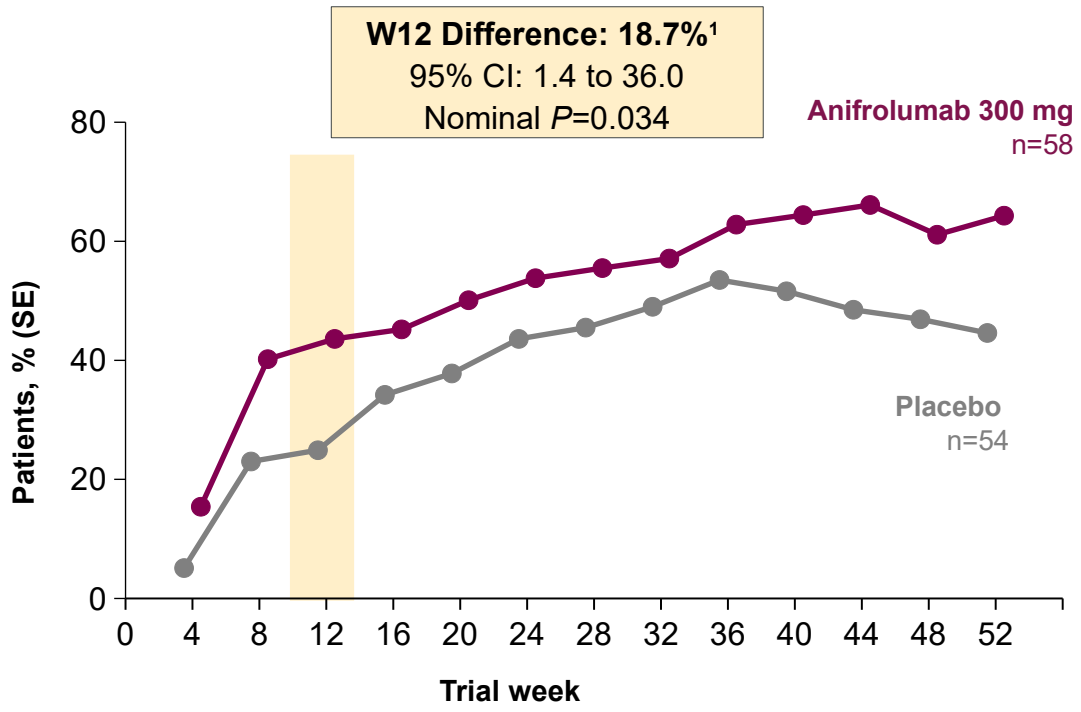
Morand EF. Article published online ahead of print February 3, 2022. *Lancet Rheumatol*. 2022.

CLASI-A Responses Over Time

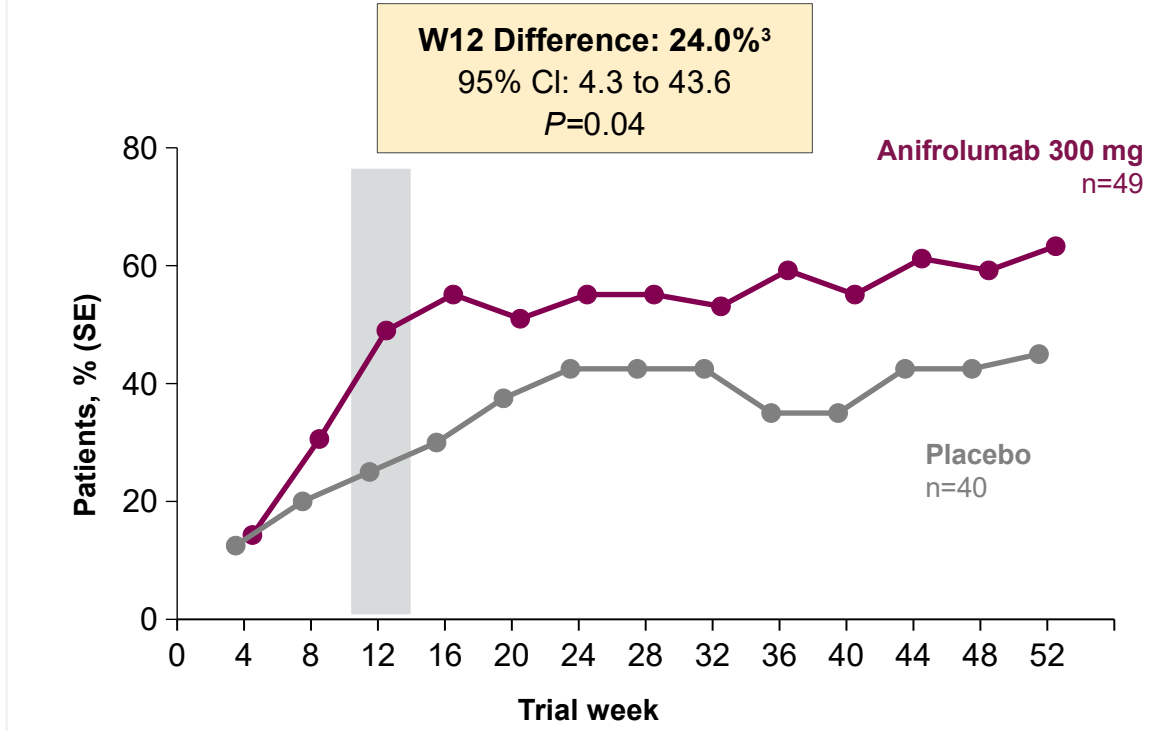
TULIP-1 and TULIP-2

Proportion of Patients With ≥50% Reduction in CLASI-A Score[a] from Baseline, by Timepoint and at Week 12

TULIP-1[1,2,b,c]



TULIP-2[2,3,d]



[a]Among patients with moderate to severe skin disease at baseline (CLASI activity score ≥10). [b]Data shown are from the amended rules for restricted medications analysis. [c]The primary endpoint of TULIP-1, SRI(4) response at Week 52, was not statistically significant; data for the CLASI activity score endpoint were not formally compared. [d]Responder rates, treatment differences, associated 95% CIs, and *P*-values were calculated using a stratified Cochran–Mantel–Haenszel approach with stratification factors matching those in the TULIP studies.

1. Furie RA, et al. *Lancet Rheumatol.* 2019;1:e208–e219. 2. Data on File, REF-120095, AZPLP. 3. Morand EF, et al. Supplementary Appendix. *N Engl J Med*. 2020;382:211–221.

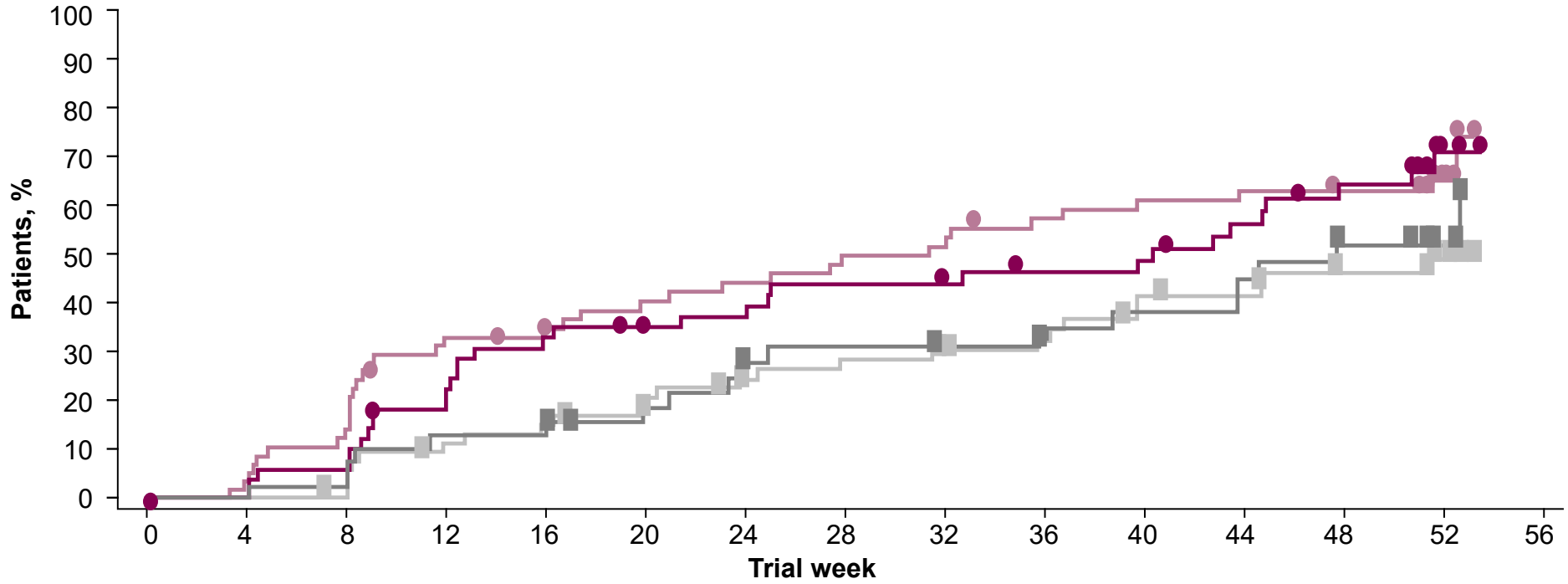
Time to Onset of Sustained CLASI-A Response

TULIP-1 and TULIP-2

Patients With CLASI-A Response Sustained Through Week 52[a]

TULIP-1[b]
HR: 1.91
95% CI: 1.14 to 3.27

TULIP-2[b]
HR: 1.55
95% CI: 0.87 to 2.85



Number at risk:

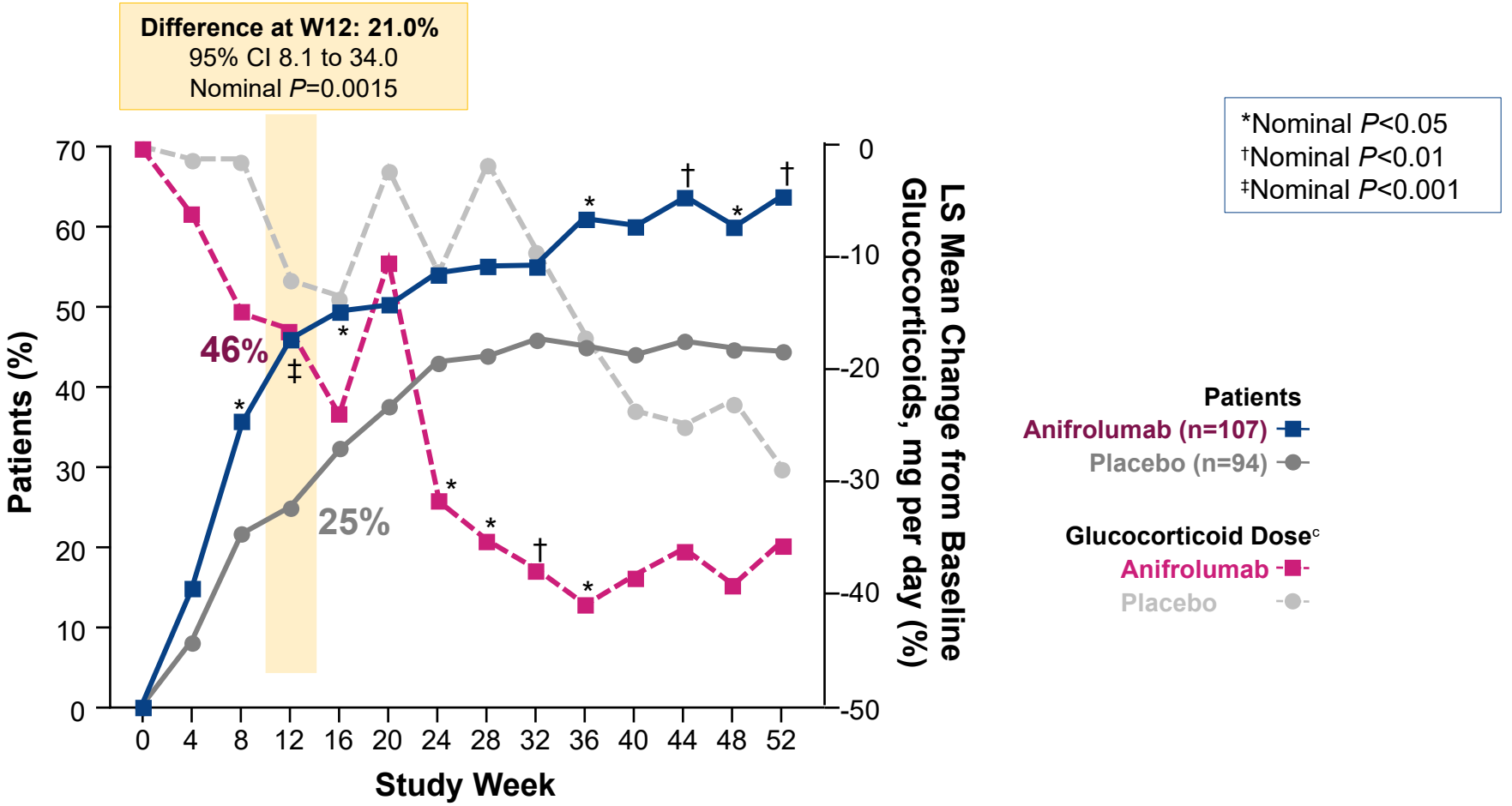
TULIP-1	Anifrolumab 300 mg	58	56	50	38	36	32	30	28	26	22	21	20	19	16	0
	Placebo	54	54	54	48	46	43	39	36	35	33	28	25	22	18	0
TULIP-2	Anifrolumab 300 mg	49	49	46	39	32	30	28	25	25	22	22	17	14	8	0
	Placebo	40	40	38	32	32	27	23	21	20	20	18	18	15	10	0

[a]A response was defined as ≥50% reduction in CLASI activity score among patients with at least moderately active skin disease (CLASI activity score ≥10) at baseline. [b]HRs and 95% CIs were estimated using a Cox regression model with covariates of treatment group and stratification factors as covariates.

Werth VP, et al. Oral presentation 0985. Presented at: American College of Rheumatology Annual Meeting (All Virtual); November 5–9, 2020.

CLASI-A Response Over Time[a,b]

Pooled TULIP-1 and TULIP-2

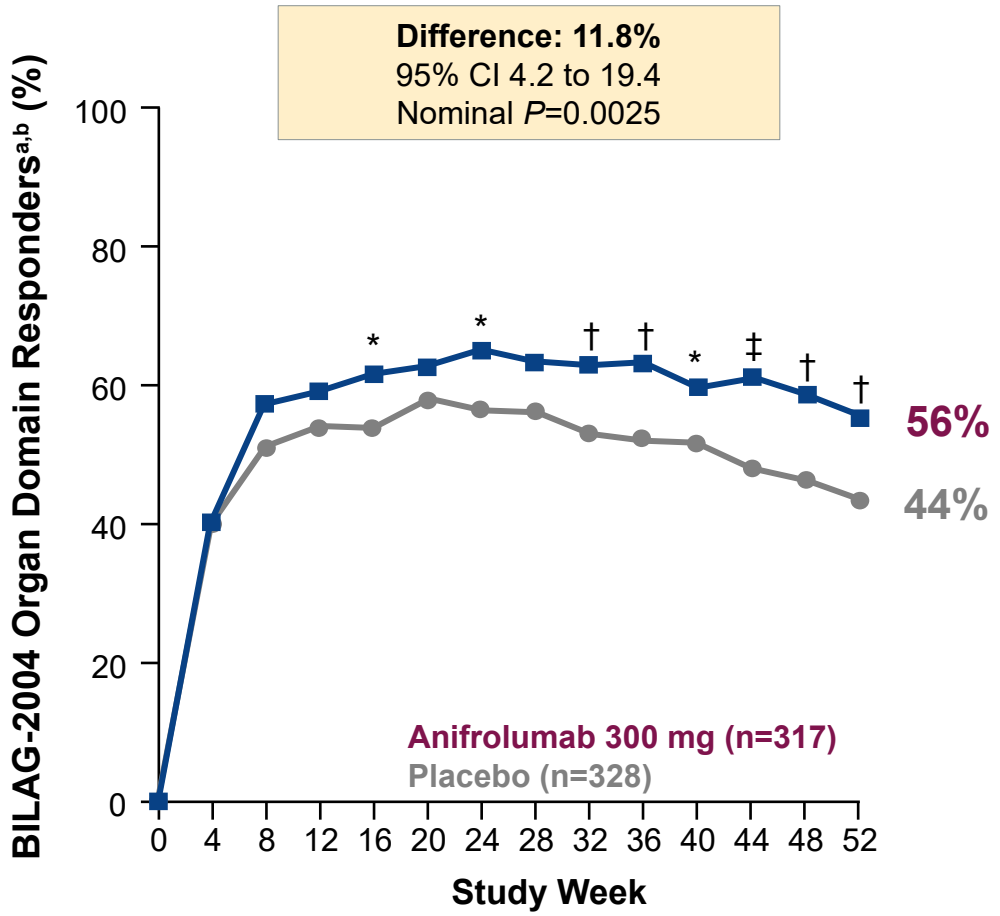


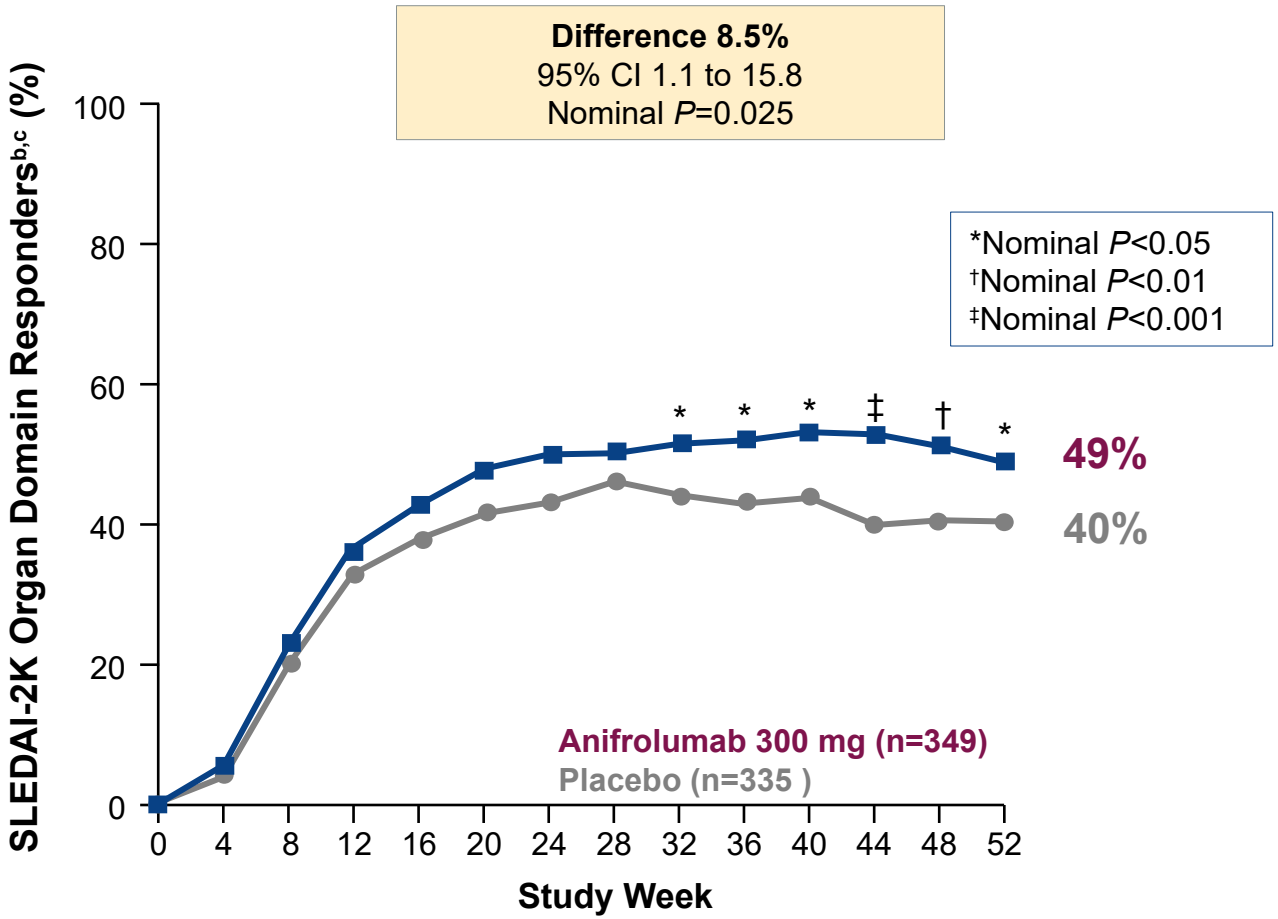
[a]CLASI response is defined as 50% or more reduction in CLASI-A from baseline for patients with a baseline CLASI-A of 10 or more. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]Percentage changes from baseline oral glucocorticoid dose are expressed as LS means. Negative LS mean values indicate a reduction in daily dose.

Morand EF. Article published online ahead of print February 3, 2022. *Lancet Rheumatol*. 2022.

Musculoskeletal Organ Domain Improvement at 52 Weeks

Pooled TULIP-1 and TULIP-2



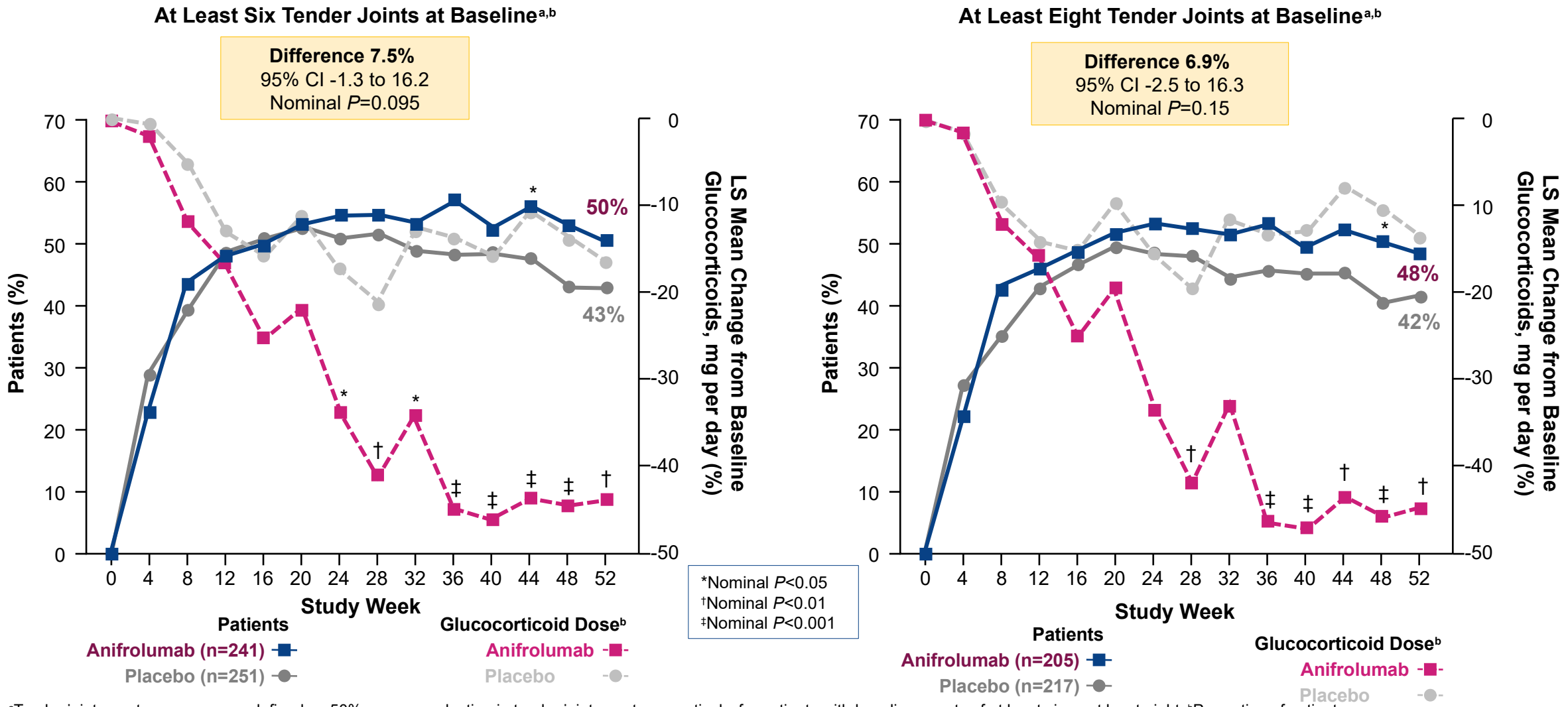


[a]BILAG-2004 responders are defined as patients with a reduction in baseline BILAG-2004 organ domain A or B score at each timepoint. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach with stratification factors matching those in the TULIP studies. [c]SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score.

Morand EF. Article published online ahead of print February 3, 2022. *Lancet Rheumatol*. 2022.

Tender Joints at Week 52

Pooled TULIP-1 and TULIP-2



[a]Tender joint count responses are defined as 50% or more reduction in tender joint count, respectively, for patients with baseline counts of at least six or at least eight. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]Percentage changes from baseline oral glucocorticoid dose are expressed as LS means. Negative LS mean values indicate a reduction in daily dose.

Morand EF. Article published online ahead of print February 3, 2022. *Lancet Rheumatol*. 2022.

Anifrolumab Efficacy Across the Clinical Trial Program

Secondary Endpoints

Endpoints		Anifrolumab 300 mg n/N (%)	Placebo n/N (%)	Treatment Difference (95% CI)	*P*-value
Sustained glucocorticoid reduction[c]	MUSE[1]	31/55 (56.4)	17/64 (26.6)	12.8, 29.8[b], 46.8	NR
	TULIP-1[1,2,a]	50/103 (48.8)	33/102 (32.1)	3.5, 16.7, 29.8	0.013[2]
	TULIP-2[1,3]	45/87 (51.5)	25/83 (30.2)	6.8, 21.2, 35.7	0.01[1]
≥50% reduction in CLASI, Week 12	MUSE[1]	13/27 (48.1)	4/26 (15.4)	9.4, 32.8[b], 52.2	NR
	TULIP-1[1,2,a]	25/58 (43.6)	14/54 (24.9)	1.4, 18.7, 36.0	NS[2]
	TULIP-2[1,3]	24/49 (49.0)	10/40 (25.0)	4.3, 24.0, 43.6	0.04[1]
≥50% reduction in active joints, Week 52	MUSE[1]	42/58 (72.5)	24/58 (41.6)	13.6, 30.9[b], 48.2	NR
	TULIP-1[1,3,a]	37/70 (52.9)	22/68 (32.4)	4.7, 20.7, 36.7	NR
	TULIP-2[1,3]	30/71 (42.2)	34/90 (37.5)	–10.6, 4.7, 20.0	NS[2]

Favors placebo ← –40 –20 0 20 40 60 → Favors anifrolumab

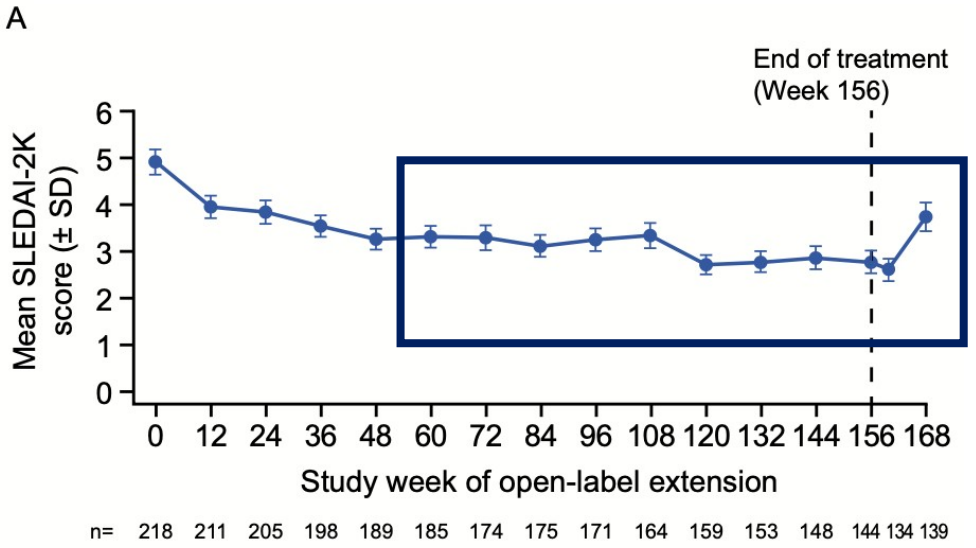
Annualized flare rate	MUSE[1]	0.53	0.72	1.31, 0.80[b], 0.49	NR
	TULIP-1[1,2,a]	0.60	0.72	1.14, 0.83, 0.60	NS[2]
	TULIP-2[1,3]	0.43	0.64	0.94, 0.67, 0.48	NS[1]

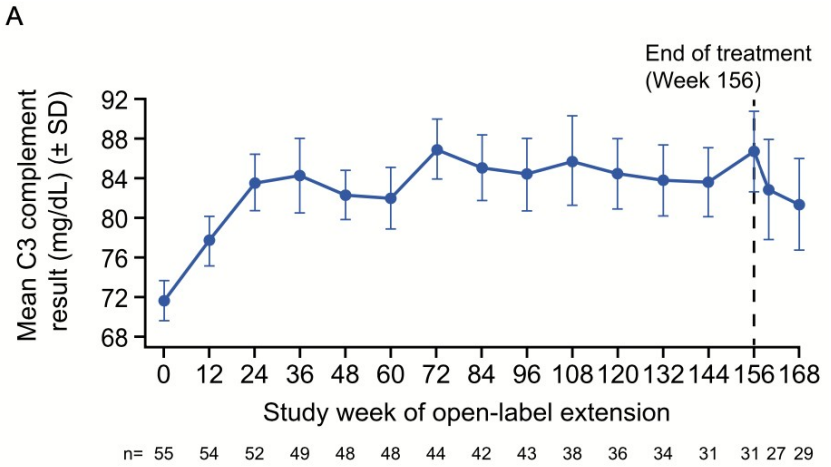
Fewer flares with placebo ← 1.5 1.25 1 0.75 0.5 0.25 → Fewer flares with anifrolumab

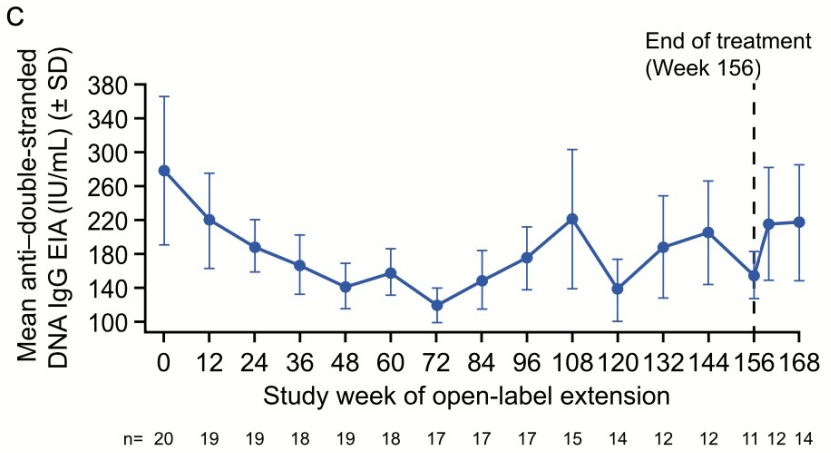
Analytic methods and definitions differ across trials.
[a]The primary endpoint of TULIP-1, SRI-4 response at Week 52, was not met, and therefore secondary endpoints were not formally tested per the statistical plan and are descriptive only. Data shown are from the amended rules for restricted medications analysis, which corrected for inappropriately classified NSAID use early in the trial.[2] [b]The primary publication of MUSE[5] expressed these data as odds ratios rather than CIs.

1. Tanaka Y, Tummala R. *Mod Rhematol.* 2020;1–12;doi:10.1080/14397595.2020.1812201. 2. Furie RA, et al. *Lancet Rheumatol.* 2019;1:e208–219. 3. Morand EF, et al. *N Engl J Med.* 2020;382:211–221. 4. Furie R, et al. *Arthritis Rheumatol.* 2017;69:376–386. 5. Furie R, et al. *Arthritis Rheumatol.* 2017;69:376–386.

Anifrolumab extension phase II







2 années supplémentaires de traitement après MUSE

Maintien de l'efficacité clinique et sérologique

Et de l'effet sur la qualité de vie

Chatham WW. Arthritis Rheumatol. 2021 May;73(5):816-825.

Anifrolumab Safety Across the Clinical Trial Program

Pooled TULIP-1, TULIP-2 and MUSE Trials

Patients, n (%)[a]		Anifrolumab 300 mg n=459	Placebo n=466
Any AE		399 (86.9)	370 (79.4)
Serious AE		54 (11.8)	78 (16.7)
AE with outcome of death		2 (0.4)	0
AE leading to discontinuation		19 (4.1)	24 (5.2)
Any AE occurring in ≥5% of patients in the anifrolumab group	Nasopharyngitis[b]	75 (16.3)	44 (9.4)
	Upper respiratory tract infection[b]	71 (15.5)	45 (9.7)
	Urinary tract infection	55 (12.0)	63 (13.5)
	Bronchitis[b]	45 (9.8)	20 (4.3)
	Infusion-related reaction	43 (9.4)	33 (7.1)
	Headache	37 (8.1)	45 (9.7)
	Herpes zoster[b]	**28 (6.1)**	**6 (1.3)**
	Back pain	24 (5.2)	20 (4.3)
	Sinusitis	24 (5.2)	24 (5.2)
	Cough	23 (5.0)	15 (3.2)

[a]An AE during the intervention period was defined as an AE with a date of onset on or after the day of the first dose of anifrolumab or placebo and on or before the day of the last dose of anifrolumab or placebo plus 28 days. [b]AEs more common in the anifrolumab 300 mg group than in the placebo group (ie, ≥5% difference, or ≥5% incidence in the anifrolumab group and at least twice the reported rate of the placebo group).

Tummala R, et al. *Lupus Sci Med*. 2021:8:e000464. doi:10.1136/lupus-2020-000464.

Anifrolumab Safety Across the Clinical Trial Program

Pooled TULIP-1, TULIP-2 and MUSE Trials

AEs of special interest, n (%)[a,b,c]	Anifrolumab 300 mg n=459	Placebo n=466
Non-opportunistic serious infection	22 (4.8)	26 (5.6)
Opportunistic infection	1 (0.2)	1 (0.2)
Anaphylaxis	0	0
Malignancy	3 (0.7)	3 (0.6)
Herpes zoster	28 (6.1)	6 (1.3)
Active TB	0	0
Latent TB[d]	4 (0.9)	1 (0.2)
Influenza	12 (2.6)	9 (1.9)
Non-SLE-related vasculitis	0	2 (0.4)
Major adverse cardiovascular event	1 (0.2)	3 (0.6)

[a]An AE during the intervention period was defined as an AE with a date of onset on or after the day of the first dose of anifrolumab or placebo and on or before the day of the last dose of anifrolumab or placebo plus 28 days. [b]AEs of special interest differed between the individual MUSE and TULIP trials and were identified using standardized MedDRA queries (SMQ) and custom Preferred Term groupings. [c]Hypersensitivity was included as an AE of special interest in MUSE but not in the TULIP trials and is not included in this table. [d]Patients with latent TB (not active TB) were interferon gamma release assay positive without radiographic or clinical manifestations of active TB.

Tummala R, Abreu G, Pineda L, et al. *Lupus Sci Med*. 2021:8:e000464. doi:10.1136/lupus-2020-000464.

Anifrolumab long-terme

Table 2. AEs, SAEs, deaths, AESIs, and EAIRs in any category during treatment and follow-up during weeks 52–216 (LTE years 2–4)*

	LTE anifrolumab 300 mg (n = 257; exposure 683.5 patient-years†)		LTE placebo (n = 112; exposure 250.3 patient-years†)	
	No. (%)	EAIR (per 100 patient-years)‡	No. (%)	EAIR (per 100 patient-years)‡
Any AE	226 (87.9)	33.1	94 (83.9)	37.6
Any SAE (including events with outcome of death)	58 (22.6)	8.5	28 (25.0)	11.2
Any AE with outcome of death	3 (1.2)	0.4	1 (0.9)	0.4
Any DAE	17 (6.6)	2.5	8 (7.1)	3.2
Any AE of severe intensity	43 (16.7)	6.3	13 (11.6)	5.2
Any AESI	75 (29.2)	11.0	24 (21.4)	9.6
Any AESI of non-opportunistic serious infections	25 (9.7)	3.7	9 (8.0)	3.6
Any AESI of herpes zoster	23 (8.9)	3.4	7 (6.3)	2.8
Any AESI of latent tuberculosis§	16 (6.2)	2.3	2 (1.8)	0.8
Any AESI of influenza	15 (5.8)	2.2	2 (1.8)	0.8
Any AESI of major acute cardiovascular events¶	5 (1.9)	0.7	3 (2.7)	1.2
Any AESI of malignancy	2 (0.8)	0.3	2 (1.8)	0.8
Any AESI of anaphylaxis	0	0	0	0
Any AESI of opportunistic infections	0	0	3 (2.7)	1.2
Any AESI of vasculitis	0	0	0	0

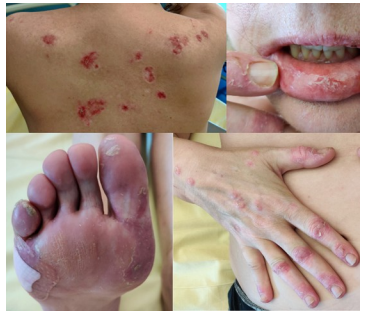
* Data presented are solely from the extension period. Only analyses of descriptive statistics were performed. AE = adverse event; SAE = serious AE; DAE = AE leading to treatment discontinuation; AESI = AE of special interest; LTE = long-term extension.

Effets indésirables similaires (8.5 par traitement-période sous anifro / 11.2 placebo)
Pas plus de cancer ni événements cardiovasculaires
Moins de corticoïdes
Amélioration SLEDAI
Plus de COVID (mais pas graves)

Kalunian KC. Arthritis Rheumatol. 2023 Feb;75(2):253-265.

Anifrolumab : la vraie vie

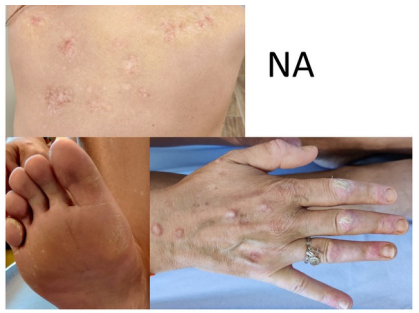
Cas clinique



Poussée cutanée
Thalidomide 50 mg/j**:**
Amélioration +/- complète
Diminution 50mg/j 1j/2
Mauvaise tolérance : constipation, myalgie

Belimumab SC 200 mg/semaine
Arrêt septembre 2021 échec et majoration symptômes dépressifs

Juin 2020 — Avril 2021 — Juin 2021



NA

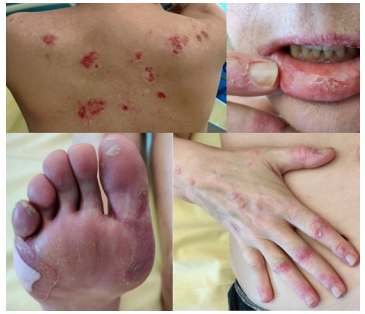
Arrêt thalidomide
Atteinte cutanée + articulaire
Méthotrexate 20mg/semaine +
prednisone 20mg/j

Arrêt mai 2021 : nausées, diarrhées

Discussion alternatives thérapeutiques ?
Mise sous anifrolumab ATU

Anifrolumab : la vraie vie

Cas clinique

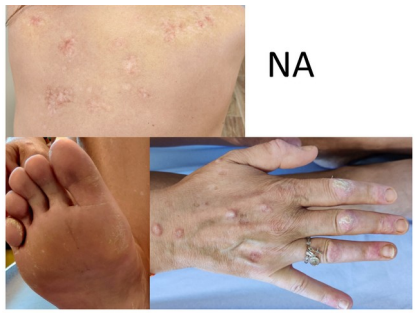


Poussée cutanée
Thalidomide 50 mg/j**:**
Amélioration +/- complète
Diminution 50mg/j 1j/2
Mauvaise tolérance : constipation, myalgie

Belimumab SC 200 mg/semaine
Arrêt septembre 2021 échec et majoration symptômes dépressifs

Mise sous anifrolumab
-Test Farr 9 N<7
-C3, C4 normaux
-CLASI activité 35
-Atteinte articulaire active
NAD=8 BAG=0
-SLEDAI =10
-PGA 2,5

Juin 2020 — Avril 2021 — Juin 2021



NA

Arrêt thalidomide
Atteinte cutanée + articulaire
Méthotrexate 20mg/semaine +
prednisone 20mg/j

Arrêt mai 2021 : nausées, diarrhées

Discussion alternatives thérapeutiques ?
Mise sous anifrolumab ATU

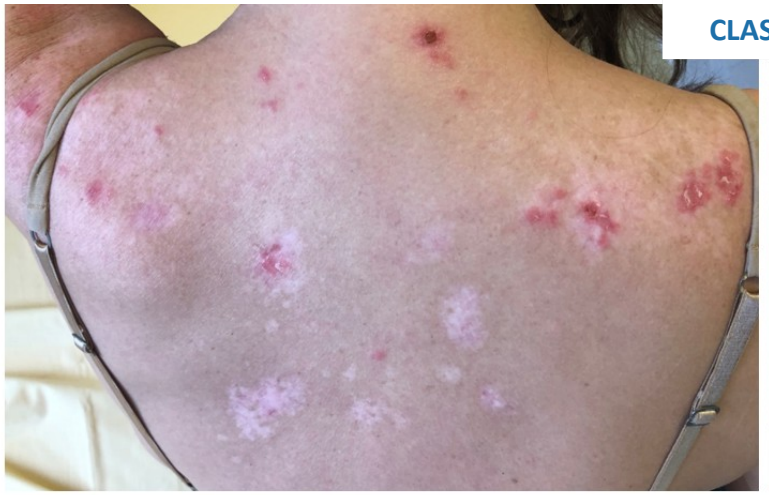
Anifrolumab : la vraie vie

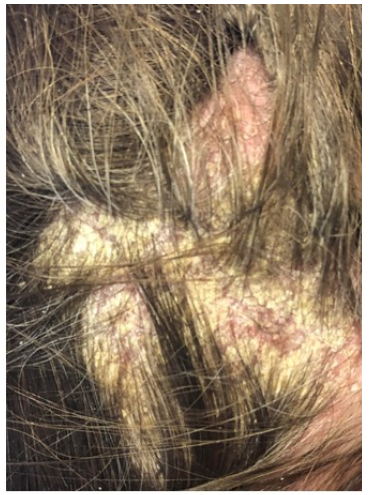
Cas clinique

Anifrolumab IV 300mg, une injection de 30 min tous les mois

M0

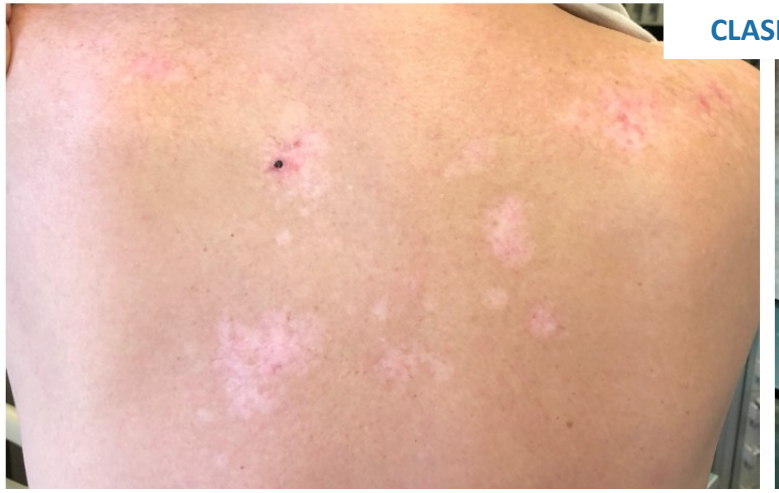
CLASI 35





M1

CLASI 18



NA

Disparition des douleurs articulaires

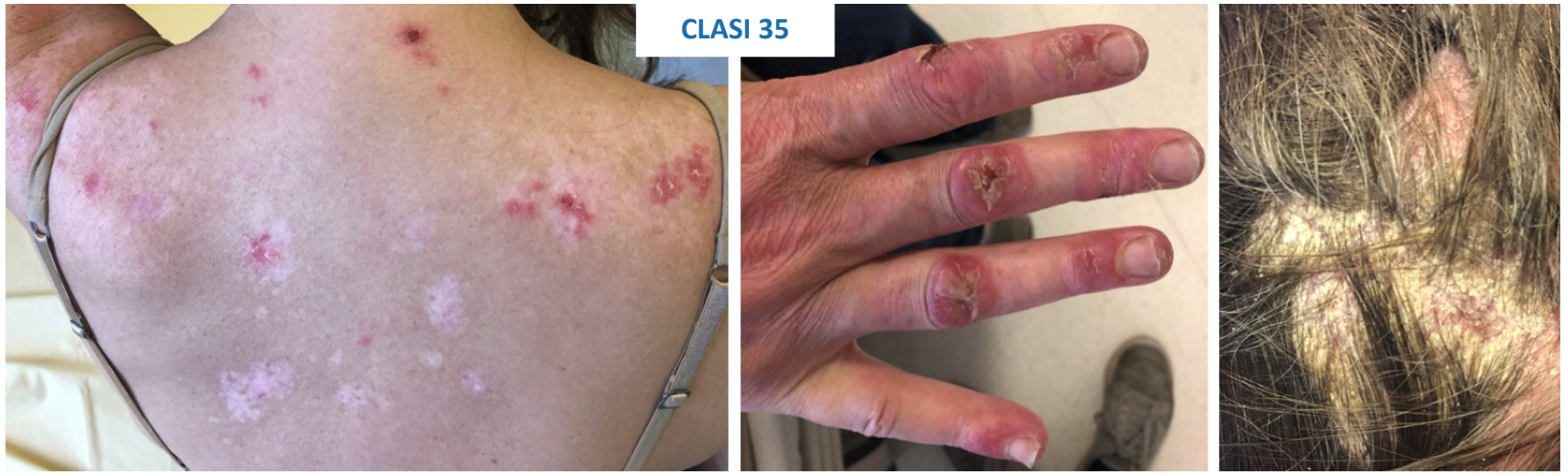
Anifrolumab : la vraie vie

Cas clinique

Anifrolumab IV 300mg, une injection de 30 min tous les mois

M0

CLASI 35



M2

CLASI 18

Disparition des douleurs articulaires

Cas clinique

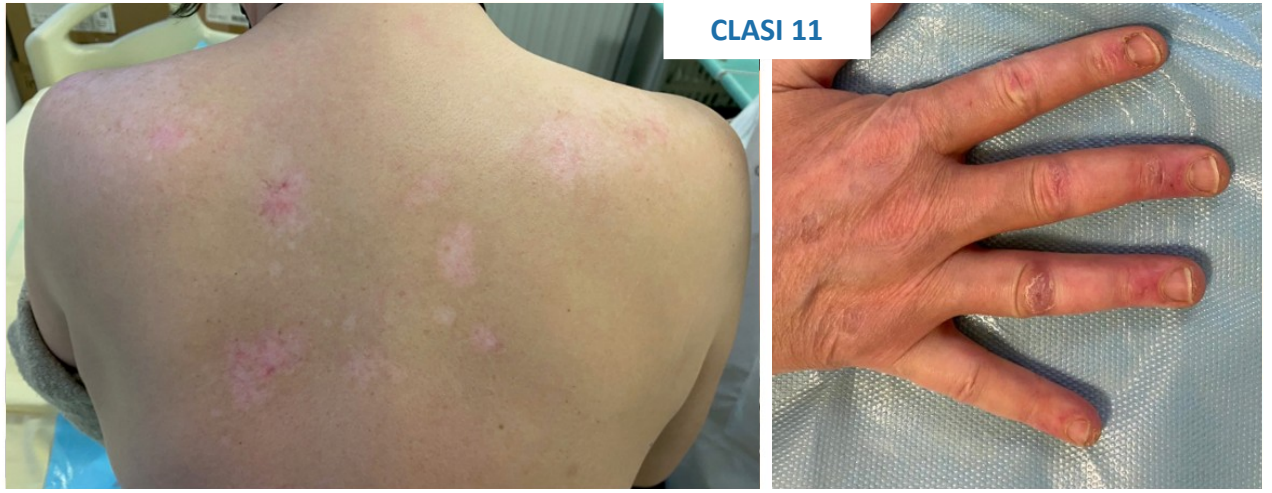
Anifrolumab IV 300mg, une injection de 30 min tous les mois

M0

CLASI 35

M4

CLASI 11



NA

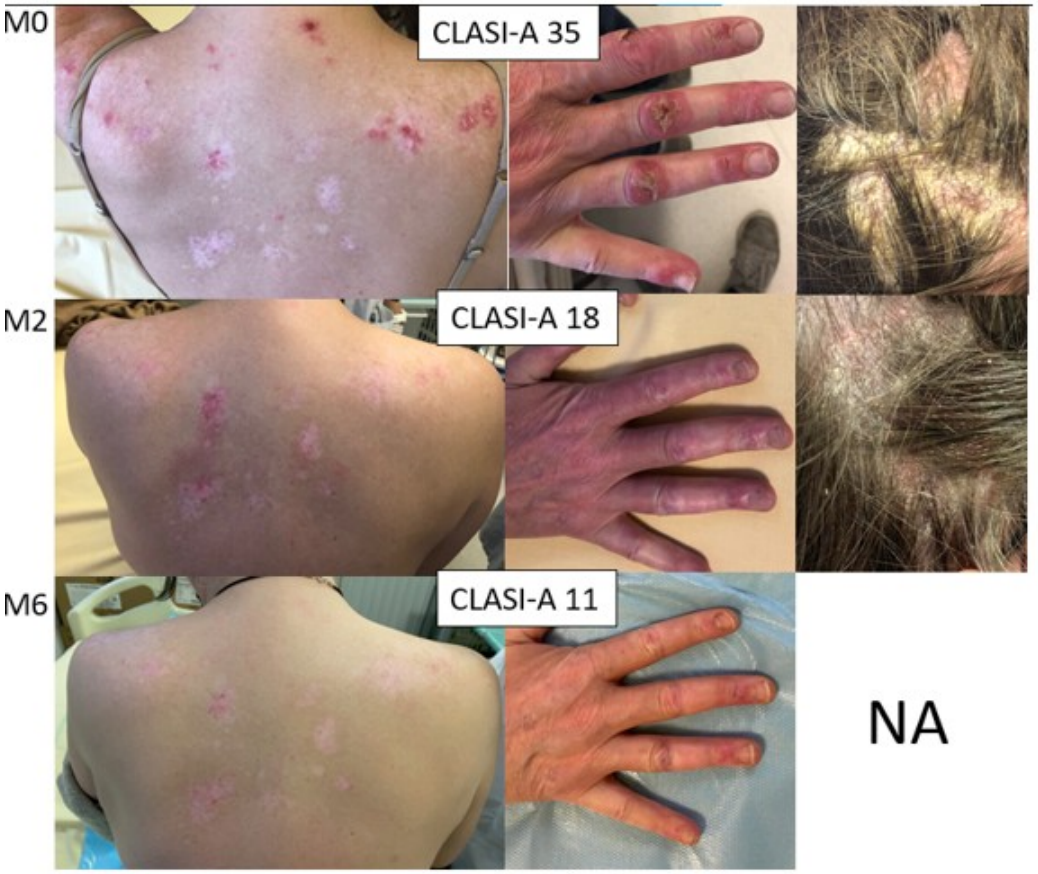
Disparition des douleurs articulaires

4

Biothérapies belimumab, anifrolumab et autres

Anifrolumab

Patiente 1



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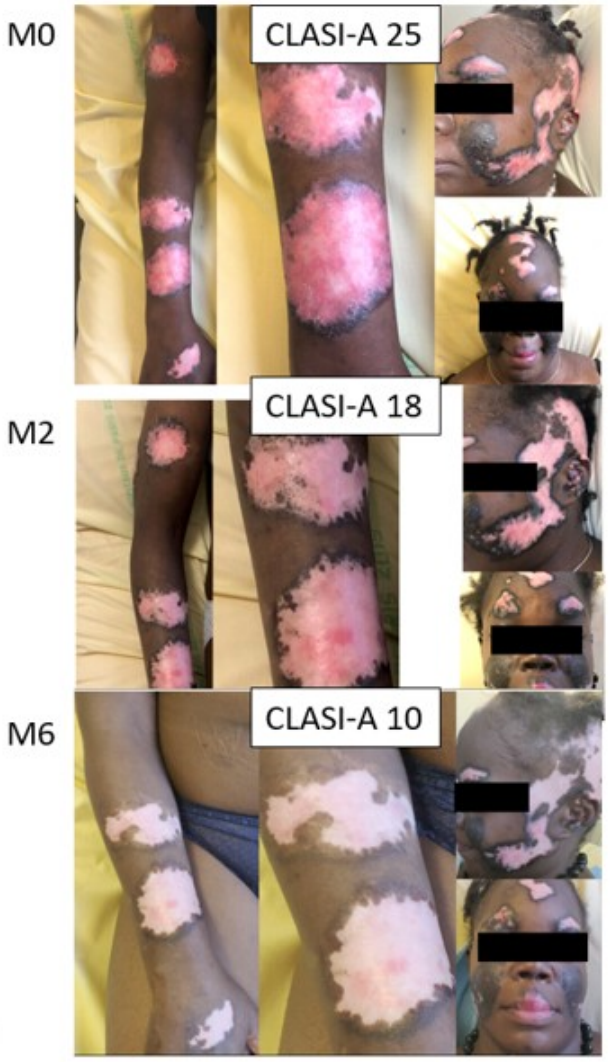
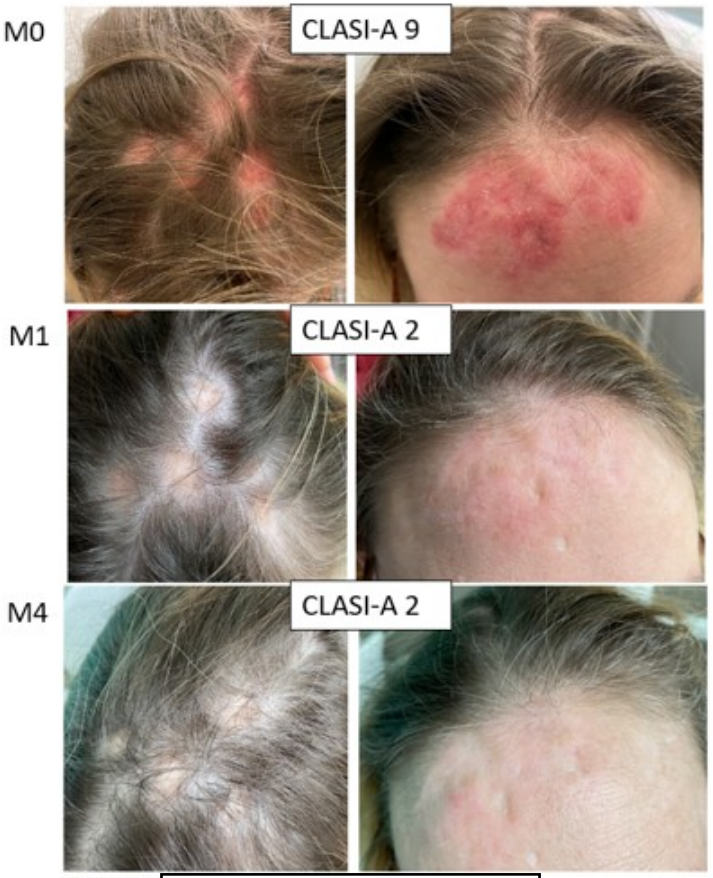
Patiente 2



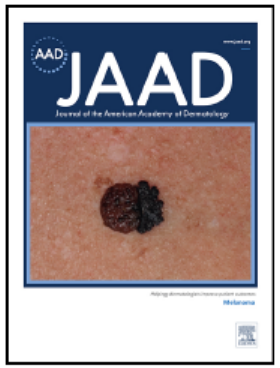
Patiente 3



Dr Jousse-Joulin

Anifrolumab : la vraie vie

Journal Pre-proof



Rapid Efficacy of anifrolumab in refractory cutaneous lupus erythematosus: a prospective study of 11 patients with systemic lupus erythematosus

François Chasset, MD, PhD, Léa Jaume, MD, Alexis Mathian, MD, PhD, Noémie Abisror, MD, Amélie Dutheil, MD, Annick Barbaud, MD, PhD, Diane Kottler, MD, Céline Girard, MD, Sandrine Jousse-Joulin, MD, Marie Tauber, MD, Cristina Bulai Livideanu, MD, Véronique Avettand-fenoel, MD, PhD, Raphael Lhote, MD, Micheline Pha, MD, Zahir Amoura, MD, MSc, for the EMSED (Etude des maladies systémiques en dermatologie) study group

PII: S0190-9622(23)00354-7

DOI: https://doi.org/10.1016/j.jaad.2023.02.044

Reference: YMJD 17483

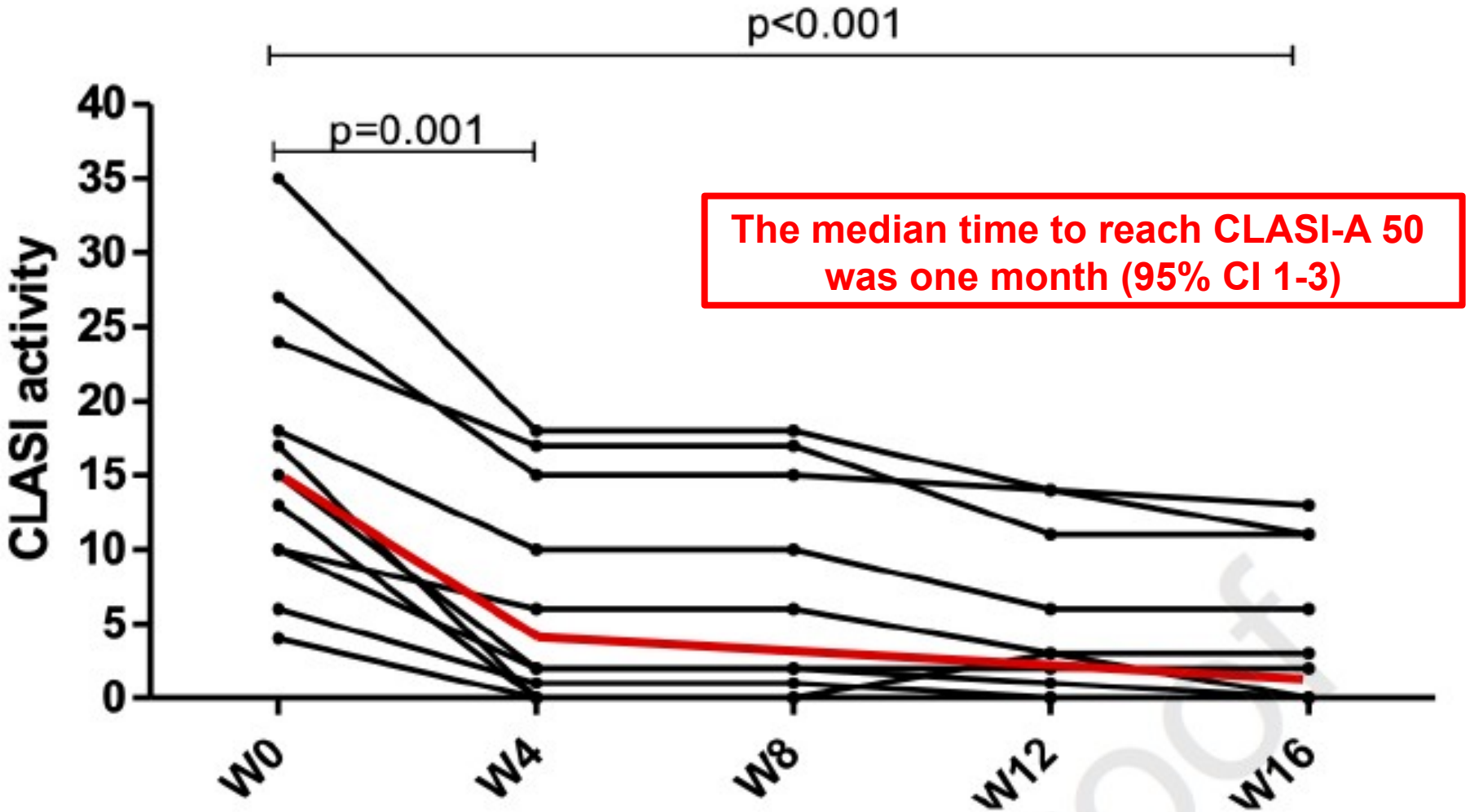
To appear in: *Journal of the American Academy of Dermatology*

Received Date: 5 December 2022

Revised Date: 26 January 2023

Accepted Date: 20 February 2023

Anifrolumab : la vraie vie



Anifrolumab : la vraie vie

- **The median SELENA-SLEDAI score significantly decreased from 8 (4-22) at baseline to 4 (0-10) at week 16 (p=0.002)**
- **All 5 patients with baseline articular involvement had disappearance of their clinical symptoms.**
- **The median dose of prednisone decreased from 10 mg/day (0-15) to 5 mg/day (0-10).**

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Merci de votre attention

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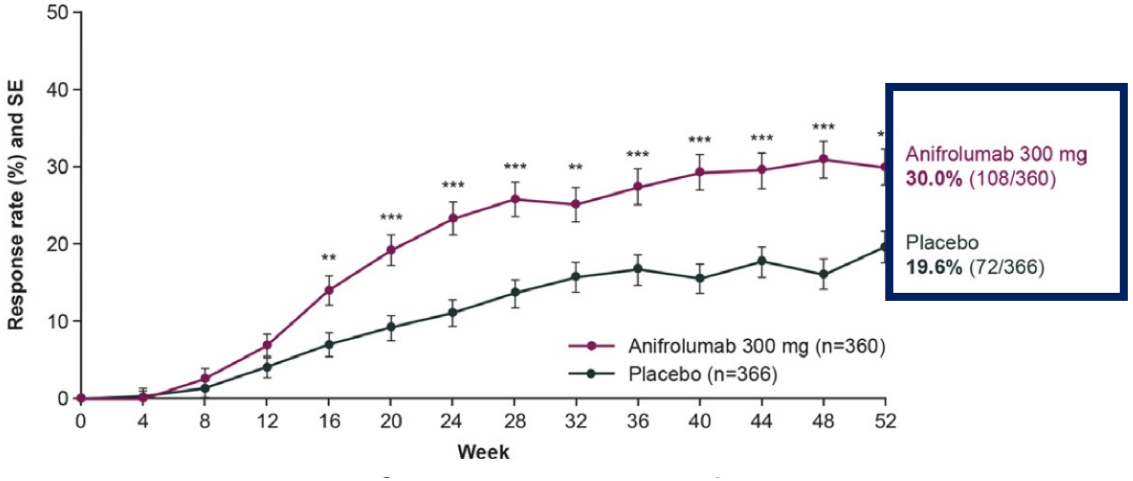
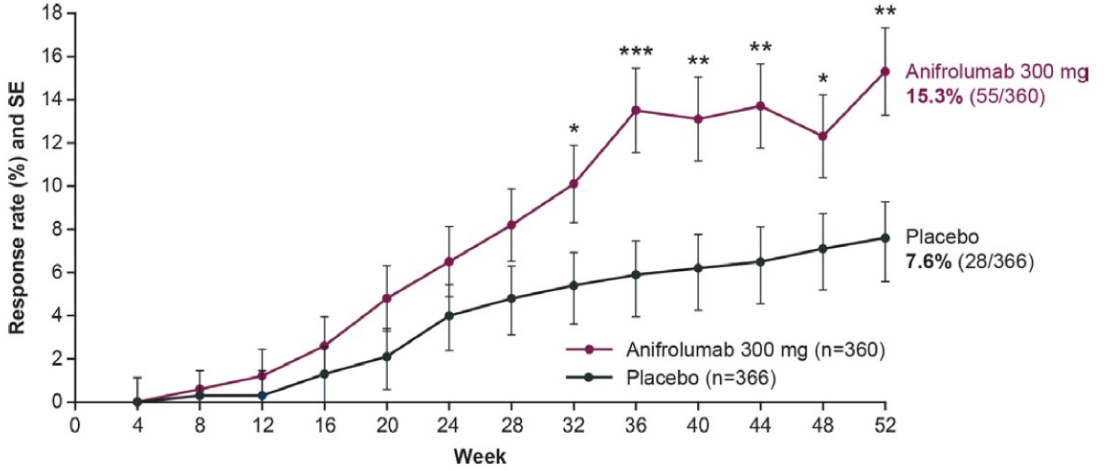
Anifrolumab

Obtention d'une activité faible



Obtention d'une rémission



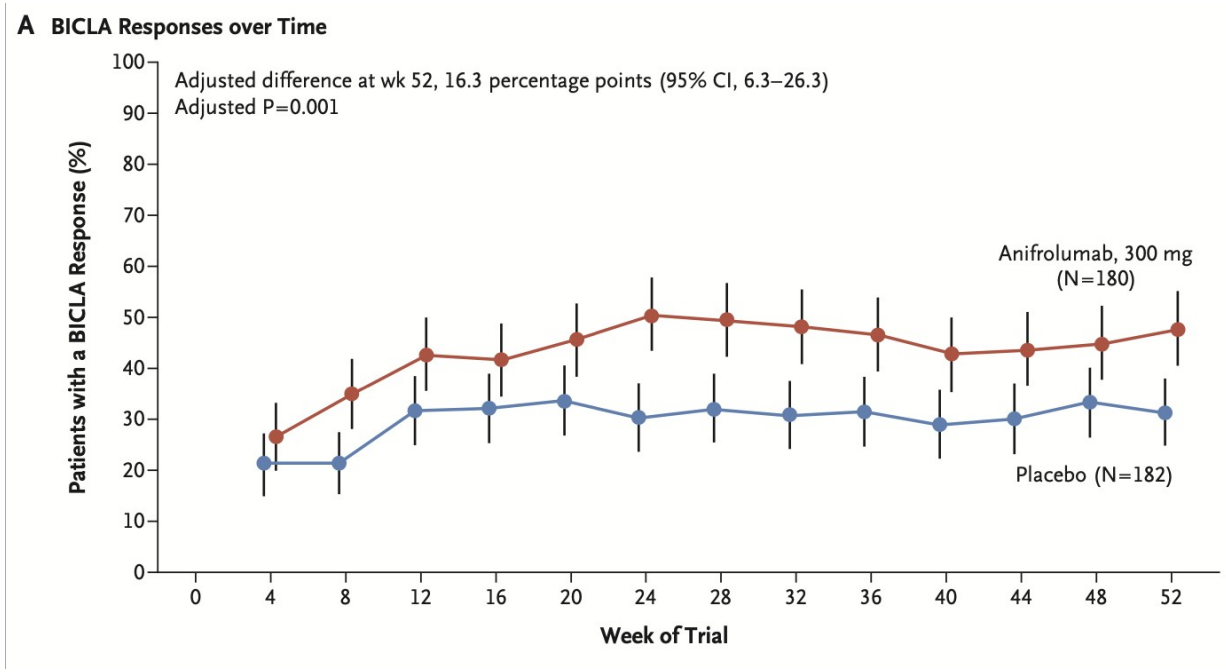
AMM de cohorte depuis Février 2022
Analyses combinées TULIP 1-2
Amélioration vers 16 semaines

Morand EF. Ann Rheum Dis. 2023 Jan 23:annrheumdis-2022-222748.

	MUSE (Phase 2b) (n=307)	TULIP-1 (Phase 3) (n=457)	TULIP-2 (Phase 3) (n=362)
Population	Patients lupiques de 18 à 65 ans modérément à sévèrement actifs (SLEDAI-2K au moins 6 avec autres critères additionnels) avec présence d'autoanticorps et au moins un traitement parmi hydroxychloroquine, corticothérapie, ou immunosuppresseur Exclusion des patients avec atteinte rénale ou neuropsychiatrique sévère	Patients lupiques de 18 à 70 ans modérément à sévèrement actifs (SLEDAI 2K au moins 6 avec autres critères additionnels) avec présence d'auto-anticorps et au moins un traitement parmi hydroxychloroquine, corticothérapie, ou immunosuppresseur Exclusion des patients avec atteinte rénale ou neuropsychiatrique sévère	Patients lupiques de 18 à 70 ans modérément à sévèrement actifs (SLEDAI 2K au moins 6 avec autres critères additionnels) avec présence d'auto-anticorps et au moins un traitement parmi hydroxychloroquine, corticothérapie, ou immunosuppresseur Exclusion des patients avec atteinte rénale ou neuropsychiatrique sévère
Intervention	Randomisation 3 groupes 1 :1 :1 - Placebo - Anifrolumab 300 milligrammes toutes les 4 semaines pendant 48 semaines - Anifroumab 1000 milligrammes toutes les 4 semaines pendant 48 semaines	Randomisation 3 groupes 2 :1 :2 - Placebo - Anifrolumab 150 milligrammes toutes les 4 semaines pendant 48 semaines - Anifrolumab 300 milligrammes toutes les 4 semaines pendant 48 semaines	Randomisation 2 groupes 1 :1 - Placebo - Anifrolumab 300 milligrammes toutes les 4 semaines pendant 48 semaines
Critère de jugement principal	SRI-4 et réduction de la corticothérapie à 24 semaines (moins de 10 milligrames par jour d'équivalent prednisone, et au moins (ou pareil) que la dose initiale (des 12 premières semaines)	SRI-4 à 52 semaines	BICLA à 52 semaines
Résultat principal	34.3% dans le groupe anifrolumab 300 milligrammes (p=0.014 versus placebo) 28.8% dans le groupe anifrolumab 1000 milligrammes (**p=0.063** versus placebo) versus 17.6% dans le groupe placebo	**36% dans le groupe anifrolumab 300, 40% dans le groupe placebo (p=0.41).**	47.8% dans le groupe anifrolumab ont atteint le critère principal versus 31.5% dans le groupe placebo (p=0.001)
Effets indésirables	Zona (5.1% dans le groupe 300 milligrammes, 9.5% dans le groupe 1000 milligrammes) Une myélite virale (HSV) dans le groupe anifrolumab 300 Infections des voies aériennes supérieures (36.4% dans le groupe anifrolumab 300 et 41.9% dans le groupe anifrolumab 1000 versus 28.7 dans le groupe placebo) Absence de décès	Zona (5% dans le groupe anifrolumab 150 et 6% dans le groupe 300) Tuberculose (1 cas bras placebo et 1 cas bras anifrolumab 300) Infections des voies aériennes supérieures (10% placebo, 17% anifrolumab 150, 12% anifrolumab 300) 1 décès dans le groupe anifrolumab 300 (infection pulmonaire après 2 perfusions d'anifrolumab)	Bronchites (12.2% sous anifrolumab versus 3.8% sous placebo) Infections des voies aériennes supérieures (21.7% versus 9.9%) Zona (7.2% versus 1.1%) 1 décès du groupe anifrolumab (pneumopathie)

Furie RA. Lancet Rheumatol 2019;1(4):e208-19
Morand EF. N Engl J Med. 2020;382(3):211-21.

Anifrolumab TULIP 2



Adverse events with frequency of >5% in the anifrolumab group	Placebo	Anifro
Upper respiratory tract infection	18 (9.9)	39 (21.7)
Nasopharyngitis	20 (11.0)	28 (15.6)
Infusion-related reaction	14 (7.7)	25 (13.9)
Bronchitis	7 (3.8)	22 (12.2)
Urinary tract infection	25 (13.7)	20 (11.1)
Herpes zoster	2 (1.1)	13 (7.2)
Sinusitis	9 (4.9)	12 (6.7)
Arthralgia	6 (3.3)	10 (5.6)
Back pain	3 (1.6)	10 (5.6)
Cough	6 (3.3)	10 (5.6)

Bronchites
Zona

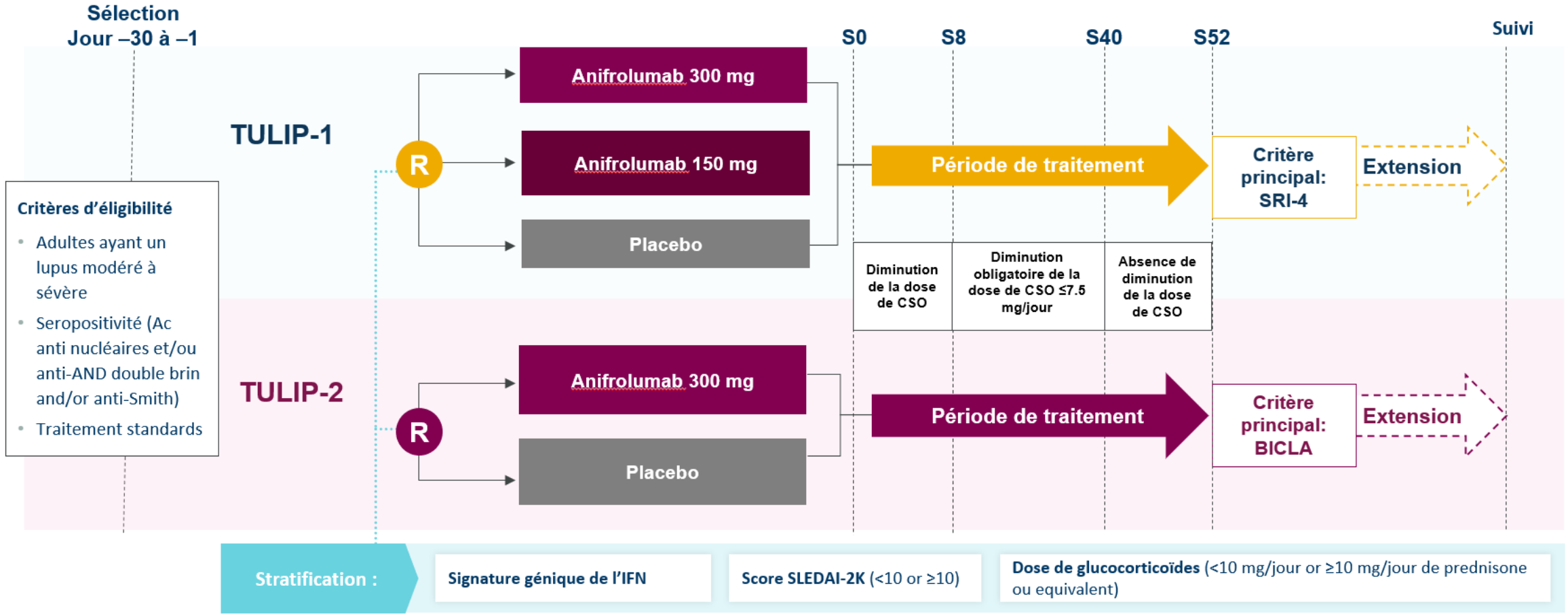
BICLA = amélioration partielle mais dans tous les organes
SRI-4 = amélioration complète dans certains organes

Morand EF. N Engl J Med. 2020 Jan 16;382(3):211-221.

4

Biothérapies belimumab, anifrolumab et autres

Anifrolumab

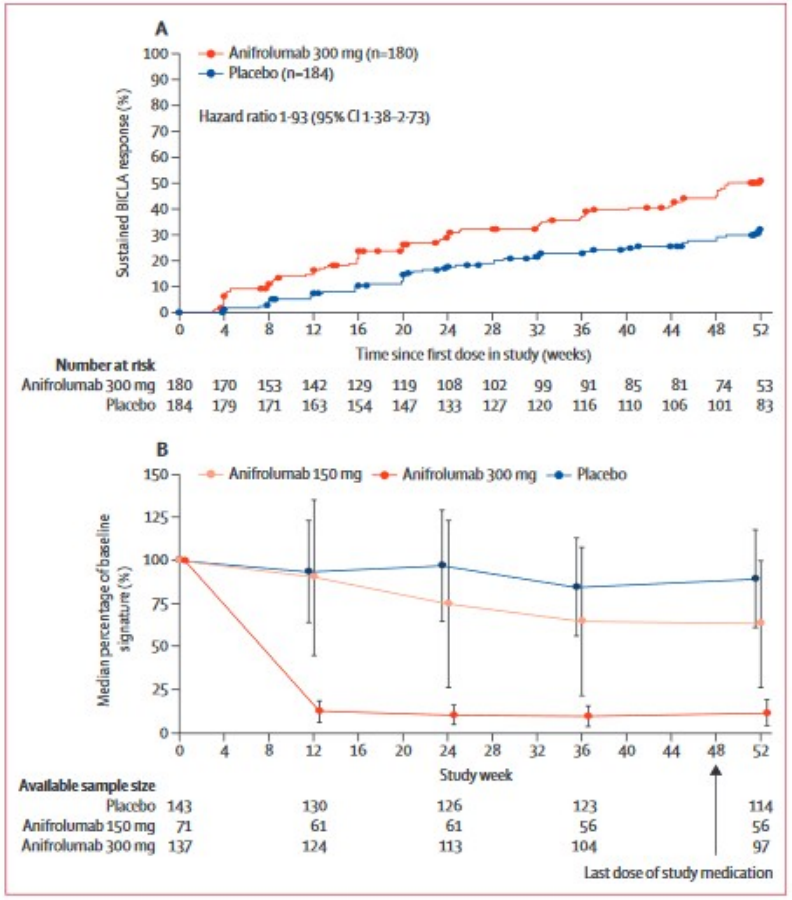


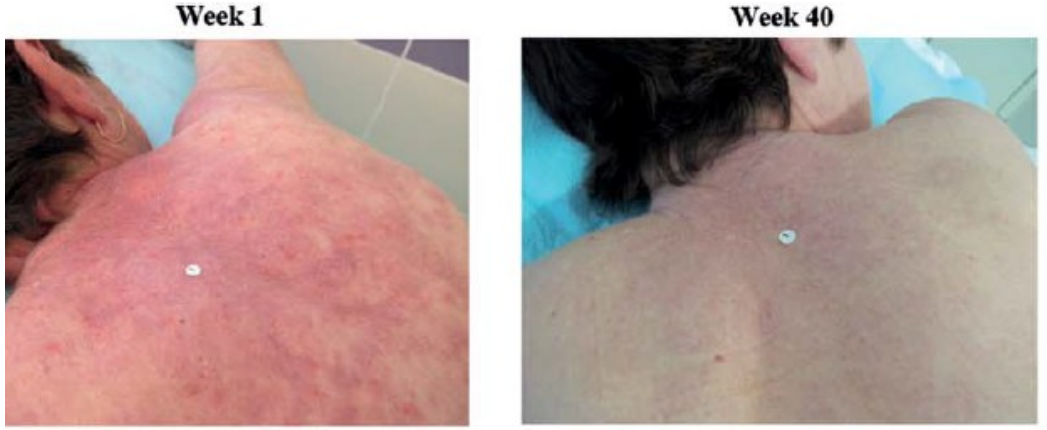
4

Biothérapies belimumab, anifrolumab et autres

Anifrolumab

- Ac monoclonal anti-récepteur IFN de type I





Patient was receiving anifrolumab 300 mg Q4W

MUSE
Phase 2

TULIP 1 Essai phase III négatif mais tendance CLASI

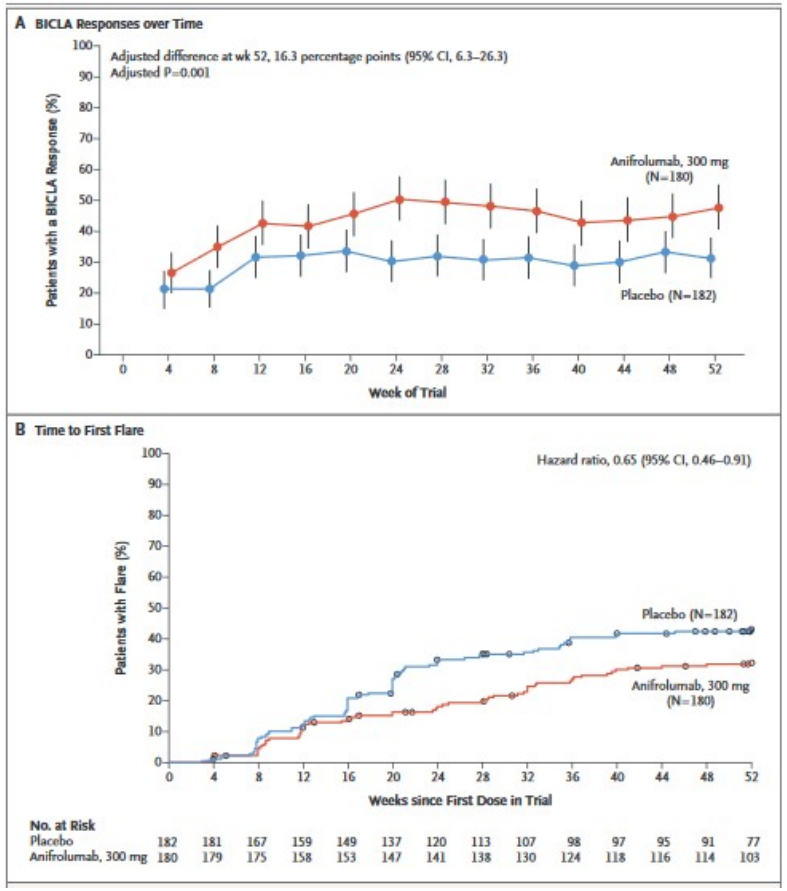
	Prespecified analysis			
	Placebo (n=184)	Anifrolumab 300 mg (n=180)	Difference (95% CI)*	Nominal p value†
Primary outcome				
SRI-4 week 52	74/184 (40%)	65/180 (36%)	−4·2 (−14·2 to 5·8)	0·412
Key secondary outcomes				
SRI-4 week 52 in interferon gene signature test—high patients	59/151 (39%)	53/148 (36%)	−3·4 (−14·4 to 7·6)	0·549
SRI-4 week 24	75/184 (41%)	74/180 (42%)	0·6 (−9·4 to 10·6)	0·905
Sustained oral corticosteroid dose reduction to target at week 52‡	33/102 (32%)	42/103 (41%)	8·9 (−4·1 to 21·9)	0·180
≥50% reduction in CLASI activity score from baseline to week 12§	14/54 (25%)	24/58 (42%)	17·0 (−0·3 to 34·3)	0·054
Annualised flare rate through week 52¶	0·72	0·60	0·83 (0·60 to 1·14)	0·258

Furie Arthritis Rheumatol 2017
Furie Lancet 2019

4

Biothérapies belimumab, anifrolumab et autres

Anifrolumab



N=362 patients
Anifrolumab IV 300mg/4 semaines

Table 2. Primary and Key Secondary Efficacy End Points.

End Point	Placebo (N=182)*	Anifrolumab, 300 mg (N=180)*	Difference (95% CI)*	Adjusted P Value†
	number/total number (percent)		*percentage points*	
Primary end point: BICLA response at wk 52‡	57/182 (31.5)	86/180 (47.8)	16.3 (6.3 to 26.3)	0.001
Key secondary end points				
BICLA response at wk 52 in patients with a high type I interferon gene signature	46/151 (30.7)	72/150 (48.0)	17.3 (6.5 to 28.2)	0.002
Glucocorticoid reduction to target dose, sustained from wk 40 to wk 52§	25/83 (30.2)	45/87 (51.5)	21.2 (6.8 to 35.7)	0.01
≥50% Reduction in CLASI activity from baseline to wk 12¶	10/40 (25.0)	24/49 (49.0)	24.0 (4.3 to 43.6)	0.04
≥50% Reduction in both swollen and tender joints from baseline to wk 52‖	34/90 (37.5)	30/71 (42.2)	4.7 (–10.6 to 20.0)	0.55**
Annualized flare rate through wk 52††	0.64	0.43	0.67 (0.48 to 0.94)‡‡	0.08**

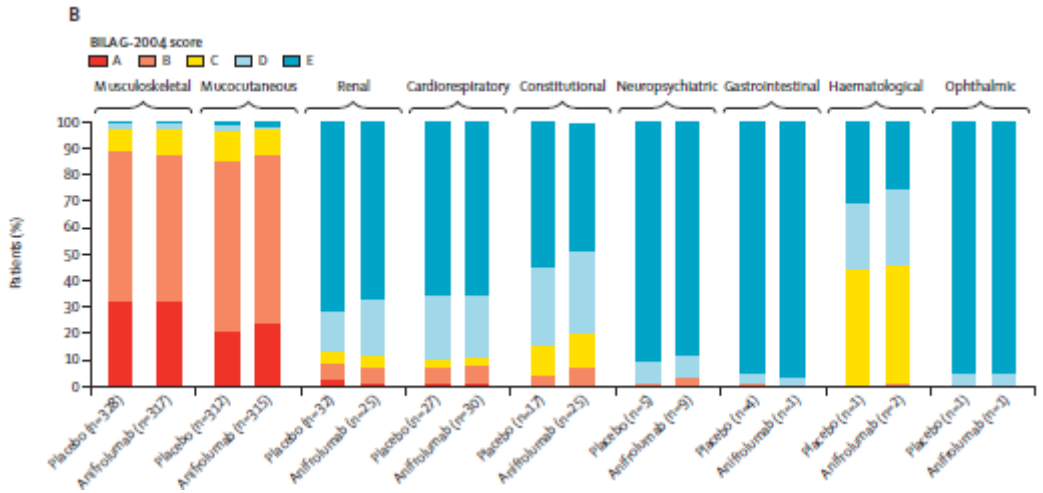
ATU de cohorte entre aout 2021 mai 2022 en échec ou C.I au belimumab

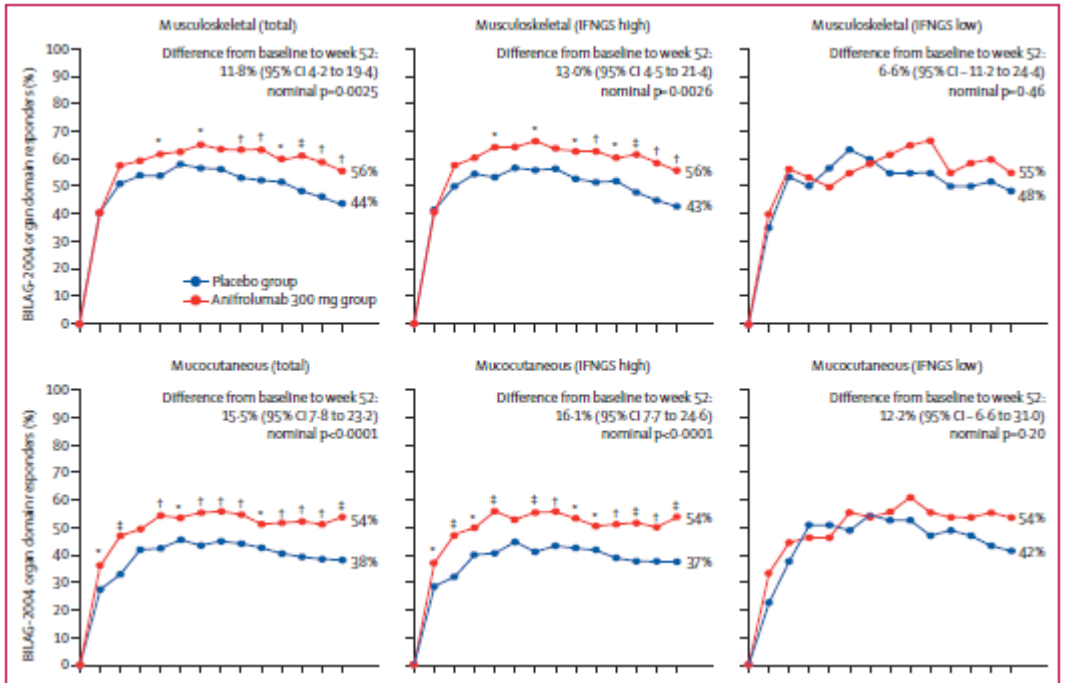
Morand E, NEJM 2020

4

Biothérapies belimumab, anifrolumab et autres

Anifrolumab





Analyse poolé TULIP 1 et TULIP 2 **n=726 patients**
Amélioration significatif des scores **cutanées et articulaires** selon BILAG et SLEDAI-2K
Amélioration supérieure dans groupe avec signature IFN-I élevée

Parmi CLASI ≥ 10 à S52, CLASI-50% chez 49/107 (46%) vs 24/94 (25%) p=0,0015

Morand EF, Lancet 2022

4

Biothérapies belimumab, anifrolumab et autres

Anifrolumab

Table 1 AEs in patients during treatment in pooled MUSE, TULIP-1 and TULIP-2 data

	Anifrolumab 300 mg (n=459)		Placebo (n=466)		EAIR risk difference (anifrolumab 300 mg – placebo) (95% CI)
	n (%)	EAIR	n (%)	EAIR	
Any AE*	399 (86.9)	290.1	370 (79.4)	225.2	NR
SAE	54 (11.8)	13.6	78 (16.7)	20.7	−7.2 (−12.5 to −1.9)
Death	2 (0.4)	0.5	0	0	0.5 (−0.5 to 1.7)
DAE	19 (4.1)	4.5	24 (5.2)	6.0	−1.4 (−4.7 to 1.7)
AESI†‡	61 (13.3)	15.5	47 (10.1)	12.2	3.3 (−1.5 to 8.2)
Non-opportunistic serious infections	22 (4.8)	5.4	26 (5.6)	6.6	−1.3 (−4.7 to 2.1)
Opportunistic infections	1 (0.2)	0.2	1 (0.2)	0.2	−0.0 (−1.2 to 1.1)
Anaphylaxis	0	0	0	0	0
Malignancy	3 (0.7)	0.7	3 (0.6)	0.7	−0.0 (−1.5 to 1.4)
Herpes zoster	28 (6.1)	6.9	6 (1.3)	1.5	5.4 (2.8 to 8.4)
Active TB	0	0	0	0	0
Latent TB§	4 (0.9)	1.0	1 (0.2)	0.2	0.7 (−0.5 to 2.2)
Influenza	12 (2.6)	2.9	9 (1.9)	2.3	0.6 (−1.7 to 3.0)
Non–SLE-related vasculitis	0	0	2 (0.4)	0.5	−0.5 (−1.8 to 0.4)
Major adverse cardiovascular event	1 (0.2)	0.2	3 (0.6)	0.7	−0.5 (−2.0 to 0.7)

Données poolées phase II (MUSE) et phase III (TULIP 1&2). Tummala Lupus Science and Medicine 2021, 8:e000464. doi:10.1136/lupus-2020-000464

SRI Treatment Response

Index	Change from Baseline
SELENA-SLEDAI	☐ Reduction ≥4 points in score
BILAG	☐ No new level A scores and ≤1 new level B score
PGA	☐ ≤0.3 increase in score

BICLA Treatment Response

Index	Change from Baseline
BILAG-2004	☐ Improvement in all level A and B scores
	☐ No new level A scores or two new level B scores
SLEDAI-2000	☐ No worsening of total score
PGA	☐ ≤10% worsening
Treatment failure	☐ No treatment failure defined as non-protocol treatment