A Phase 2/3 Study of Afimetoran, an Oral Equipotent TLR7/TLR8 Inhibitor, in Active Cutaneous Lupus Erythematosus

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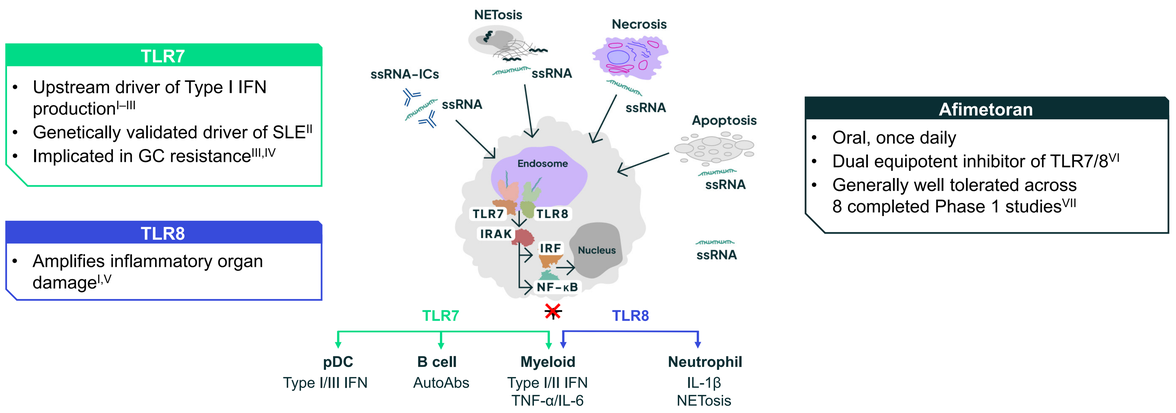
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Poster no. 8

Background: rationale for targeting TLR7/8 in lupus

- Cutaneous lupus erythematosus (CLE) is a chronic autoimmune disease often characterized by disfiguring skin lesions, with or without systemic manifestations,[1,2] and is associated with a substantial quality-of-life burden;[2–6] therapeutic options for CLE remain limited, with available regimens constrained by suboptimal efficacy and toxicity[7–10]
- Immune dysregulation converging on toll-like receptors (TLRs) 7 and 8 is central to lupus immunopathology (**Figure 1**)[11–13]
- Afimetoran is an investigational, selective, oral, once-daily, equipotent inhibitor of TLR7 and TLR8[14–16]

Figure 1. Mechanism of disease in CLE

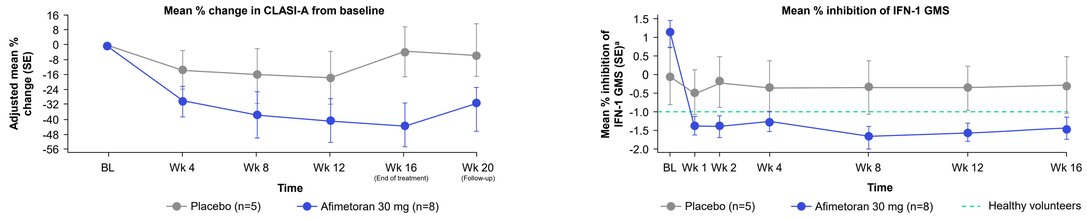


AutoAbs, autoantibodies; CLE, cutaneous lupus erythematosus; GC, glucocorticoid; IL, interleukin; IRAK, interleukin-1 receptor-associated kinase; IRF, interferon regulatory factor; NET, neutrophil extracellular trap; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; pDC, plasmacytoid dendritic cell; SLE, systemic lupus erythematosus; ssRNA, single-stranded RNA; ssRNA-ICs, single-stranded RNA immune complexes; TLR, toll-like receptor; TNF-α, tumor necrosis factor-alpha. I. Bender AT et al. *Immunohorizons*. 2020;4(2):93–107. II. Brown GJ et al. *Nature*. 2022;605(7909):349–356. III. Guiducci C et al. *Nature*. 2010;465(7300):937–941. IV. Zhao Q et al. *Ann Rheum Dis*. 2023;82(Suppl 1):892. V. Huang Q-Q, Pope RM. *Curr Rheumatol Rep*. 2009;11(5):357–364. VI. Hosein F et al. *ACR Open Rheumatol*. 2025;7(7):e70059. VII. Data on File. Beeline Medicines Corporation.

Phase 1b efficacy signal for afimetoran in CLE

- A Phase 1b randomized, double-blind, placebo-controlled study (N=13) evaluated afimetoran vs placebo in participants with active CLE (NCT04493541; **Figure 2**):[14]
  - CLASI-A reduction with afimetoran was evident and sustained through treatment and follow-up. At Week 16, the mean reduction from baseline in CLASI-A score was 42.6% with afimetoran vs 3.4% with placebo, equating to a difference of 39.2 percentage points;[14] 50% of patients receiving afimetoran achieved CLASI-50 at Week 16 vs 0% with placebo[14]
  - Type I IFN gene signature was suppressed from Week 1 to healthy-volunteer levels and remained low through Week 20 (4 weeks after last dose; data not shown)

Figure 2. Phase 1b results: rapid, meaningful skin improvements[14]



[a]Normalized to placebo BL. GMS; whole blood DxTerity platform
BL, baseline; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity; GMS, gene module score; IFN, interferon; SE, standard error; Wk, week

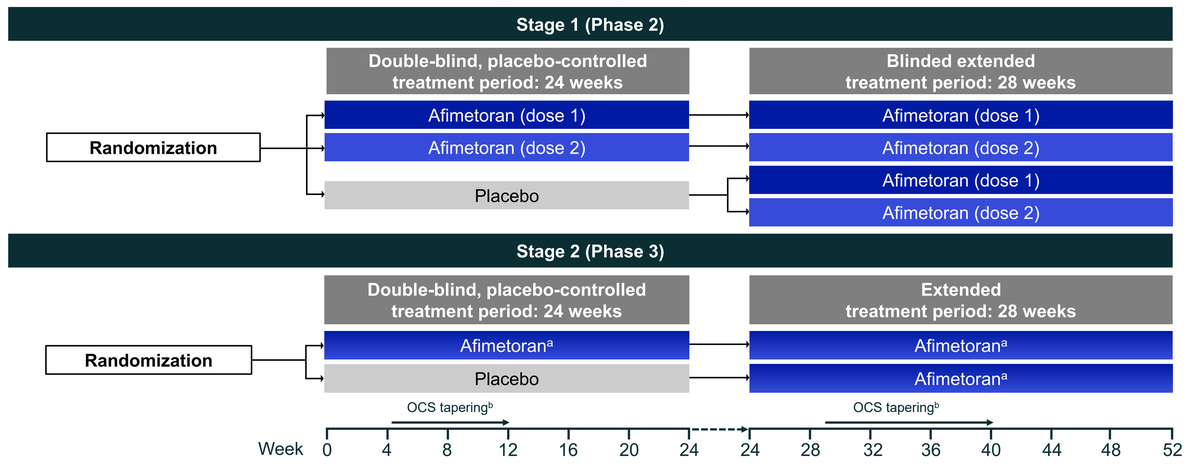
Ongoing study of afimetoran in CLE

- DISCOVERY (N=390) is a two-stage, operationally seamless, Phase 2/3, randomized, double-blind, placebo-controlled, multicenter study (NCT07881120; **Figure 3**)
- In Stage 1 (Phase 2), participants will be randomized to receive afimetoran (dose 1 or dose 2), or placebo, once daily; results will determine the afimetoran dose for Stage 2 (Phase 3), in which participants will be randomly assigned to receive afimetoran or placebo, once daily
- Both stages include a 24-week double-blind period followed by a 28-week extension in which all participants will receive afimetoran

Clinically driven study objective

- Evaluate the efficacy and safety of afimetoran compared with placebo in participants with active CLE with or without systemic manifestations and refractory and/or intolerant to antimalarials

Figure 3. Study design



Afimetoran and placebo will be dosed once daily. Participants in Stage 1 will not be eligible to participate in Stage 2. OCS, oral corticosteroid
[a]Afimetoran dose for Stage 2 of the study (Phase 3) will be selected based on results of Stage 1; [b]OCS tapering will be implemented for participants receiving >5 mg/day prednisone or equivalent at screening and randomization, as clinically indicated per investigator judgment

Selected inclusion criteria

- Adults aged ≥18 years (≥16 years in regions where this is the legal age of consent) with a histologically confirmed diagnosis of subacute and/or chronic CLE, with or without systemic manifestations
- CLASI-A score ≥10 (or ≥8 to <10, excluding scores for mucosal ulcer and alopecia items)
- Refractory to or intolerant of antimalarials
- Stable background lupus standard of care permitted

Selected exclusion criteria

- Active severe lupus nephritis or neuropsychiatric SLE
- Drug-induced lupus
- Clinically significant active or chronic infection (eg, HIV, hepatitis B/C, active or untreated latent tuberculosis)
- Other dermatologic conditions that might interfere with study assessments
- Prior afimetoran treatment or other TLR7/8 antagonist

Selected study endpoints

	Stage 1 (Phase 2)	Stage 2 (Phase 3)
Primary	• **Percent change from baseline in CLASI-A total score at Week 24**	• **CLASI-70 response at Week 24**
Secondary	• CLASI-70 and CLASI-50 responses, and CLASI-A total score of 0–3, at Weeks 12, 16, and 24 • CLA-IGA-R Erythema and OMC scores of 0–1 at Week 24 • CLE-QoL, DLQI total scores, and PtGA skin disease activity at Week 24	• CLASI-50 response and CLASI-A total score of 0–3 at Week 24 • CLA-IGA-R Erythema score of 0–1 at Week 24 • PtGA skin disease activity at Week 24 • Maintenance of response at Weeks 24 and 52
Safety	Incidence of TEAEs and SAEs (both stages)	

CLA-IGA-R, Cutaneous Lupus Activity Investigator's Assessment – Revised; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-A, CLASI – Activity; CLE, cutaneous lupus erythematosus; CLE-QoL, CLE Quality of Life; DLQI, Dermatology Life Quality Index; OMC, Other Morphologic Characteristics; PtGA, patient global assessment; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Study strengths

- This is a **two-stage, operationally seamless, Phase 2/3 study** evaluating afimetoran in **participants with active CLE with or without systemic manifestations and refractory and/or intolerant to antimalarials**, for whom no targeted therapies are approved
  - Participants will be assigned by chance to receive afimetoran or placebo for 24 weeks, **in addition to their existing standard-of-care therapy**
  - After Week 24, **all participants will receive afimetoran** for a further 28 weeks, for a total of 52 weeks of treatment
- The clinically driven design of the study will enable efficient dose selection in **Stage 1 (Phase 2)**, with the selected dose to be evaluated against placebo in **Stage 2 (Phase 3)**

Scan the QR code to obtain a copy of the poster, or click the following link for more information about the study: https://clinicaltrials.gov/study/NCT07881120

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Disclosures

JFM has received honoraria from AbbVie, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galderma, Janssen, Moonlake, Novartis, Oruka, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB. VPW has received honoraria from Beeline Medicines Corporation. FC has received grant/research support from AstraZeneca, BMS, and GSK; participated in advisory boards related to lupus for Amgen, AstraZeneca, Beeline Medicines Corporation, Celgene, GSK, Horizon Therapeutics, Kyowa Kirin, Merck, and Novartis; and received speaking fees and honoraria from AstraZeneca, BMS, and GSK related to lupus. MP, JH, CK, MH, RS, FG, CB, KDC, and NF are employed by Beeline Medicines Corporation and hold interests in its parent company, Beeline Medicines LLC. Beeline is developing afimetoran pursuant to a license agreement with BMS. FC, JH, RS, and CB are former employees of Biogen. CB may hold Biogen stock. KDC is a former employee and current stockholder of BMS. NF is a former employee of Biogen and Nimbus Therapeutics, is currently a paid employee and officer at Beeline Medicines Corporation and has been awarded equities. NF also has equity, shares, and/or stocks in Biogen, Nimbus Therapeutics, and OMass Therapeutics. NF is a past unpaid consultant to Rome Therapeutics and has historically received consulting fees from Actus Bio, Apini Therapeutics, Atara Biotherapeutics, Bain Capital, Generation Bio, Nimbus Therapeutics, and Sail Biomedicines. NF currently serves on the Board of Directors of OMass Therapeutics, is a current member of the Lupus Research Alliance (LRA) Lupus Industry Council (LIC) and Lupus ABC Research Committee, and is a former member of the LRA LIC Steering Committee.

References

1. Okon LG, Werth VP. *Best Pract Res Clin Rheumatol*. 2013;27(3):391–404.
2. Elmgren J, Nyberg F. *Front Med*. 2023;9:984229.
3. Hesselvig JH et al. *Br J Dermatol*. 2018;179(5):1095–1101.
4. Ogunsanya ME et al. *Int J Womens Dermatol*. 2018;4(3):152–158.
5. Klein R et al. *J Am Acad Dermatol*. 2011;64(5):849–858.
6. Joseph AK et al. *Lupus Sci Med*. 2021;8(1):e000514.
7. Niebel D et al. *Am J Clin Dermatol*. 2023;24(4):521–540.
8. Kuhn A et al. *J Eur Acad Dermatol Venereol*. 2017;31(3):389–404.
9. Chasset F, Francès C. *Drugs*. 2019;79(11):1199–1215.
10. Childs BA, Merola JF. *J Clin Aesthet Dermatol*. 2026;19(1):17–26.
11. Klein B et al. *Nat Rev Rheumatol*. 2025;21(12):703–718.
12. Brown GJ et al. *Nature*. 2022;605(7909):349–356.
13. von Hofsten S et al. *Int J Mol Sci*. 2024;25(10):5351.
14. Hosein F et al. *ACR Open Rheumatol*. 2025;7(7):e70059.
15. Zhao Q et al. *Ann Rheum Dis*. 2023;82(Suppl 1):892.
16. Harrison M et al. *Arthritis Rheumatol*. 2021;73(Suppl 9):3690–3691.

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