ACR Convergence 2023
November 10–15, 2023; San Diego, CA, USA

Safety, tolerability, and exploratory efficacy of afimetoran, a TLR7/8 inhibitor, in patients with cutaneous lupus erythematosus: a phase 1b randomized, double-blind, placebo-controlled study

Fareeda Hosein,[1] Stanislav Ignatenko,[2] Kristina Chadwick,[1] Lin Zhu,[1] Frédéric Baribaud,[1] Thanh Bach,[1] Hazem Karabeber,[1] Michelle Dawes,[1] Leon Carayannopoulos,[1] Gopal Krishna[1]

[1]Bristol Myers Squibb, Princeton, NJ, USA; [2]Charité Research Organisation GmbH, Berlin (Mitte) Germany

Disclosures and Mitigation Statement

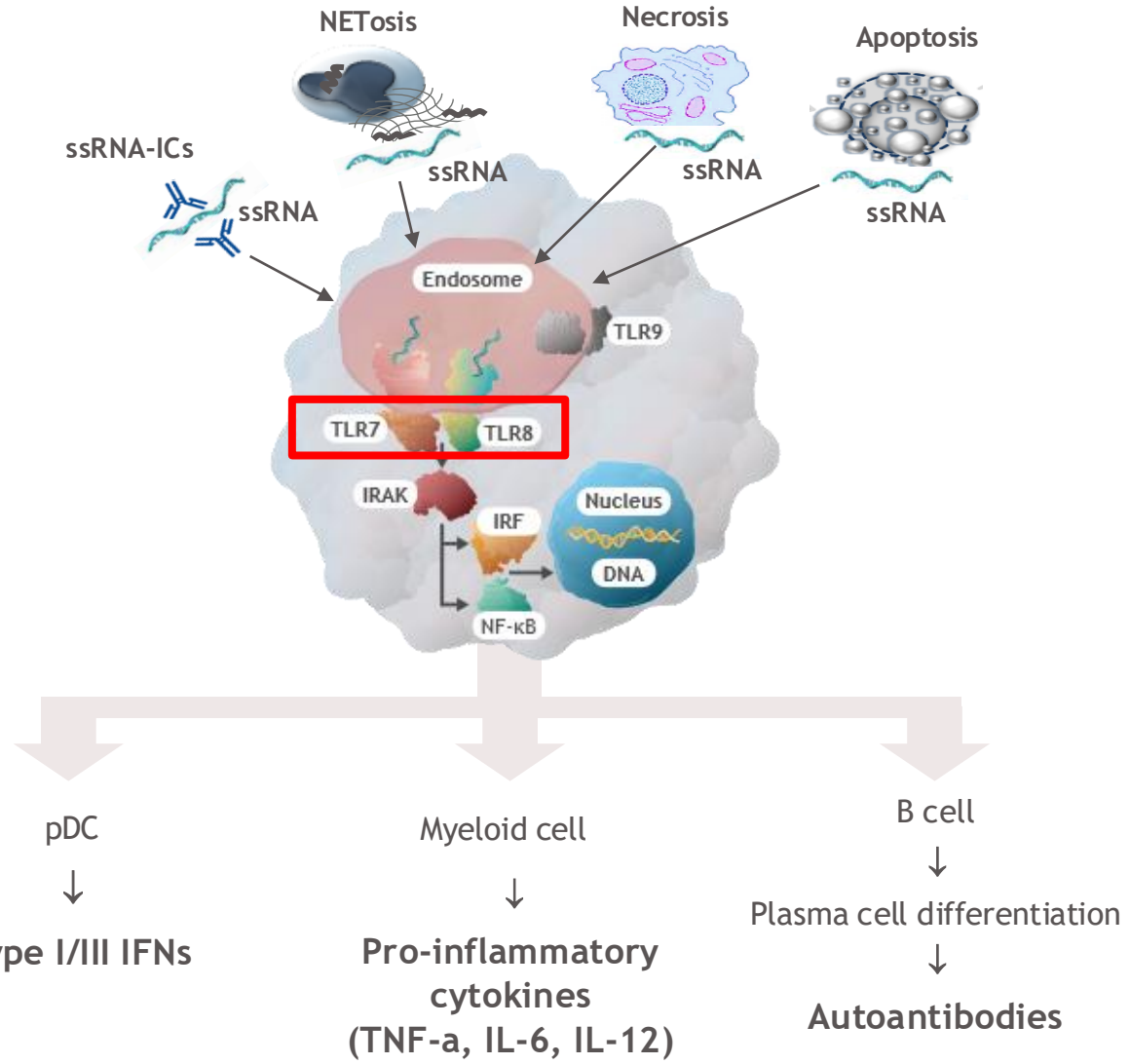
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Introduction

- Cutaneous lupus erythematosus (CLE) can be isolated or occur with systemic manifestations; no approved CLE treatment for 50 years[1,2]
- Type I IFNs are major drivers of disease[3]
- Toll-like receptor 7 (TLR7) and 8 (TLR8) are endosomal RNA sensors that stimulate Type I IFN production in lupus[4]
- Afimetoran is a first-in-class, orally bioavailable, selective and highly potent small molecule inhibitor of TLR7 and TLR8

Inhibition of ssRNA sensors, TLR7 and TLR8, is predicted to improve skin manifestations of lupus



CLE, cutaneous lupus erythematosus; IFN, interferon; IL, interleukin; IRAK4, interleukin-1 receptor-associated kinase 4; IRF, interferon regulatory factor; NFkB, nuclear factor kappa beta; pDC, plasmacytoid dendritic cell; RNA, ribonucleic acid; ssRNA, single-stranded ribonucleic acid; TLR, toll-like receptor; TNF, tumor necrosis factor.

1. Wenzel J. *Nat Rev Rheumatol* 2019;15:519-532; 2. Guo LN, et al. *Lupus Sci Med* 2021;8:e000529; 3. Petty et al. *Curr Allergy Asthma Rep* 2020;20:12; 4. Ishizaka ST, et al. *Eur J Pharmacol* 2023;957:175962.

Methods

This study investigated the safety, tolerability, and exploratory efficacy of afimetoran vs placebo in patients with CLE

Study design

- Phase 1b, randomized, double-blind, placebo-controlled study (NCT04493541)
- Patients with CLE were randomized 2:1 to oral afimetoran or placebo for 16 weeks and monitored for 4 weeks after stopping treatment

Primary endpoint

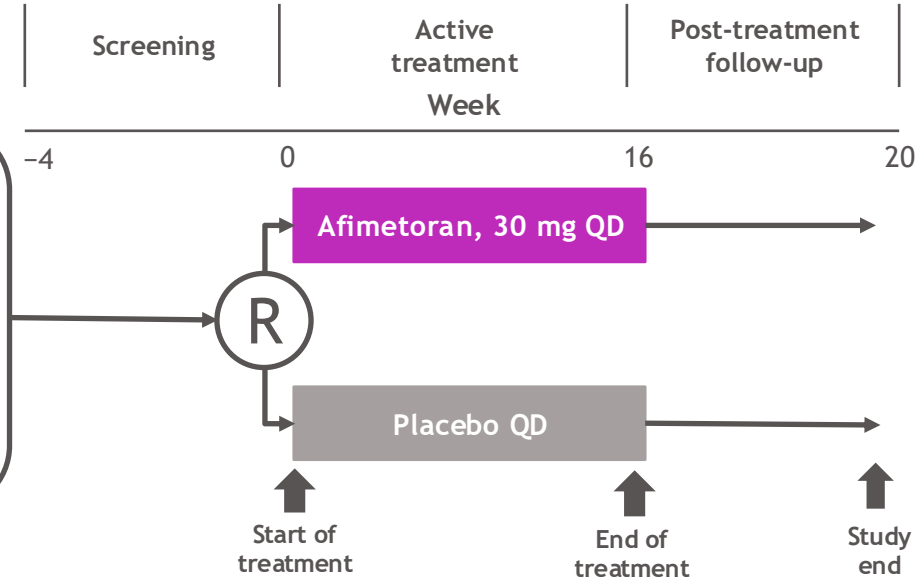
- Safety and tolerability

Secondary and exploratory endpoints

- Pharmacokinetics
- Pharmacodynamics (biomarkers)
- Efficacy as measured by CLASI-A

Inclusion criteria:

- 18–65 years
- Met EULAR/ACR 2019 classification criteria[1] for SLE or had biopsy-proven CLE
- Modified CLASI-A score of ≥ 6
- Antinuclear antibody positive
- Antimalarial and CS use[a]



[a]Patients could remain on their background antimalarials. Oral CS were restricted to maximum dose of 20 mg/day.

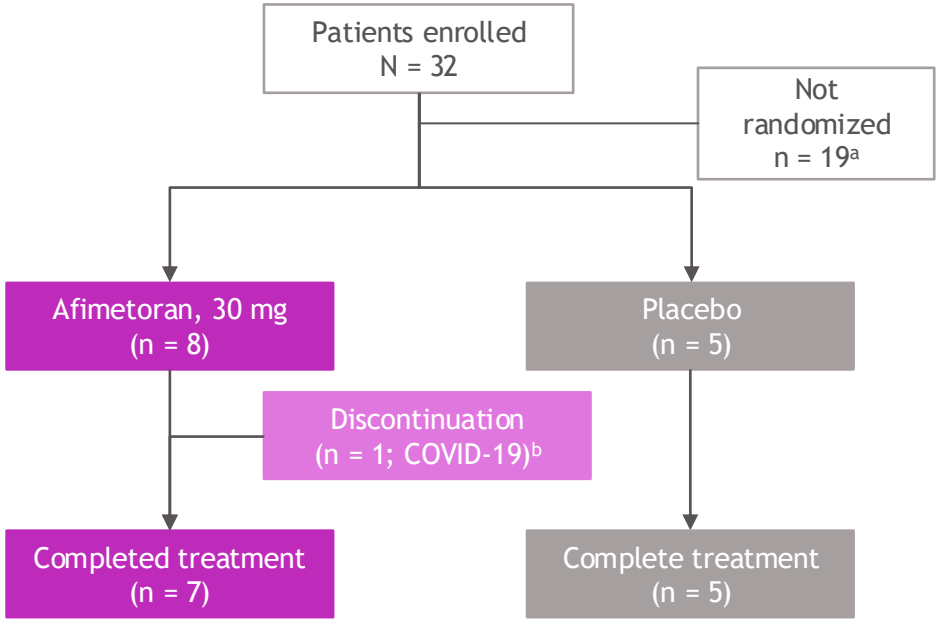
CLASI-A, CLE Disease Area and Severity Index-Activity; CLE, cutaneous lupus erythematosus; CS, corticosteroid; R, randomization; SLE, systemic lupus erythematosus.

1. Aringer M, et al. *Arthritis Rheumatol* 2019;71:1400–1412.

Patient demographics, disease characteristics and disposition

Baseline patient characteristics were generally balanced

	Afimetoran (n = 8)	Placebo (n = 5)	Total (n = 13)
Age, mean (min, max), years	46.0 (24, 62)	51.2 (30, 62)	48.0 (24, 62)
Female sex, n (%)	7 (87.5)	4 (80.0)	11 (84.6)
Body mass index, mean (min, max), kg/m²	26.6 (19.9, 31.6)	25.4 (21.6, 32.1)	26.1 (19.9, 32.1)
Weight, mean (min, max), kg	77.0 (54.2, 103.5)	74.3 (59.6, 97.2)	76.0 (54.2, 103.5)
Race, n (%)			
White	8 (100.0)	5 (100.0)	13 (100.0)
Smoking status (tobacco), n (%)			
Former	1 (12.5)	1 (20.0)	2 (15.4)
Current	6 (75.0)	2 (40.0)	8 (61.5)
Primary diagnosis, n (%)			
Cutaneous lupus erythematosus	5 (62.5)	2 (40.0)	7 (53.8)
Systemic lupus erythematosus	3 (37.5)	3 (60.0)	6 (46.2)
Subacute or discoid lupus, n (%)	6 (75.0)	5 (100.0)	11 (84.6)
Acute cutaneous lupus, n (%)	5 (62.5)	2 (40.0)	7 (53.8)
Anti-dsDNA antibody or anti-Smith antibody, n (%)	3 (37.5)	4 (80.0)	7 (53.8)
CLASI-A score, mean (min, max)	15.0 (6, 25)	11.6 (9, 16)	13.7 (6, 25)



Afimetoran vs placebo at baseline

- More current smokers
- Lower autoantibody positivity
- Higher CLASI-A scores

[a]Due to study criteria (n = 17) or other (n = 2); [b]Patient discontinuation at week 8 attributed to symptomatic COVID-19.

Safety summary

Event, n (%)	Afimetoran (n = 8)	Placebo (n = 5)
Deaths	0	0
AE	5 (62.5)	4 (80.0)
Serious AEs	0	0
AEs leading to discontinuation[a]	1 (12.5)	0
Drug-related AE[b,c]	2 (25.0)	2 (40.0)
Non-serious AE	5 (62.5)	4 (80.0)
Infections and infestations	3 (37.5)	1 (20.0)
Nervous system disorders	1 (12.5)	2 (40.0)
Injury/procedural complications	1 (12.5)	2 (40.0)
General and administration site disorders	2 (25.0)	0
Gastrointestinal disorders	1 (12.5)	1 (20.0)
Psychiatric disorders	1 (12.5)	0
Respiratory, thoracic, and mediastinal disorders	1 (12.5)	0
Blood and lymphatic system disorder	0	1 (20.0)
Musculoskeletal and connective tissue disorders	0	1 (20.0)

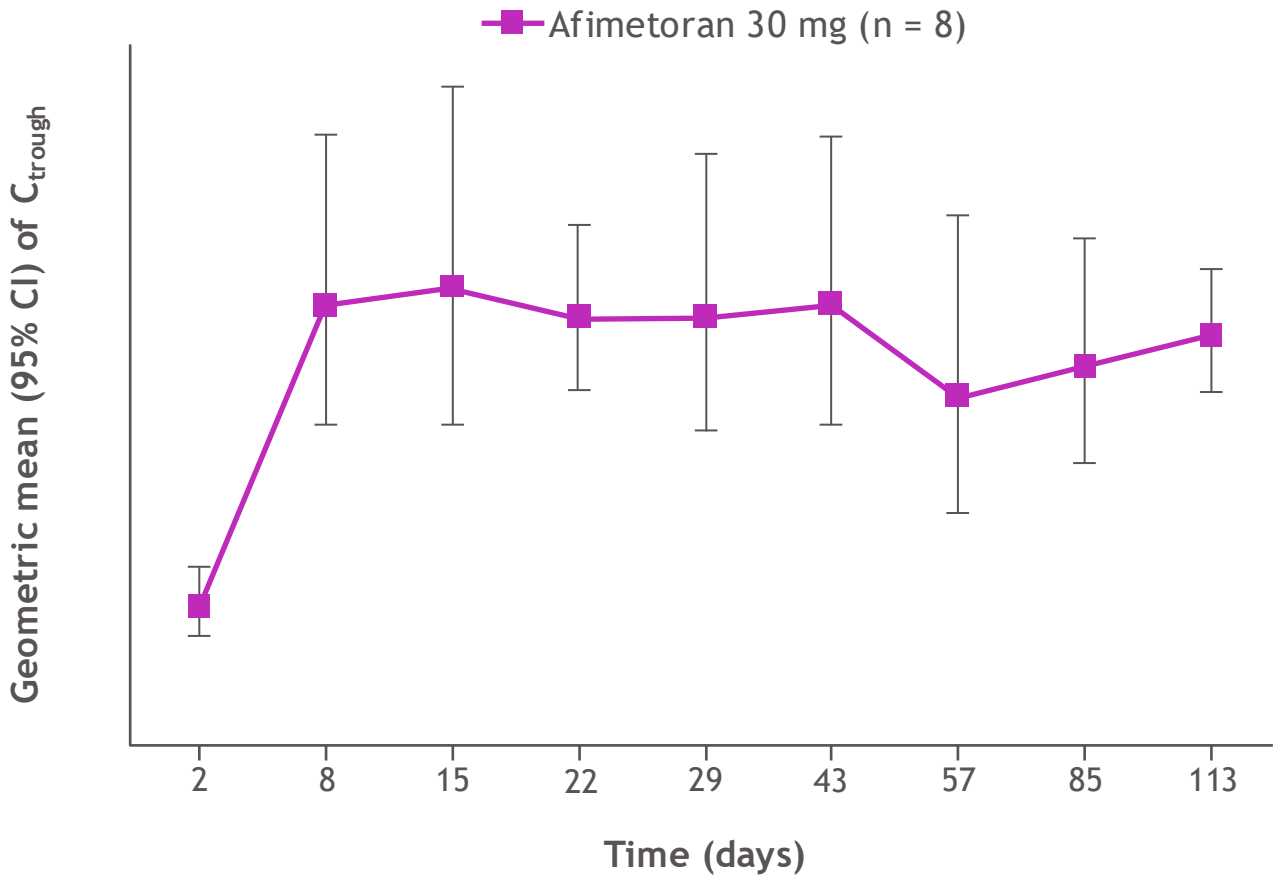
Afimetoran demonstrated a favorable safety profile and was well tolerated vs placebo

Overall, AEs were mild or moderate and resolved by the end of the study without intervention

The proportion of patients with reported AEs was lower for patients treated with afimetoran versus that on placebo (62.5% vs 80.0%)

[a]Patient discontinuation at week 8 attributed to symptomatic COVID-19; [b]Drug-related AEs were investigator assessed at each site; [c]Drug-related AEs were reported during the blinded treatment period, however after unblinding those patients were in the placebo group.

Pharmacokinetics of afimetoran

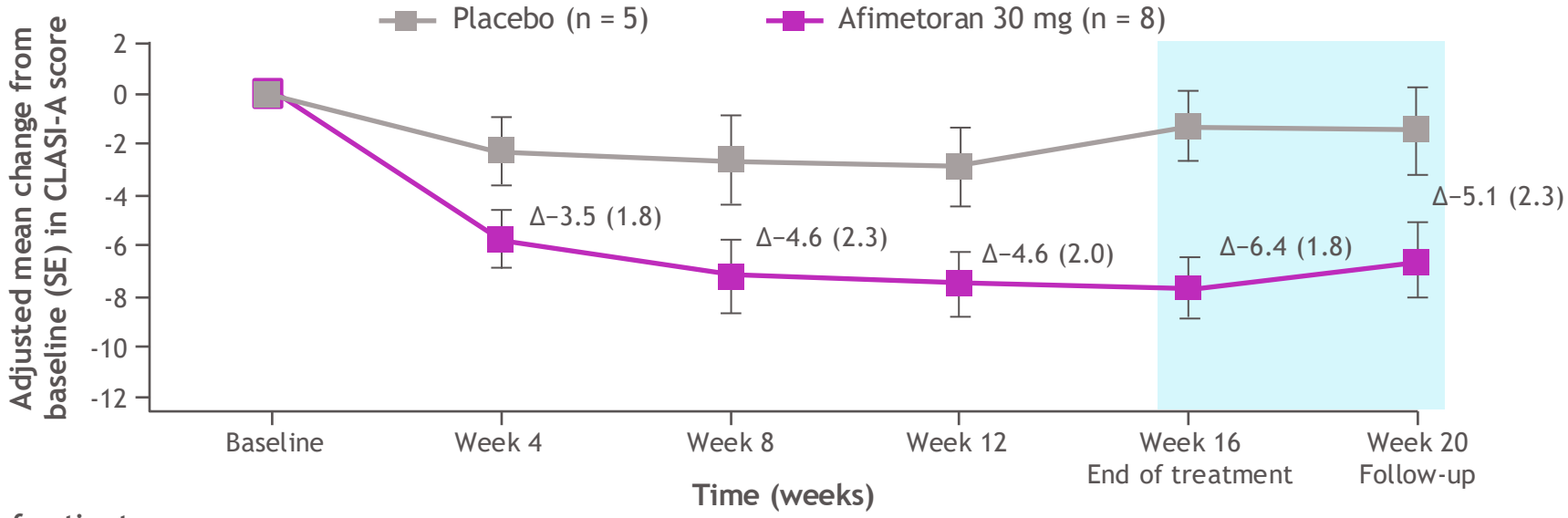


C_{trough} was consistent across visits from day 8 to day 113

Plasma concentration exceeded projected targeted inhibition concentration, over 24 hours, supporting 30 mg once daily dosing

CI, confidence interval.

Mean change in CLASI-A score

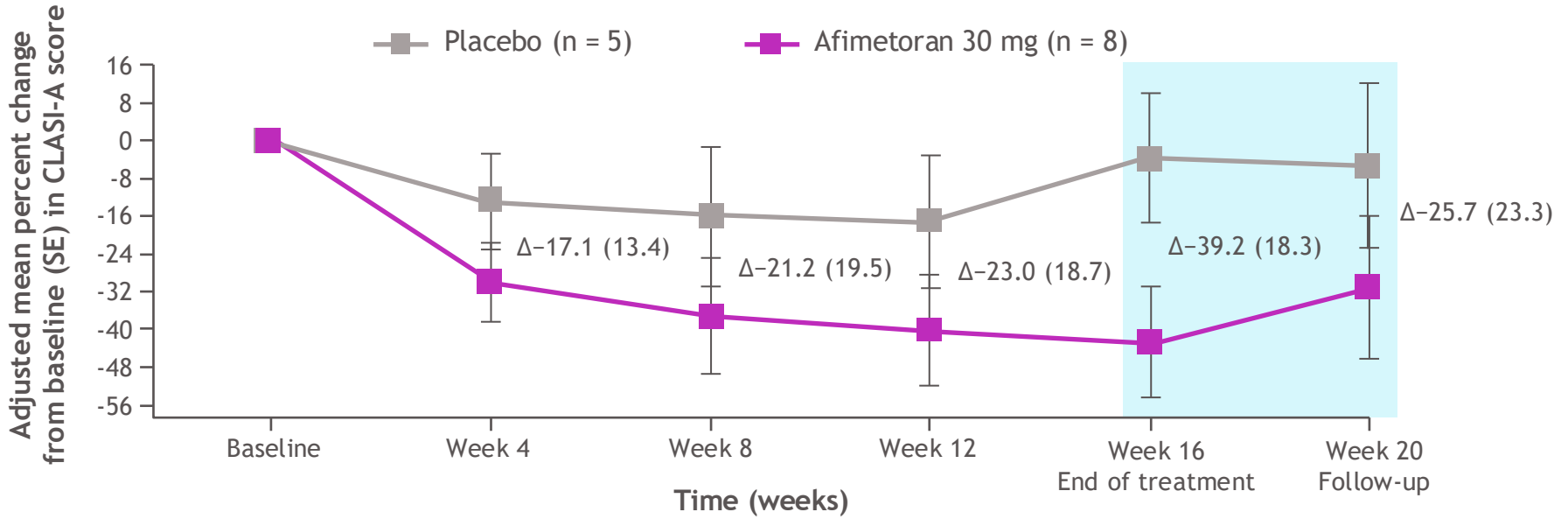


No. of patients						
Placebo QD	5	5 −2.2 (1.4)	5 −2.6 (1.7)	5 −2.8 (1.5)	5 −1.2 (1.4)	5 −1.4 (1.7)
Afimetoran 30 mg QD	8	8 −5.8 (1.1)	7 −7.2 (1.4)	7 −7.4 (1.3)	7 −7.6 (1.2)	5 −6.6 (1.5)

By week 16, the proportion of patients achieving the minimum clinically important difference in CLASI-A scores (>4 points from baseline) was higher for afimetoran (50%) vs placebo (0%)

Baseline is the last non-missing results with a collection date/time less than the date/time of the first dose of study medication.
Values shown on the figure represent the difference in adjusted mean change from baseline (SE) between afimetoran vs placebo.
Values next to number of patients represent adjusted mean change from baseline (SE) for afimetoran or placebo.

Mean percent change in CLASI-A score



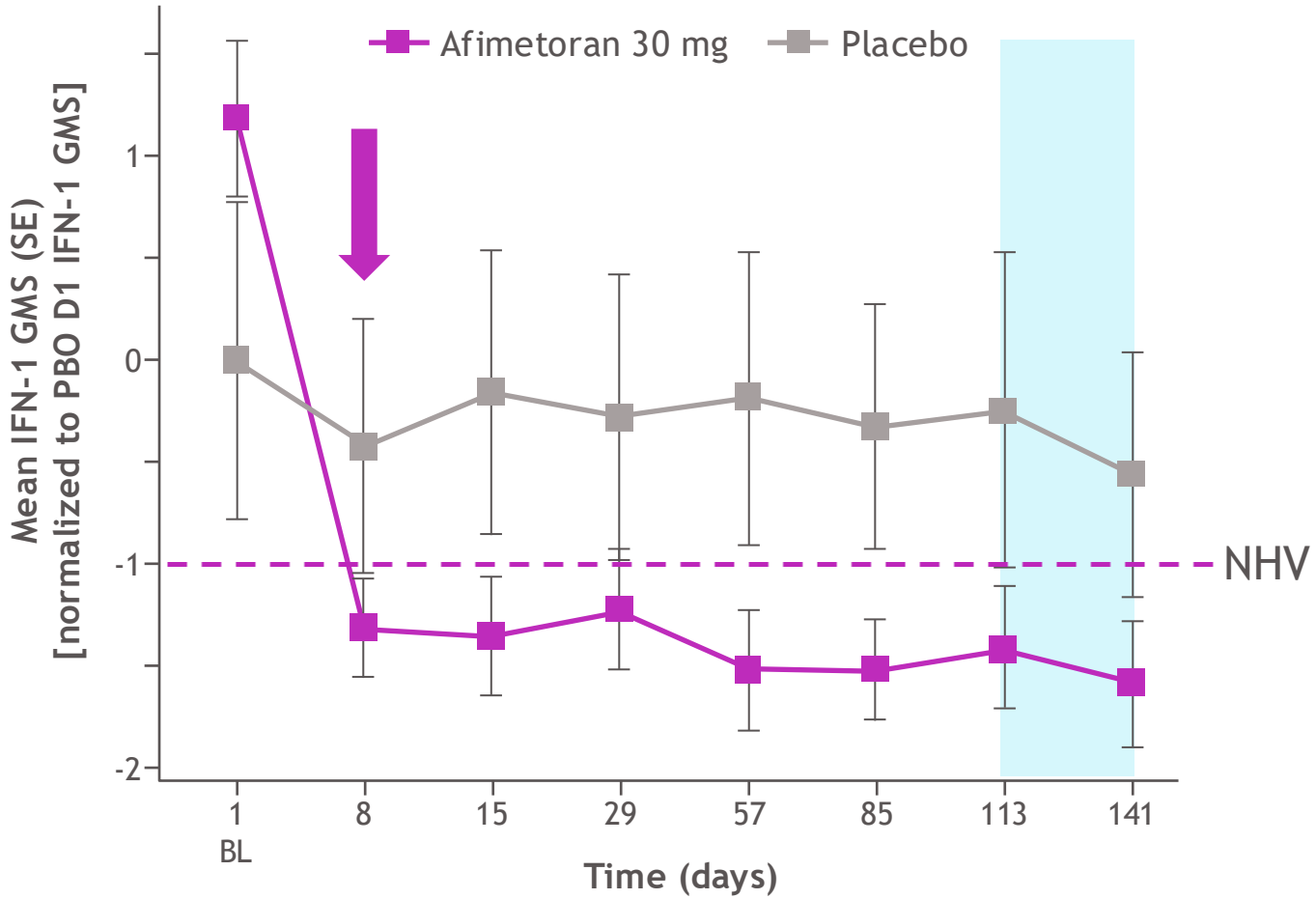
No. of patients						
Placebo QD	5	5 −13.0 (10.0)	5 −16.0 (14.7)	5 −17.2 (14.2)	5 −3.4 (13.8)	5 −5.3 (17.5)
Afimetoran 30 mg QD	8	8 −30.1 (8.4)	7 −37.2 (12.4)	7 −40.2 (11.9)	7 −42.6 (11.7)	5 −31.0 (15.1)

CLASI-50 response was higher in patients treated with afimetoran (50%) vs placebo (0%) by week 16

Baseline is the last non-missing results with a collection date/time less than the date/time of the first dose of study medication.
Values shown on the figure represent the difference in adjusted mean percent change from baseline (SE) between afimetoran vs placebo.
Values next to number of patients represent adjusted mean percent change from baseline (SE) for afimetoran or placebo.

CLASI-50, 50% change from baseline in CLASI score.

Inhibition of IFN-1 gene signature



The exploratory efficacy response (CLASI) follows the pharmacodynamic effects

Pharmacodynamic data revealed a quick response (by day 8)

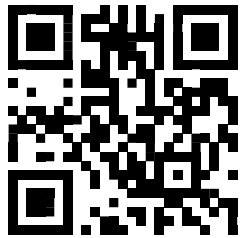
Potent and durable inhibition across several cytokines persists after treatment discontinuation

Whole blood analysis of pathway inhibition using the DxTerity platform. The Y axis displays the mean percent inhibition of IFN-1 gene module score ± SE where the mean of placebo from day 1 is subtracted. Data are reported at day 1, 8, 15, 29, 57, 85, 113, and 141; day 141 is 28 days after last dose.

BL, baseline; IFN-1, interferon 1; GMS, gene module score; NHV, normal human volunteers; PBO, placebo.

Summary

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- This is the first evidence of clinical benefit in patients with the first-in-class, orally bioavailable, potent, and selective inhibitor of TLR7/8, afimetoran
- The primary objective was met as afimetoran:
  - Demonstrated a favorable safety profile and was well tolerated versus placebo in CLE
  - Showed early and sustained clinical response as measured by CLASI-A
  - Changes in CLASI-A tracked well with changes in IFN-1 gene signature
- These results support the continued clinical investigation of afimetoran in lupus, including the ongoing phase 2b study in SLE (NCT04895696)

Acknowledgments

- The authors would like to acknowledge Jasmine Saini of Bristol Myers Squibb for her contributions to this presentation
- Professional medical writing and editorial assistance was provided by Mohammad Tauseef, PhD, at Caudex, a division of IPG Health Medical Communications, New York, NY, USA in accordance with Good Publication Practice 2022 guidelines, and was funded by Bristol Myers Squibb