A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Afimetoran, an Oral, Once-Daily Equipotent TLR7/8 Inhibitor, in Participants with Active Systemic Lupus Erythematosus

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- **TD** has received consulting fees for scientific advice from AbleZeta, Bristol Myers Squibb, Beeline Medicines, Boehringer Ingelheim, Eli Lilly, GSK, J&J, Merck, Novartis, Roche/GNE, UCB, Zenas.
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- **JTM** is a current consultant for AbbVie, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, EMD Serono, Genentech, GSK, Merck, Novartis, Remegen, Sanofi, UCB, and Zenas. She was a consultant for Kezar, Kymera, Lilly, and Takeda in the last 24 months but is not active.
- **SD, LVC, CMC, and MAM** are Bristol Myers Squibb employees and shareholders.
- **KDC** is employed by Beeline Medicines Corporation and holds interests in its parent company, Beeline Medicines, LLC , and is a former employee and current shareholder of BMS.
- **CK, FG, JL, and MJP** are employed by Beeline Medicines Corporation and hold interests in its parent company, Beeline Medicines, LLC
- **NF** is a former employee of Biogen and Nimbus Therapeutics. She is currently a paid employee and officer at Beeline Medicines Corporation and has been awarded equities. She also has equity, shares, and/or stocks in Biogen, OMass Therapeutics, and Nimbus Therapeutics. She is a past unpaid consultant to Rome Therapeutics and has historically received consulting fees from Bain Capital, Atara Biotherapeutics, Nimbus Therapeutics, Sail Biomedicines, Actus Bio, Apini Therapeutics, and Generation Bio. She currently serves on the Board of Directors of OMass Therapeutics. She 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.
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Mechanistic Rationale for Afimetoran in Lupus

Targeting TLR7- and TLR8-Mediated Immune Activation

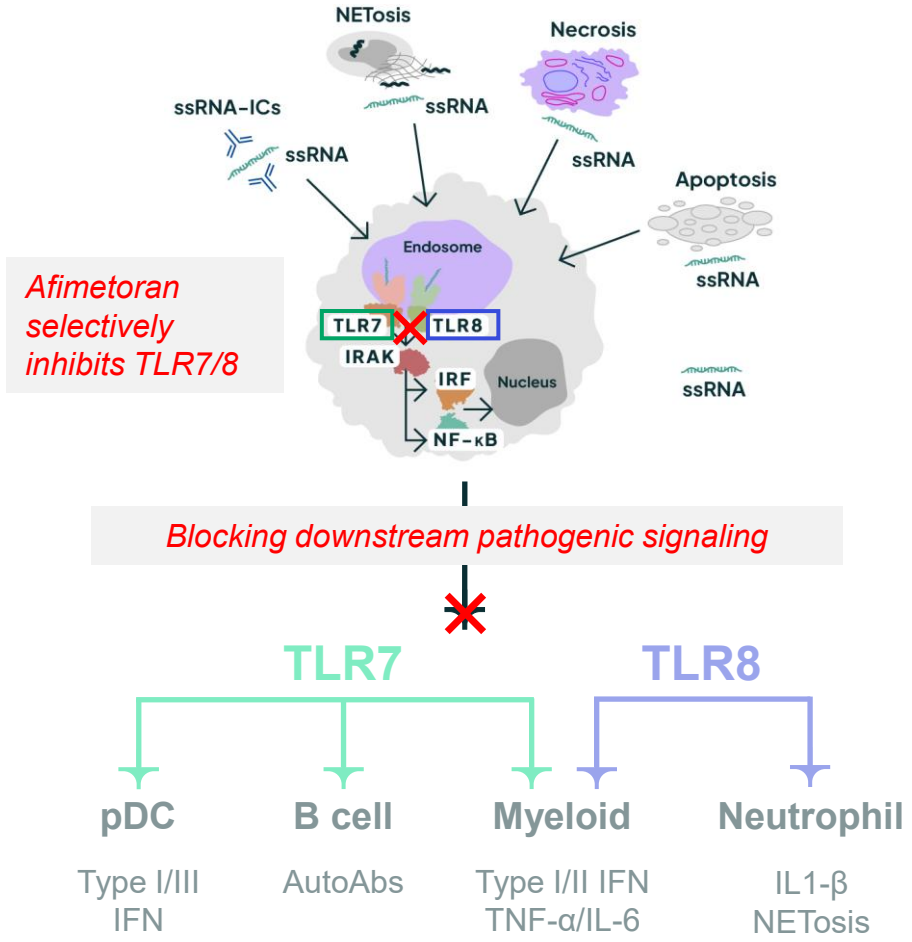
Toll-like receptors 7 (TLR7) and 8 (TLR8) are key upstream catalysts of lupus disease pathology

TLR7

- Upstream driver of Type I IFN production[1,3]
- Genetically validated driver of SLE[2]
- Implicated in glucocorticoid resistance[3,4]

TLR8

- Amplifies inflammatory organ damage[1,5,7]



Afimetoran

- **Oral, once-daily, small molecule**
- **Dual equipotent inhibitor of TLR7/8**
- **Generally, well tolerated across 8 completed Phase 1 studies**
- **In a Phase 1b study in CLE, afimetoran demonstrated reductions in Type I IFN gene signature and improved CLASI score[6]**

Figure adapted from Hosein F et al. (2025)[1,6-8]

Abbreviations: CLE, cutaneous lupus erythematosus; IFN, interferon; 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; ssRNA, single-stranded RNA; TLR7/8, Toll-like receptors 7 and 8; TNF-α, tumor necrosis factor alpha.

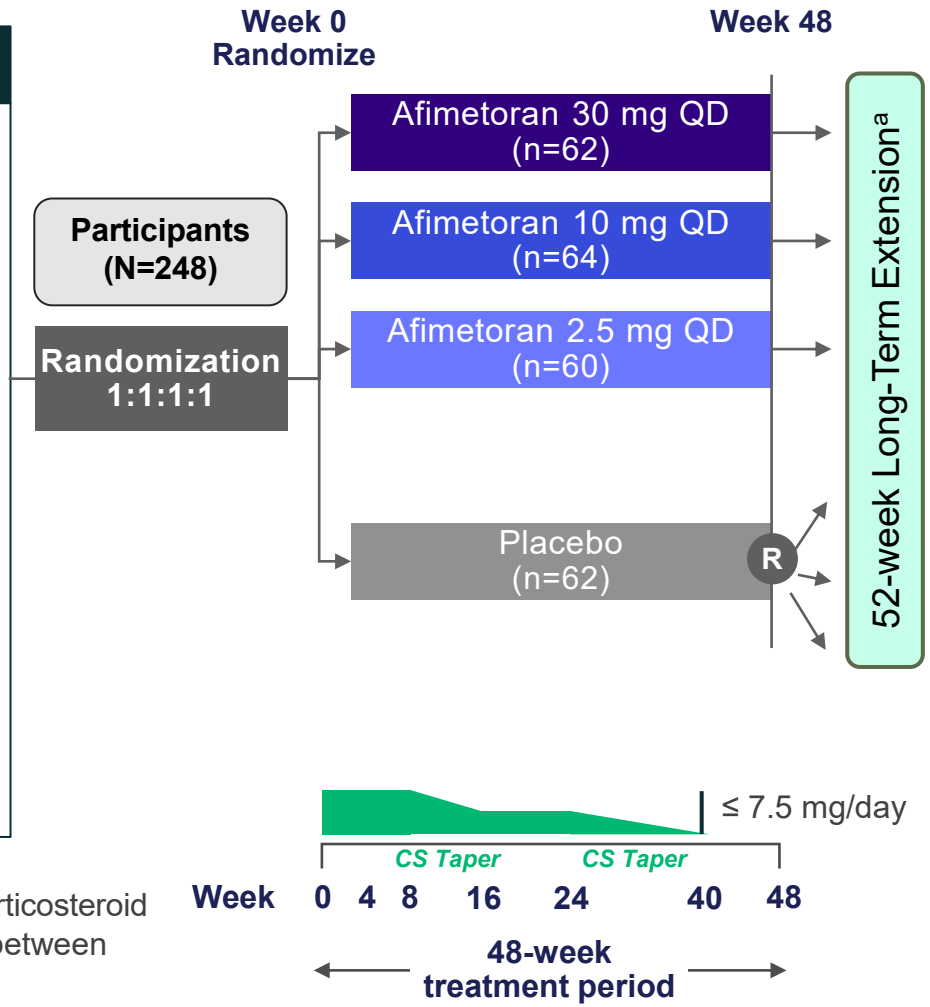
References: 1. Bender AT et al. *Immunohorizons*. 2020;4(2):93–107. 2. Brown GJ et al. *Nature*. 2022;605:349–356. 3. Guiducci C et al. Nature. 2010;465:937-941. 4. Zhao Q et al. *Ann Rheum Dis*. 2023;82(Suppl 1):891. 5. Huang QQ et al. *Curr Rheumatol Rep*. 2009;11(5):357-364. 6. Hosein F et al. ACR *Open Rheumatol*. 2025;7(7):e70059. 7. Vinuesa CG, et al. *Nat Rev Rheumatol*. 2026;22(8):479-495. 8. Maz MP et al. *J Autoimmun*. 2022;132:102865.

Phase 2 Trial Design

NCT04895696

Key Inclusion Criteria

- Aged 18–70 years
- SLE diagnosed (SLICC classification criteria) ≥12 weeks before screening
- ANA, anti-dsDNA and/or anti-Sm antibody positive
- Moderate-to-severe disease activity with joint and/or rash involvement, defined by:
  - Total Hybrid SLEDAI ≥ 6
  - Clinical Hybrid SLEDAI ≥ 4
  - BILAG-2004 1A or 2Bs
  - PGA ≥ 1
- Receiving ≥1 background SLE treatment at a stable dose before screening
- Daily corticosteroid dose ≤20 mg



Mandatory 2-phase corticosteroid tapering beginning between Weeks 4-8

Endpoint Summary

Primary Endpoint

- SLE Responder Index 4 (**SRI-4**) response rate at Week 48

Secondary Endpoints

- **BICLA** response rate at Week 48
- **LLDAS** response rate at Week 48
- **CLASI-50** response rate at Week 48[b]
- **Joint-50** response rate at Week 48[c]
- **CS Sparing** rate at Week 48[d]
- **PGA score** change from baseline at Week 48
- **SF-36 score** change from baseline at Week 48
- **Safety**

Exploratory Outcomes

- **Biomarker** changes from baseline (IFN, C3/C4, anti-dsDNA)

Abbreviations: ANA, Antinuclear Antibodies; BILAG, British Isles Lupus Assessment Group; BICLA, BILAG-Based Composite Lupus Assessment; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CS, corticosteroid; IFN, interferon; LLDAS, Lupus Low Disease Activity State; PGA, Physician Global Assessment; SF-36, Short Form 36; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index SLICC, Systemic Lupus International Collaborating Clinics.

Note: [a]52-week long-term extension period is optional; [b]Proportion of participants with a decrease of ≥ 50% from baseline CLASI-A score among those with a CLASI-A score ≥ 10 at baseline; [c]Proportion of participants who achieve a ≥ 50% reduction from baseline in both swollen and tender joints at Week 48 among those with 6 or more swollen joints and 6 or more tender joints at baseline; [d]Proportion of participants achieving corticosteroid reduction or maintenance at ≤7.5 mg/day at Week 48.

Reference: ClinicalTrials.gov. NCT04895696. Accessed October 14, 2026

Demographic and Baseline Characteristics

Baseline characteristic	Placebo n = 62	Afimetoran 2.5 mg n = 60	Afimetoran 10 mg n = 64	Afimetoran 30 mg n = 62	Total N = 248
Demographics					
Age, years, mean (SD)	42.1 (11.8)	39.0 (10.2)	44.3 (12.5)	41.1 (11.2)	41.6 (11.6)
Female, n (%)	56 (90.3)	59 (98.3)	58 (90.6)	59 (95.2)	232 (93.5)
Disease characteristics					
SLE duration, years, mean (SD)	9.0 (7.55)	8.4 (7.15)	10.4 (8.82)	8.7 (6.39)	9.1 (7.53)
hSLEDAI score, mean (SD)	10.6 (3.32)	10.2 (2.84)	10.9 (2.96)	10.9 (3.24)	10.7 (3.09)
hSLEDAI ≥ 10, n (%)	40 (64.5)	36 (60.0)	46 (71.9)	42 (67.7)	164 (66.1)
BILAG-2004, n (%)					
≥1 A grade	29 (46.8)	27 (45.0)	21 (32.8)	28 (45.2)	105 (42.3)
≥2 B grades	36 (58.1)	35 (58.3)	43 (67.2)	35 (56.5)	149 (60.1)
CLASI activity score (0–70), mean (SD)	7.0 (5.83)	8.6 (6.82)	8.2 (5.53)	8.0 (5.90)	7.9 (6.02)
CLASI ≥ 10, n (%)	14 (22.6)	22 (36.7)	21 (32.8)	16 (25.8)	73 (29.4)
IFN-high at baseline, n (%)[a]	37 (67.3)	33 (66.0)	37 (67.3)	35 (66.0)	142 (66.7)
Number of active joints (0–40), mean (SD)	7.7 (4.95)	7.7 (4.35)	7.6 (4.93)	7.2 (4.45)	7.6 (4.66)
Concomitant medications, n (%)					
Oral corticosteroids	50 (80.6)	49 (81.7)	49 (76.6)	54 (87.1)	202 (81.5)
Mean (SD) daily oral corticosteroid dose mg[b]	9.5 (4.6)	10.6 (5.7)	10.1 (5.3)	9.1 (4.6)	9.8 (5.1)
< 10 mg/d, n (%)	32 (51.6)	30 (50)	34 (53.1)	31 (50)	127 (51.2)
≥ 10 mg/d, n (%)	30 (48.4)	30 (50)	30 (46.9)	31 (50)	121 (48.8)
Antimalarials	53 (85.5)	50 (83.3)	52 (81.3)	53 (85.5)	208 (83.9)
Immunomodulators	34 (54.8)	33 (55.0)	22 (34.4)	29 (46.8)	118 (47.6)

- **Approximately 80% of afimetoran-treated patients completed 48 weeks of treatment, compared to 69.4% of placebo-treated patients**
- **Patient compliance was >94% in afimetoran-treated arms**
- **Overall rate of completion was aligned with similar 48-week SLE trials**

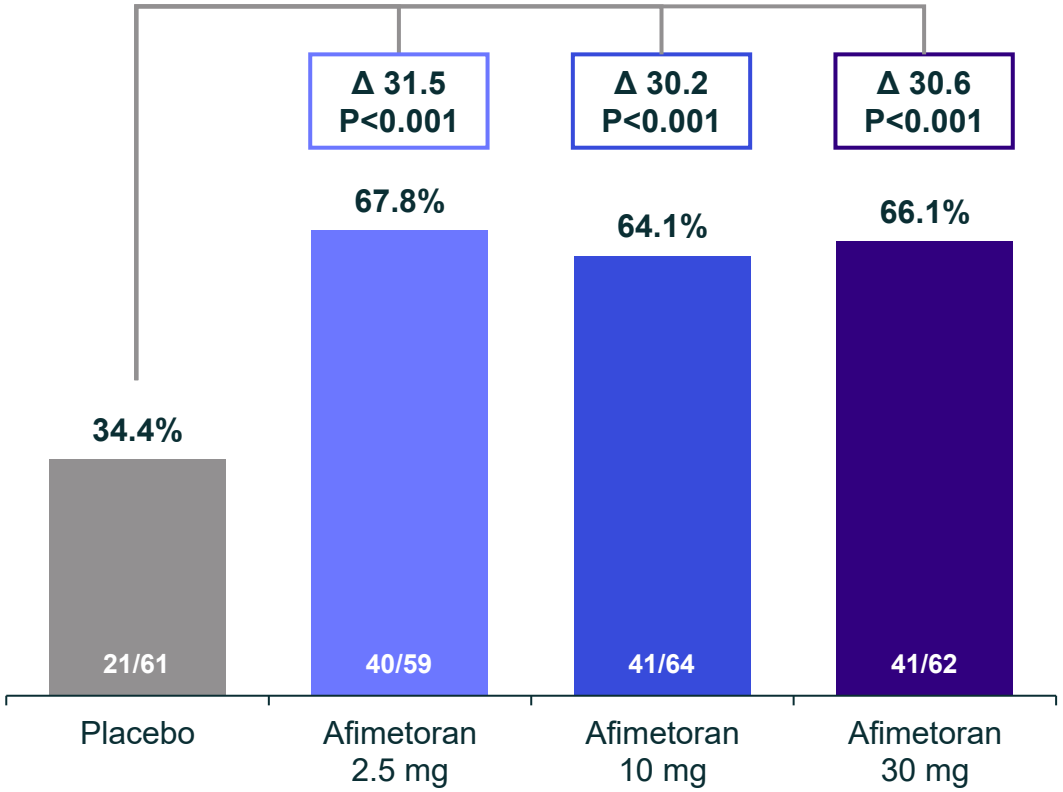
Abbreviations: BILAG, British Isles Lupus Assessment Group; CS, corticosteroids; CLASI, Cutaneous Lupus Disease Area and Severity Index; hSLEDAI, hybrid Systemic Lupus Erythematosus Disease Activity Index; IFN, interferon; QD, once daily; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

Note: [a]Based on 213 participants with IFN levels available at baseline. [b]Includes patients on CS at baseline. BILAG-2004 1A or 2B: Having at least one A grade or at least two B grades. Oral CS is identified as medications administered orally with WHO Drug Global Dictionary preferred name containing one of the following terms: prednisone, prednisolone, methylprednisolone, meprednisone, triamcinolone, cortisone, hydrocortisone, dexamethasone, betamethasone, deflazacort. Active Joint: A joint that is both tender and swollen.

Primary Endpoint: SLE Responder Index 4 (SRI-4)

The primary endpoint was met across all afimetoran dose groups (p<0.001 for all doses)

	Placebo N = 62	Afimetoran 2.5 mg N = 60	Afimetoran 10 mg N = 64	Afimetoran 30 mg N = 62
n	61	59	64	62
Responders	21	40	41	41
Response Rate (95% CI)	34.43 (22.73, 47.69)	67.80 (54.36, 79.38)	64.06 (51.10, 75.68)	66.13 (52.99, 77.67)
Δ vs. pbo (95% CI)	NA	31.5 (14.5, 48.5)	30.2 (13.2, 47.2)	30.6 (13.3, 47.8)
Odds ratio vs. pbo (95% CI)	NA	4.18 (1.83, 9.54)	3.57 (1.61, 7.90)	3.66 (1.64, 8.15)
P-value	NA	0.0004	0.0009	0.0006



Difference of over 30% vs. placebo for every afimetoran dose group at Week 48

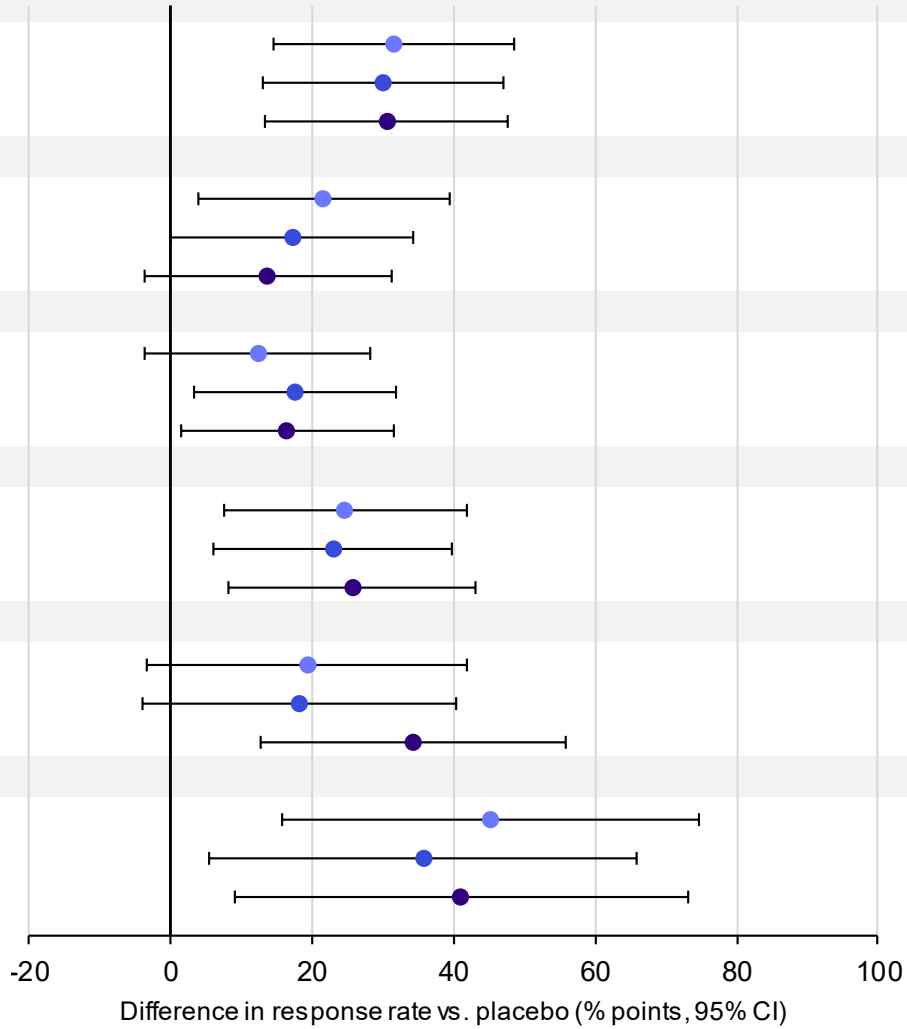
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CRF, case report form; CS, corticosteroid; ICE, intercurrent event; NA, not applicable; N, number of randomized participants; n, number of evaluable participants; pbo, placebo; SLE, systemic lupus erythematosus; SRI-4, SLE Responder Index-4

Note: Response rate 95% CI: Clopper-Pearson. Difference, odds ratio, 95% CIs, p-value: CMH test stratified by CRF factors from CRF data. ICE=Intercurrent event. Non-responder due to ICE: Responders or those with missing data become non-responders due to ICE. ICE#1: Terminated study participation for any reason before Week 48; ICE#2: Had oral CS dose >7.5 mg QD prednisone or equivalent after Week 40; ICE#3: Any burst of CS (oral or systemic) rescue therapy after Week 16 in response to increased SLE activity*unless it is one single ≤5 mg/day CS dose increase for up to 14 days during Weeks 24-40 that does not extend beyond Week 40. *Note: During CS taper (permitted during Weeks 4-16, 24-40), stepping back to the previous dose level is not considered rescue. ICE#4: Termination of study treatment prior to Week 48; ICE#5: Initiation or increase in oral CS dose after Week 40 for disease under study. ICE#6: Initiation or increase in dose of non-CS SLE medication (excluding analgesics, nonoral and non-topical NSAIDs) for disease under study prior to Week 48; ICE#7: Initiation of prohibited immunomodulatory medications prior to Week 48 for disease under study.

Primary and Secondary Efficacy Endpoint Summary

Secondary endpoints demonstrate consistency with SRI-4 and clear activity across disease measures at Week 48

Endpoint / Dose	Response Rate	Placebo Rate	Difference	Odds Ratio (95% CI)
SRI-4 (Primary)				
Afimetoran 2.5 mg	67.8% (40/59)	34.4% (21/61)	+31.5 (14.5, 48.5)	4.18 (1.83, 9.54)
Afimetoran 10 mg	64.1% (41/64)		+30.2 (13.2, 47.2)	3.57 (1.61, 7.90)
Afimetoran 30 mg	66.1% (41/62)		+30.6 (13.3, 47.8)	3.66 (1.64, 8.15)
BICLA				
Afimetoran 2.5 mg	50.8% (30/59)	27.9% (17/61)	+21.6 (3.8, 39.4)	2.50 (1.14, 5.46)
Afimetoran 10 mg	42.9% (27/63)		+17.2 (0.1, 34.2)	2.14 (0.97, 4.70)
Afimetoran 30 mg	38.7% (24/62)		+13.8 (-3.6, 31.2)	1.81 (0.83, 3.92)
LLDAS				
Afimetoran 2.5 mg	35.6% (21/59)	21.3% (13/61)	+12.3 (-3.6, 28.1)	1.96 (0.81, 4.75)
Afimetoran 10 mg	39.1% (25/64)		+17.6 (3.2, 32.0)	3.02 (1.14, 7.99)
Afimetoran 30 mg	37.1% (23/62)		+16.5 (1.4, 31.6)	2.59 (1.02, 6.55)
CS Sparing (≤7.5mg QD)				
Afimetoran 2.5 mg	75.0% (45/60)	50.0% (31/62)	+24.7 (7.5, 41.8)	3.00 (1.34, 6.73)
Afimetoran 10 mg	71.9% (46/64)		+23.0 (6.2, 39.9)	2.74 (1.26, 5.98)
Afimetoran 30 mg	74.2% (46/62)		+25.7 (8.3, 43.0)	2.89 (1.33, 6.27)
Joint-50 (≥6 Active BL Joints)[a]				
Afimetoran 2.5 mg	62.2% (23/37)	42.9% (15/35)	+19.3 (-3.3, 42.0)	2.19 (0.85, 5.63)
Afimetoran 10 mg	61.0% (25/41)		+18.1 (-4.1, 40.3)	2.08 (0.83, 5.22)
Afimetoran 30 mg	77.1% (27/35)		+34.3 (12.8, 55.8)	4.50 (1.60, 12.66)
CLASI-50 (≥10 BL CLASI-A)[a]				
Afimetoran 2.5 mg	66.7% (14/21)	21.4% (3/14)	+45.2 (15.8, 74.7)	7.33 (1.53, 35.11)
Afimetoran 10 mg	57.1% (12/21)		+35.7 (5.6, 65.9)	4.89 (1.05, 22.83)
Afimetoran 30 mg	62.5% (10/16)		+41.1 (9.1, 73.1)	6.11 (1.20, 31.16)



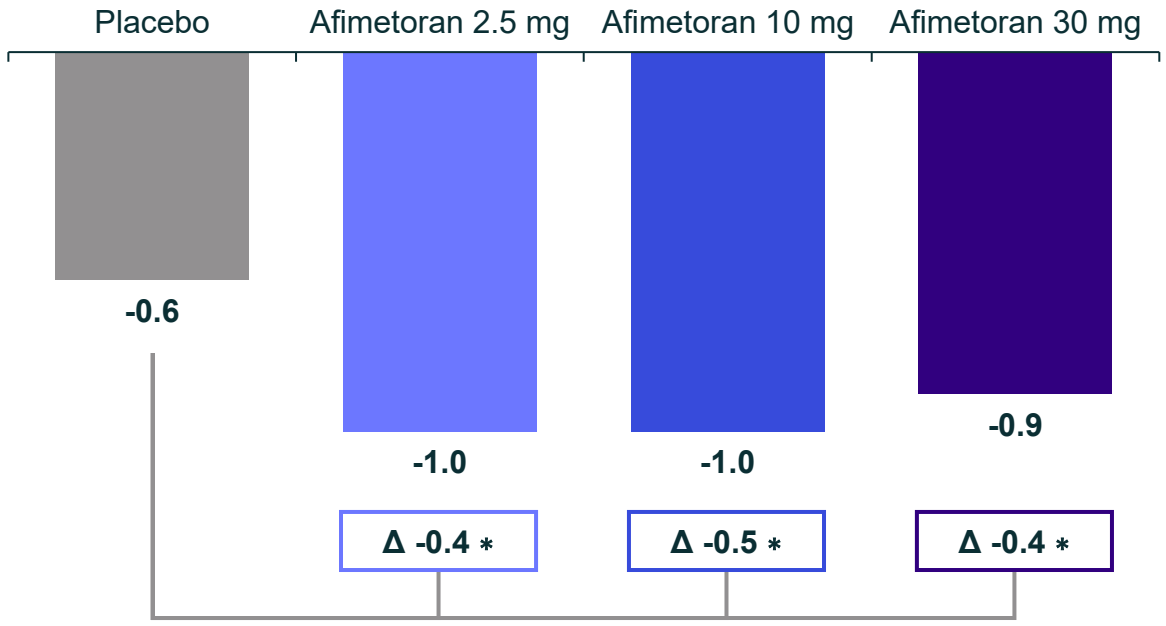
Abbreviations: BICLA, BILAG-based Composite Lupus Assessment; BL, baseline; CLASI, Cutaneous Lupus Disease Area and Severity Index; CS, corticosteroid; LLDAS, Lupus Low Disease Activity State; QD, once daily; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

Note: 95% CI for difference in response versus placebo: Wald method and unadjusted odds ratio CLASI-50: A decrease of ≥50% from baseline CLASI-A score among participants who had a score ≥10 at baseline. Joint-50 (40-joint count): A ≥50% reduction from baseline active joint count among participants with ≥6 active joints at baseline. CS Spare: CS reduction or maintenance to ≤7.5 mg/day (all systemic CS dose, no ICE#3). [a]Difference and Odds Ratio for Joint-50 and CLASI-50 presented on an as-observed basis.

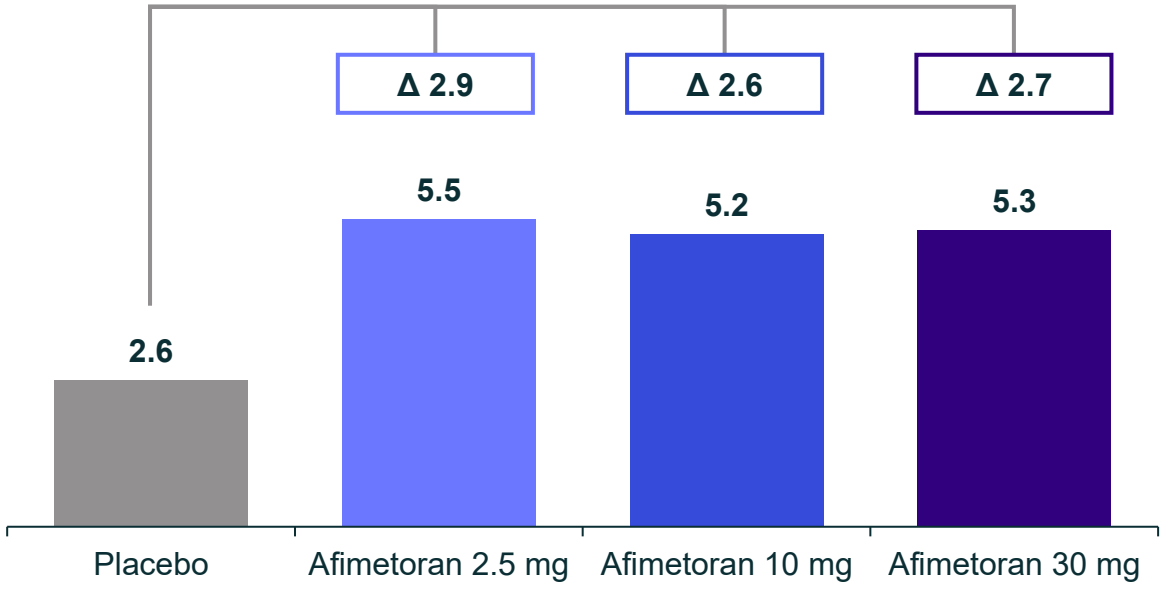
Selected Secondary Endpoints

PGA score and SF-36 (physical component) change from baseline at Week 48

Physician Global Assessment (PGA) of Disease Activity



SF-36 (Physical Component)



- **PGA of Disease Activity was assessed using a continuous horizontal visual analog scale (VAS) from SELENA-SLEDAI**
- **A 0.3-point change is considered clinically meaningful[1a], and was observed in all afimetoran treatment arms**

- **In SLE, the clinically important difference (minimally important difference or MCID) for the SF-36 is commonly accepted as an improvement of at least 4 points in individual domain scores and at least 2.5 points in the physical or mental component summary scores[1]**

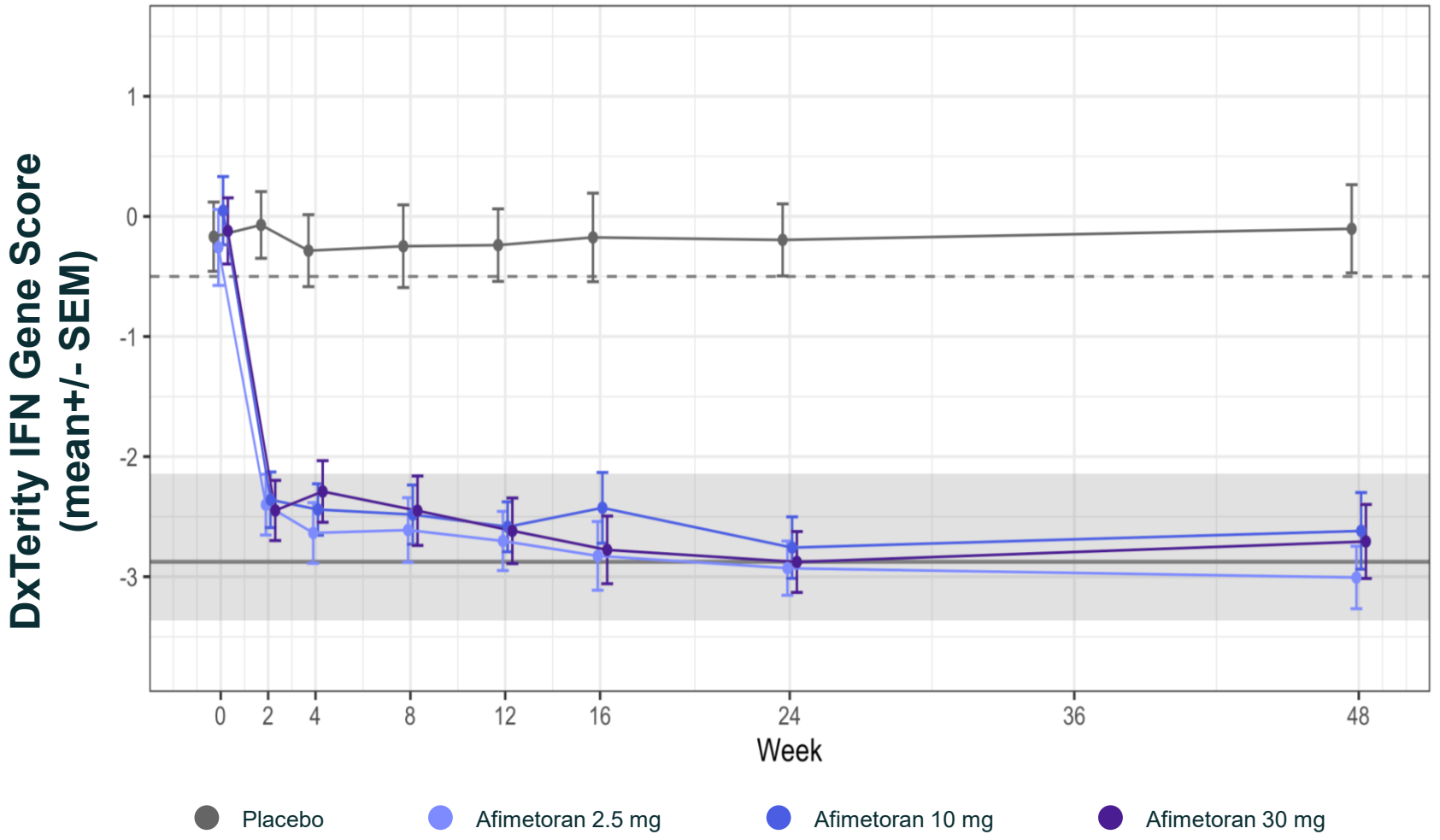
Abbreviations: MCID, minimally clinically important difference; MMRM, mixed model for repeated measures; PGA, Physician Global Assessment; SF-36, 36-Item Short Form Health Survey; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; VAS, visual analog scale

Note: [a]Derived from component of SRI response, defined as no deterioration from baseline in PGA by ≥0.3 points. PGA LS means based on the mixed effect with repeated measure model (MMRM) including treatment, visit, treatment-by-visit interaction, and randomization strata as the fixed effects, change from baseline within each participant as repeated measurements, baseline value as a covariate. Covariance structure is UN. The analysis uses main estimand where measurements after the occurrence of intercurrent event are set as the measurement at baseline. SF-36=36-item Short Form Health Questionnaire; high scores indicating better health status. * = 95% confidence interval for differences excludes zero. Secondaries not controlled for multiplicity.

Reference: 1. Furie et al.. *Lupus Sci Med.* 2014.1(1):e000031.

Type I IFN Gene Expression Level Over Time

Early pharmacodynamic effects seen on IFN signature



- **Pharmacodynamic effects seen as early as first assessment (Week 2) and were consistent over full duration of treatment up to Week 48**
- **For 2.5 mg, 10 mg, and 30 mg once-daily doses, the reduction from baseline in Type I IFN gene expression was near-maximal with minimal dose-dependent differences**

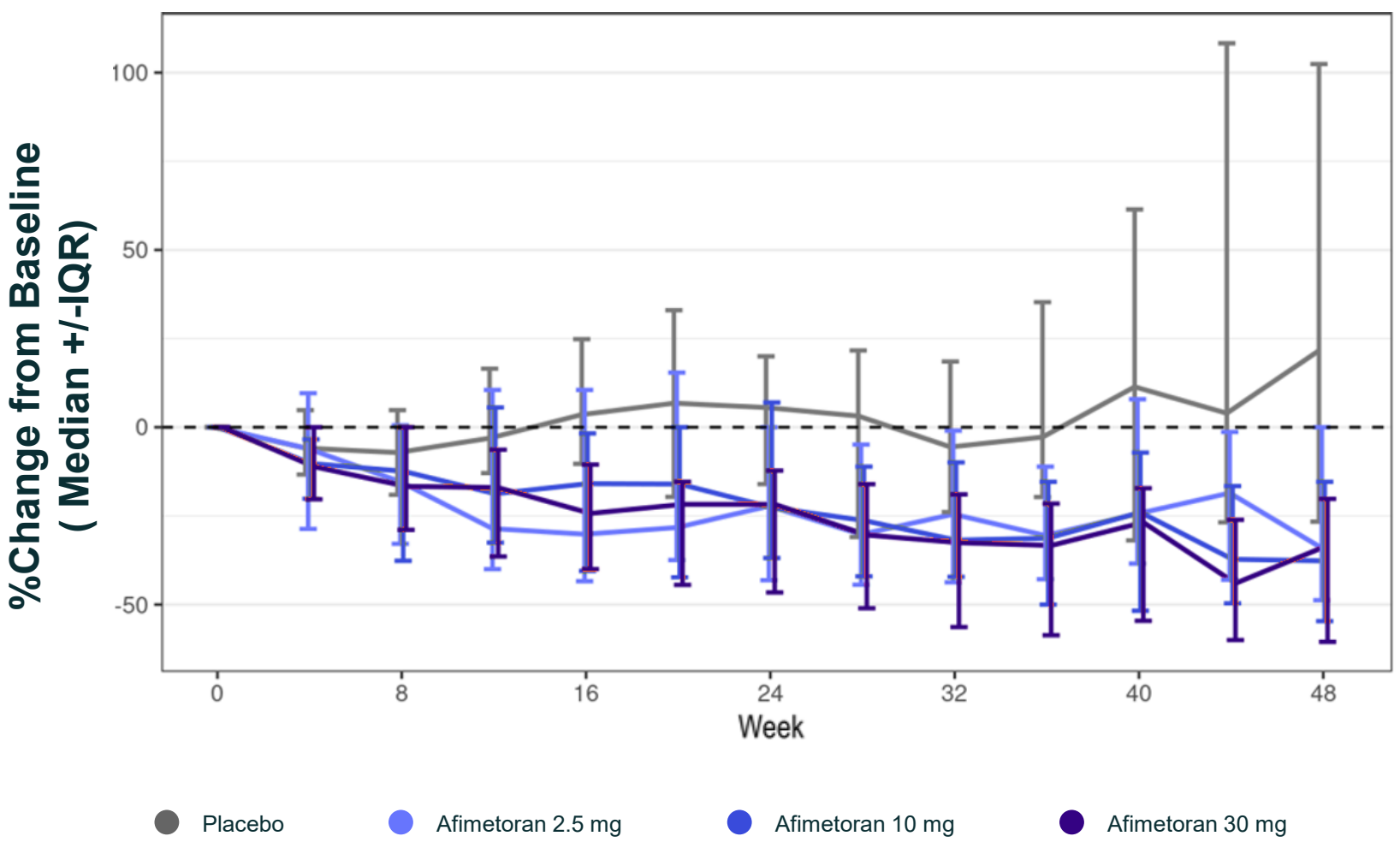
Normal Range

Abbreviations: IFN, interferon; QD, once daily

Note: Gray shaded region depicts the normal range; the continuous line depicts the normal median; the dotted line depicts the cutoff for IFN high/low (-0.5); error bars represent standard error of the mean.

Percent Change from Baseline in Anti-dsDNA Antibodies

Observed decrease across all afimetoran doses in participants with elevated levels at baseline



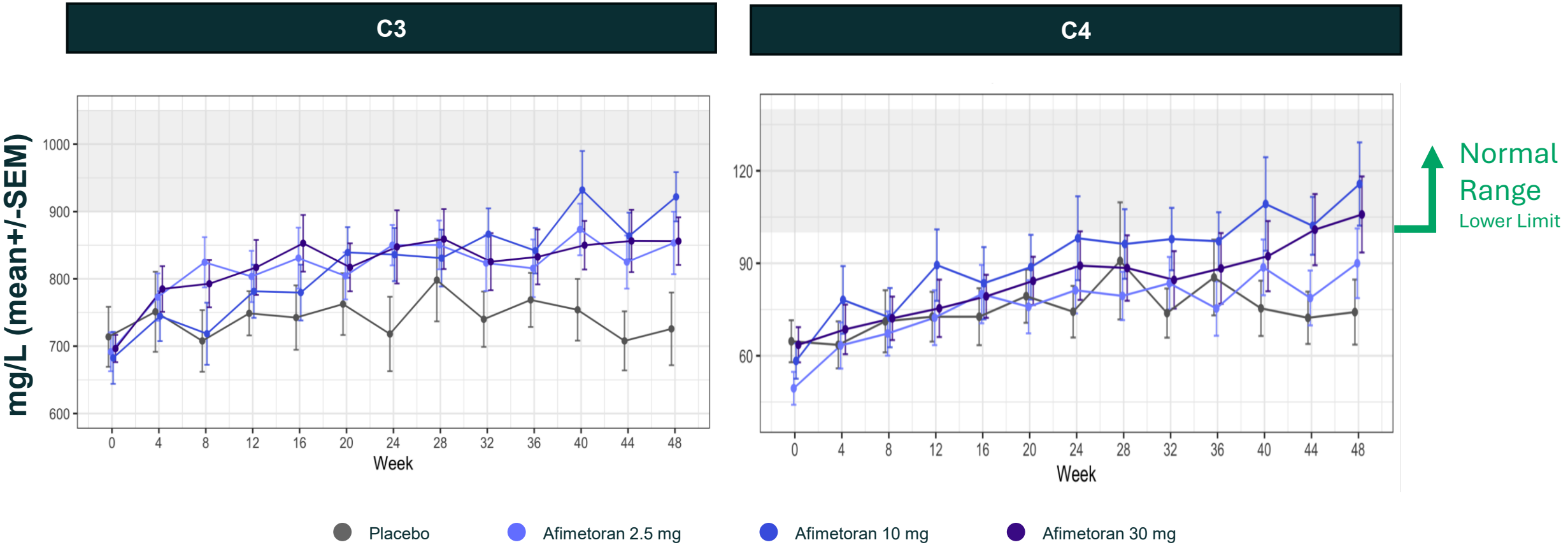
- **Reduction in anti-dsDNA antibodies suggests effect on differentiation of autoreactive plasma cells**

Abbreviations: anti-dsDNA, anti-double-stranded DNA

Note: Error bars represent Inter Quartile Range. Elevated anti-dsDNA at baseline was defined as >4 IU/mL; the dotted line depicts baseline value.

Absolute Change Over Time in C3/C4

Observed increase in afimetoran-treated patients with low complement at baseline



Afimetoran treatment was associated with progressive increases in C3 and C4 toward the normal reference range, while placebo-treated participants showed no consistent improvement

Abbreviations: C3/C4, complement components 3 and 4

Note: Error bars represent standard error of the mean. Low C3 at baseline was defined as <900mg/L. Low C4 at baseline was defined as <100mg/L.

Safety

Afimetoran was generally well tolerated over the 48-week treatment period

Safety parameter, n (%)	Placebo n = 62	Afimetoran 2.5 mg n = 60	Afimetoran 10 mg n = 64	Afimetoran 30 mg n = 62	Afimetoran Total N = 186
Overall TEAE	49 (79.0)	54 (90.0)	55 (85.9)	52 (83.9)	161 (86.6)
Mild	15 (24.2)	17 (28.3)	20 (31.3)	20 (32.3)	57 (30.6)
Moderate	28 (45.2)	35 (58.3)	32 (50.0)	31 (50.0)	98 (52.7)
Severe	6 (9.7)	2 (3.3)	3 (4.7)	1 (1.6)	6 (3.2)
TESAE	8 (12.9)	4 (6.7)	3 (4.7)	4 (6.5)	11 (5.9)
Drug-related TESAE	4 (6.5)	--	--	2 (3.2)	2 (1.1)
TEAE leading to any drug DC	6 (9.7)	1 (1.7)	3 (4.7)	2 (3.2)	6 (3.2)
Infections and Infestations AEs	33 (53.2)	40 (66.7)	38 (59.4)	34 (54.8)	112 (60.2)
Infections and Infestations SAEs	3 (4.8)	1 (1.7)	--	2 (3.2)	3 (1.6)

- No deaths occurred; SAE incidence was comparable across all dose levels and lower than in placebo arm
- Drug-related AEs leading to discontinuation were low in all treatment arms and less than placebo
- No new safety signals observed across reported adverse events, laboratory results, and ECG parameters
- Infections were the most reported AE across all afimetoran arms
- Incidence of serious infections for afimetoran was lower than placebo

Abbreviations: AE, adverse event; DC, discontinuation; ECG, electrocardiogram; QC, quality control; SAE, serious adverse event; TESAE, treatment-emergent serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

Efficacy

- Primary endpoint of SRI-4 at Week 48 was met, with a greater than 30% improvement compared to placebo and p<0.001 across all three afimetoran doses
- Secondary endpoints were directionally consistent with the primary endpoint and demonstrated improvements in skin, joints, steroid sparing, and quality of life measures

PK/PD

- Across all afimetoran doses, IFN gene score suppression was rapid and near maximal by Week 2, with improvements also observed in C3/C4 and anti-dsDNA in patients with abnormal baseline levels

Safety

- All doses of afimetoran were well tolerated with 48 weeks of treatment and most AEs were mild to moderate; low rates of discontinuations and serious infections and no new safety signals were identified

Treatment with afimetoran, an investigational, oral, once-daily, dual equipotent inhibitor of TLR7/8 resulted in improvements in overall disease activity, trend towards normalization of lupus-associated biomarkers, and a favorable safety profile through 48 weeks of treatment, supporting further advancement into pivotal development for SLE and CLE

Abbreviations: AE, adverse event; anti-dsDNA, anti-double-stranded DNA; C3/C4, complement components 3 and 4; IFN, interferon; SRI-4, SLEDAI Responder Index-4; TLR7/8, Toll-like receptors 7 and 8.