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Cenerimod in Japanese patients with moderate to severe SLE: A Phase 2, randomized, double-blind, parallel-group, multicenter trial

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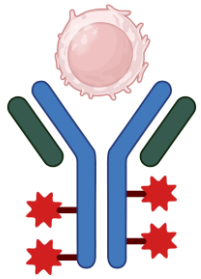
Background

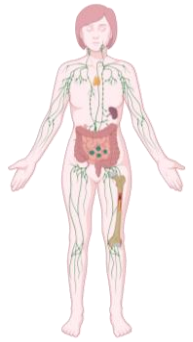
Cenerimod Novel MoA acting on the three main pillars of SLE pathogenesis

Cenerimod is a potent, oral, selective Sphingosine-1-phosphate 1 ($S1P_1$) receptor modulator.



$S1P_1$ receptor modulation can

Inhibit the egress of autoreactive T- and B-cells out of the lymph node.
Reduce pro-inflammatory cytokines, importantly IFN-alpha and IFN-gamma.
Prevent the migration of APCs to the lymph nodes (prevent the priming of new autoreactive T- and B-cells).



Overall, cenerimod's immunomodulatory properties are believed to

Reduce SLE disease activity at all levels.
Reduce systemic & local inflammation.
Reduce organ & tissue damage.

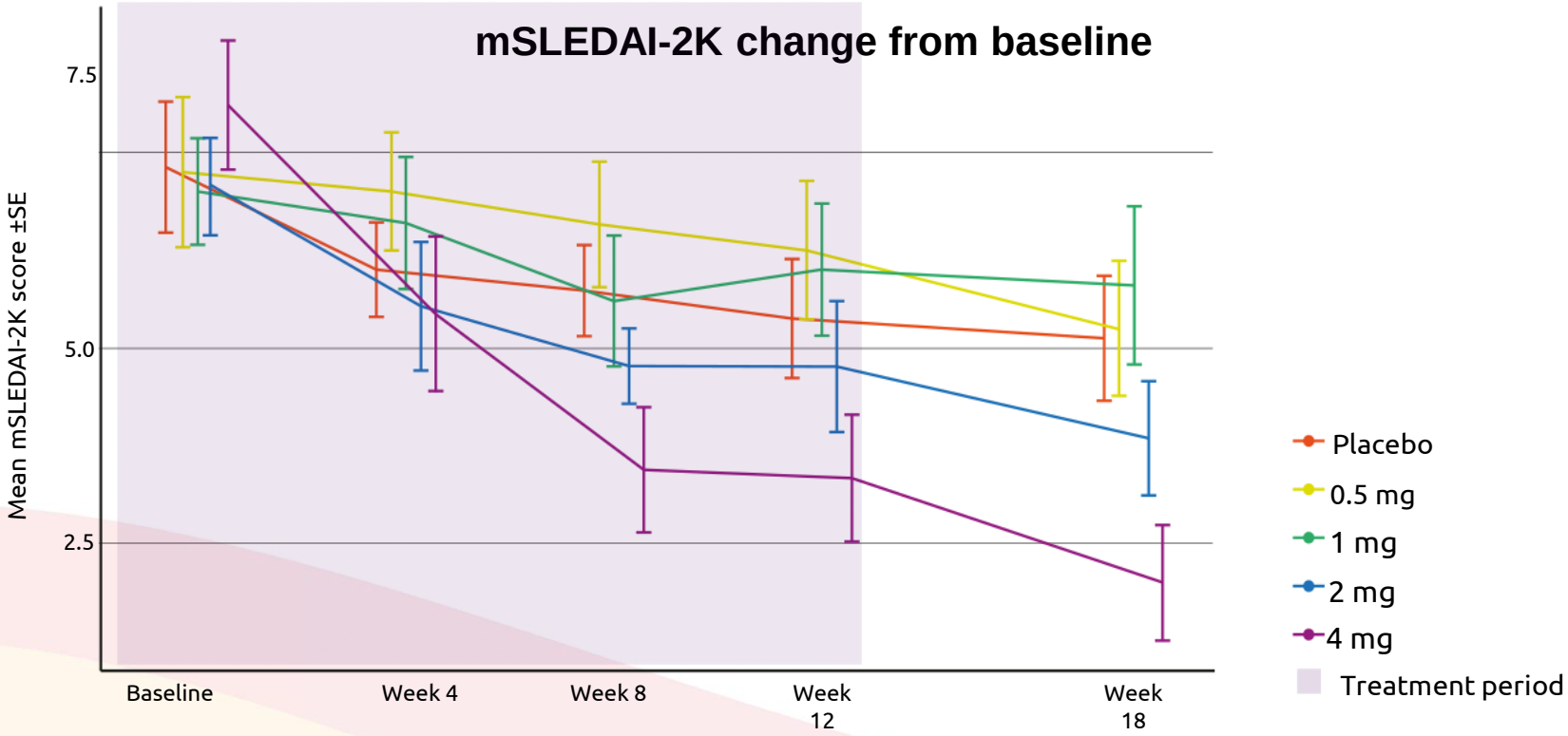
References: Strasser DS, RMD Open. 2020; Gerossier E, Arthritis Res Ther. 2021; Hermann V, Lupus Sci Med. 2019; Askanase A, Arthritis Rheumatol. 2022; Strasser DS, Arthritis Rheumatol. 2022; Hoyler T, Lupus Science & Medicine. 2023. Abstract 2023-0588 Burg N et al. Nature Review Rheumatology 2022,18; Strasser DS, Annals of the Rheumatic Diseases. Abstract. 2024;83:21-22.

Abbreviations: MOA, mechanism of action; SLE, systemic lupus erythematosus; IFN, interferon; APC, antigen-presenting cells

Background

Phase 2a efficacy and safety data

AC-064A201, 67 patients* (placebo, 0.5, 1, 2, and 4 mg)
Well tolerated at all doses tested with no associated clinically relevant safety finding.

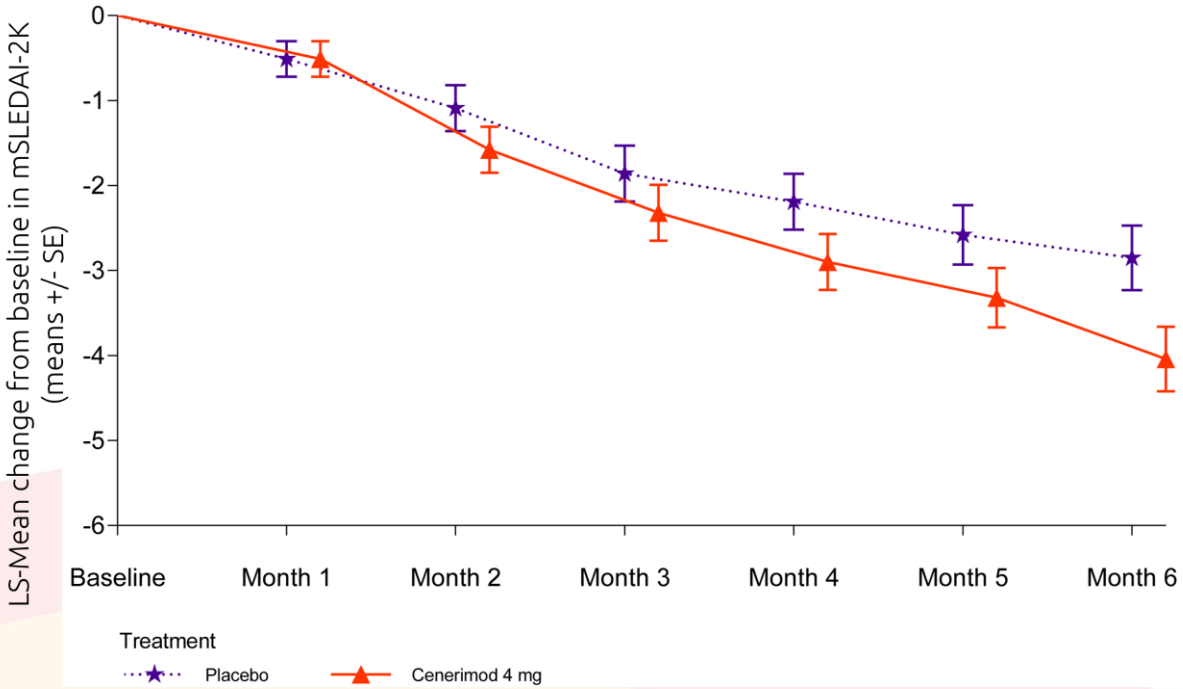


*Hermann v et al, Lupus Sci Med. 2019

Background

Phase 2b efficacy and safety data

ID-064A202 (CARE study*), 427 patients (placebo, 0.5, 1, 2, and 4 mg)
Clinically meaningful reduction in disease activity was seen with 4 mg dose at 6 months. Well tolerated over a treatment period of 6 months.



mSLEDAI-2K LSM change between cenerimod 4 mg and placebo at Month 6 (95% CI)

-1.19 (-2.25, -0.12), P=0.0291

(Nominally statistically significant)

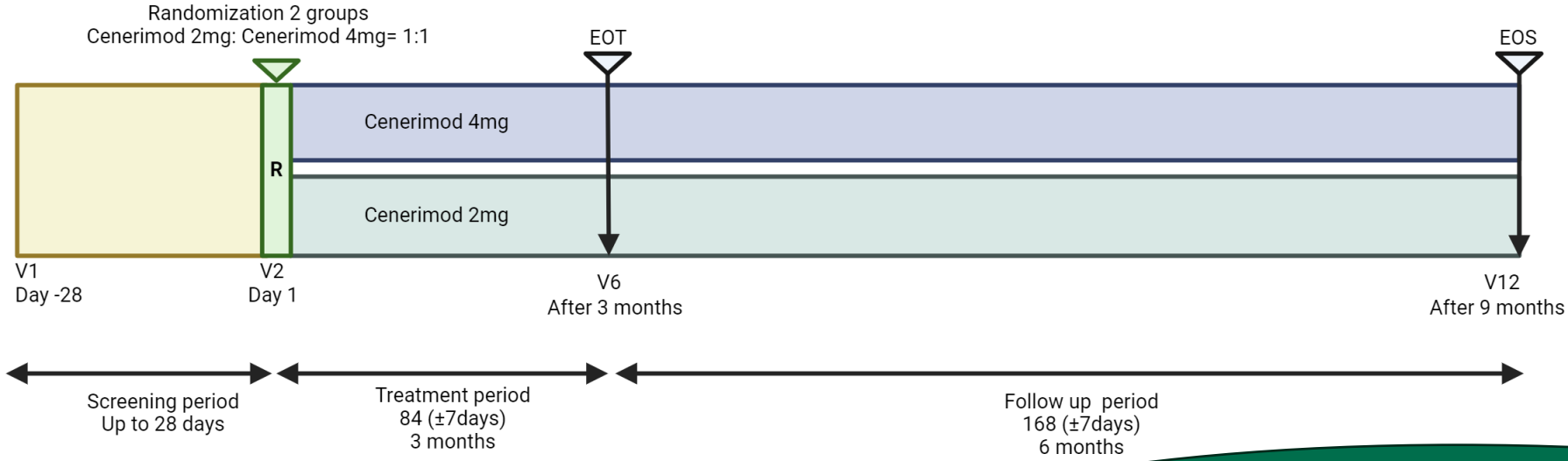
*accepted for publication in Lancet Rheumatology

Consistent safety and efficacy data were reported from both Phase 2 studies with cenerimod 4 mg showing maximum efficacy and all the tested doses (0.5, 1, 2, and 4 mg) were safe and well tolerated.

The current study **(ID-064A203)** evaluated the safety, pharmacodynamics, and efficacy of cenerimod (2 mg and 4 mg) in Japanese patients with moderate to severe SLE.
This study is a regulatory requirement for conducting a Phase 3 study in Japan.

Methodology

Randomized, double-blind, parallel-group, multicenter, phase 2 study.



V= visit, R= randomization, EOT= end of treatment, EOS= end of study

Major Inclusion criteria

- mSLEDAI-2K score of ≥ 6 points, including ≥ 2 for musculoskeletal or mucocutaneous manifestations
- History of positive ANA or dsDNA
- Stable on SLE background therapy

EOT, end of treatment (3 months of treatment);
EOS, end of study (9 months: 3 months of treatment + 6 months of follow up)

Abbreviations: mSLEDAI, modified Systemic Lupus Erythematosus Disease Activity Index 2000; SLE, systemic lupus erythematosus; ANA, Anti-Nuclear Antibody; dsDNA, double-stranded DNA

Study Objectives

Primary objective: Safety and tolerability

Primary Endpoint: TEAEs that occurred until EOS.

Secondary objectives: Pharmacodynamics and Efficacy

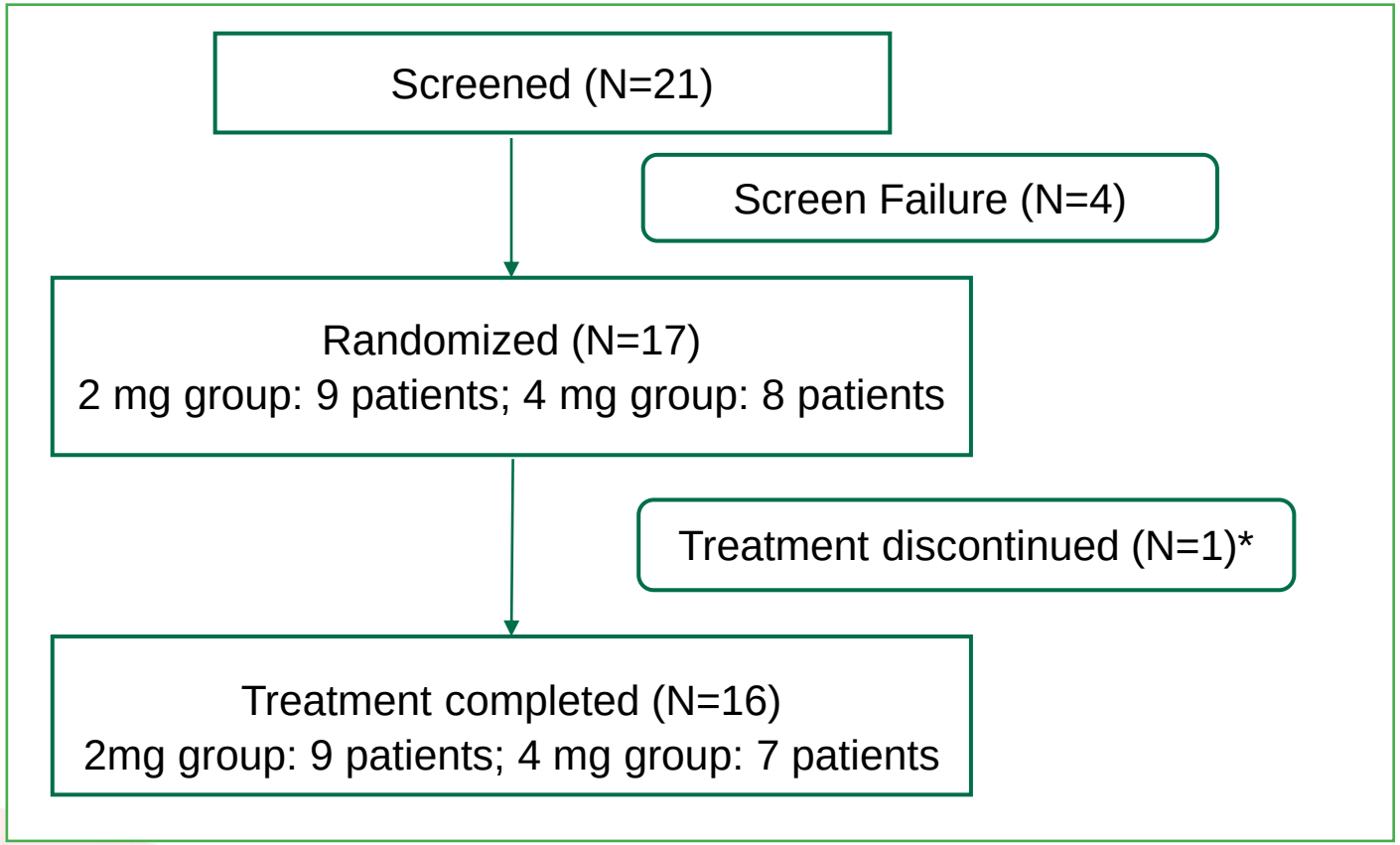
Secondary Endpoints:

- Changes in total lymphocyte count from baseline to each post-baseline assessment up to EOS.
- Change in mSLEDAI-2K score from baseline to each post-baseline assessment up to EOS.

Abbreviations: TEAE, Treatment-emergent Adverse events; EOS, end of study (9 months); mSLEDAI-2K, modified Systemic Lupus Erythematosus Disease Activity Index 2000

Results

Patient Disposition



*One subject in the cenerimod 4 mg group prematurely discontinued the study treatment due to an adverse event (non-serious peripheral edema and increased hepatic enzymes).

Demographic and baseline characteristics

Variable Statistics or category	Cenerimod 2 mg N=9	Cenerimod 4 mg N=8	Total N=17
Sex [n(%)]			
Female	7 (77.8)	8 (100)	15 (88.2)
Male	2 (22.2)	0	2 (11.8)
Age (years)			
Mean ± SD	42 ± 13.90	40.4 ± 10.04	41.2 ± 11.89
Minimum, Maximum	19, 61	30, 56	19, 61
Race [n(%)]			
Asian	9 (100)	8 (100)	17 (100)
SLEDAI-2K total score			
Mean ± SD	7 ± 2.4	9.3 ± 3.06	8.1 ± 2.88
Minimum, Maximum	2, 10	5, 14	2, 14
PGA score			
Mean ± SD	0.947 ± 0.46	1.534 ± 0.62	1.223 ± 0.60
Minimum, Maximum	0.36, 1.83	0.78, 2.22	0.36, 2.22
BPI-SF pain severity score			
Mean ± SD	0.667 ± 0.96	2.031 ± 2.17	1.309 ± 1.74
Minimum, Maximum	0, 2.50	0, 5.50	0, 5.50
NRS-11 score: joint pain at its worst			
Mean ± SD	1.2 ±1.39	4.3 ± 3.33	2.6 ± 2.87
Minimum, Maximum	0, 4	0, 8	0, 8

Abbreviations: SLEDAI, systemic lupus erythematosus disease activity index 2000; PGA, physician global assessment; BPI-SF, brief pain inventory – short form; NSR-11, numeric rating scale

Safety analysis

Summary of overall safety events

	Cenerimod 2 mg (n=9); n (%)	Cenerimod 4 mg (n=8); n (%)
Patients with at least one TEAE	8 (88.9%)	6 (75%)
Patients with at least one SAE*	1 (11.1%)	2 (25%)
TEAE related to study drug	3 (33.3%)	4 (50%)
AE leading to study medication discontinuation	0	1 (12.5%)
AE leading to death	0	0
AE by maximum severity		
Mild	3 (33.3%)	0
Moderate	5 (55.6%)	4 (50%)
Severe	0	2 (25%)

Adverse events in ≥ 2 patients

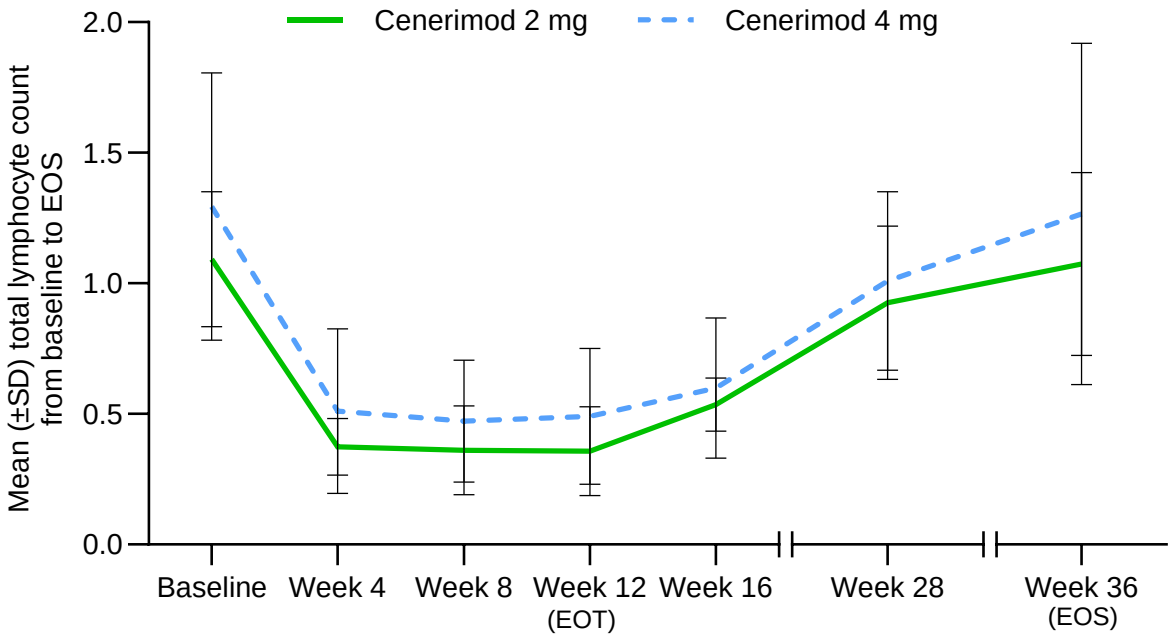
	Cenerimod 2 mg (n=9); n (%)	Cenerimod 4 mg (n=8); n (%)
Hepatic enzyme increased	1 (11.1%)	2 (25%)
Systemic lupus erythematosus	2 (22.2%)	1 (12.5%)
COVID-19	1 (11.1)	1 (12.5%)
Headache	0	2 (25.0%)
Pyrexia	0	2 (25.0%)

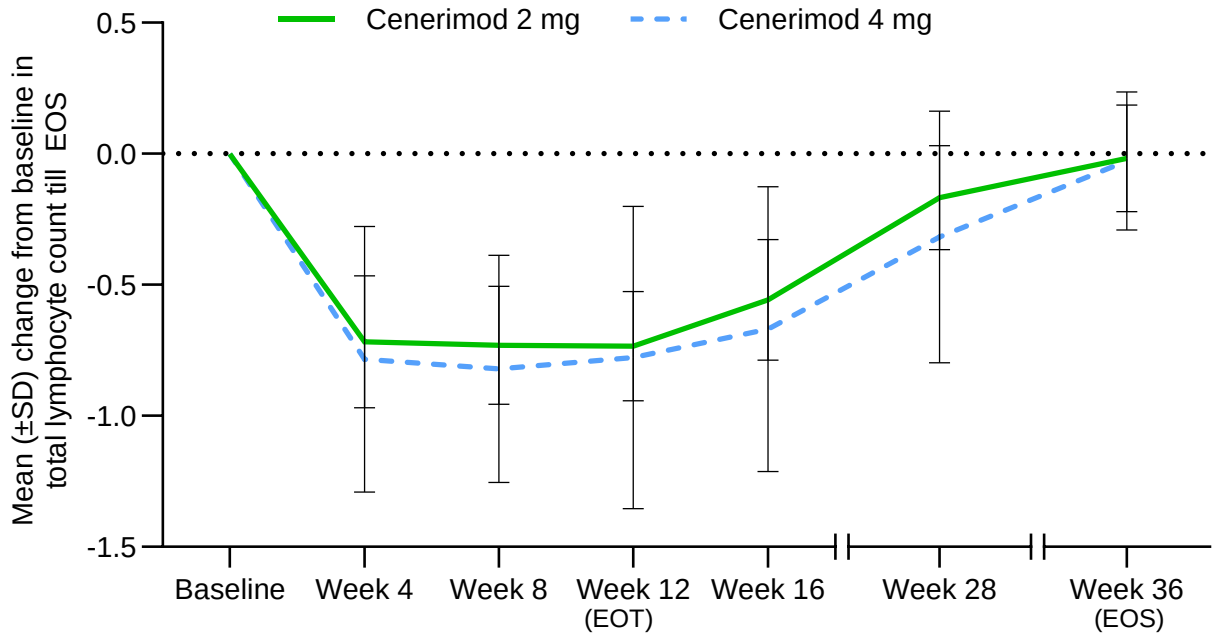
- No dose-dependent increase in the incidence of AEs was observed.
- There were no deaths reported.

*SAEs included large intestine polyp in the 2 mg group, and ulcerative colitis and aseptic meningitis in the 4 mg group.

Abbreviations: AE, Adverse event; TEAE, Treatment-emergent adverse event; SEA, Serious adverse event

Pharmacodynamic analysis





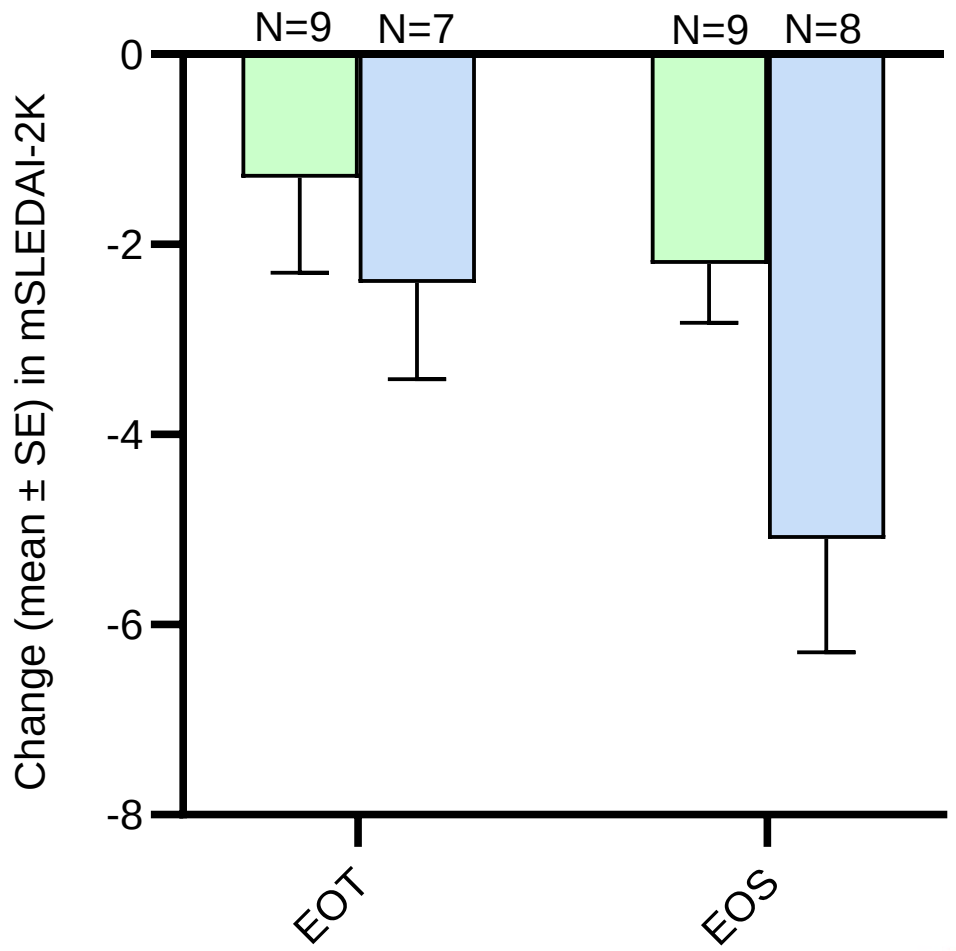
- There was no dose dependent decrease in lymphocyte counts between 4 mg and 2 mg groups.
- The lymphocyte counts at EOS recovered to baseline values. This was in accordance with the clearance of cenerimod from the blood, 6 months after EOT.

EOT, end of treatment (3 months); EOS, end of study (9 months: treatment period of 3 months + 6 months of follow up)

Efficacy analysis

- The change (mean ± SE) in mSLEDAI-2K total score from baseline to EOT was −1.3 ± 1.0 and −2.4 ± 1.02 in the 2 mg and 4 mg groups, respectively. The change from baseline to EOS was −2.2 ± 0.62 and −5.1 ± 1.19 in the 2 mg and 4 mg groups, respectively.
- The results indicate that the effect of cenerimod on disease activity may persist long after treatment ends.

Study 203: Change (mean ± SE) in mSLEDAI-2K from Baseline to EOT and EOS

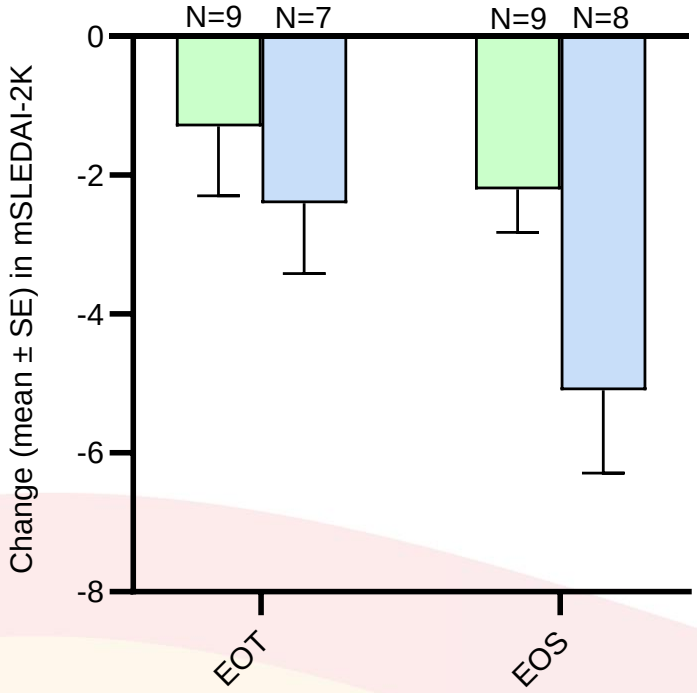


Abbreviations: EOT, end of treatment (3 months); EOS, end of study (9 months: treatment period of 3 months + 6 months of follow up)

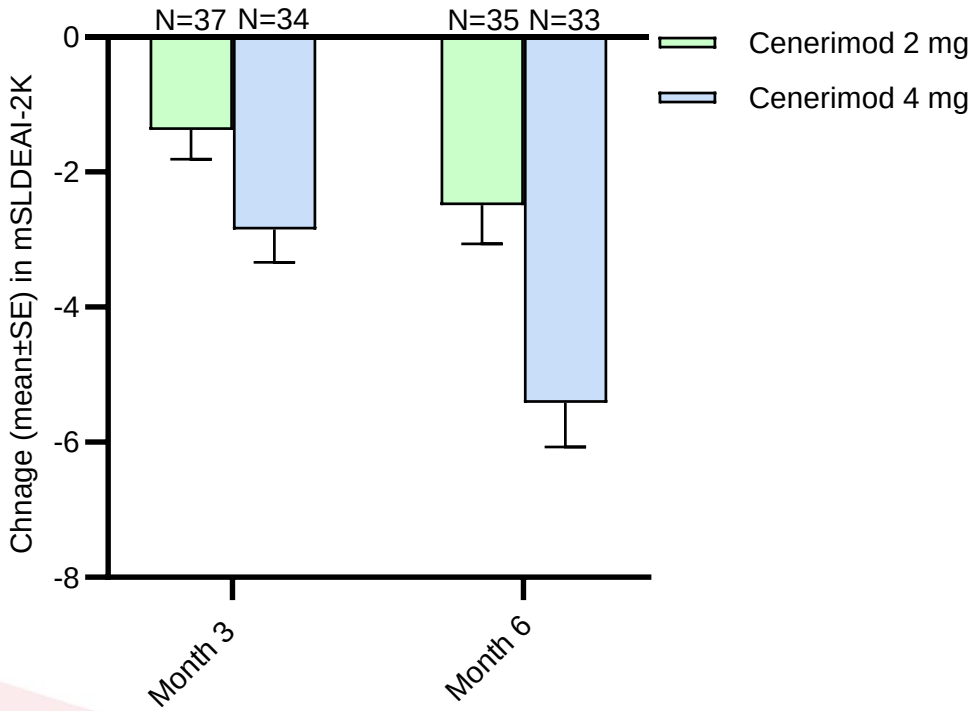
Efficacy analysis (in comparison to CARE Study)

- Higher number of Asian patients with SLE are known to have IFN-1 high gene expression.
- Comparable efficacy results between this study and CARE study (IFN-1 high subgroup) were observed.

Study 203: Change (mean ± SE) in mSLEDAI-2K from Baseline to EOT and EOS



Study 202: Change (mean ± SE) in mSLEDAI-2K from Baseline to 3 and 6 months, IFN-1 high



Abbreviations: EOT, end of treatment (3 months); EOS, end of study (9 months: treatment period of 3 months + 6 months of follow up)

Conclusion

- Both cenerimod doses were considered safe and well-tolerated.
- As expected, a decrease in lymphocyte counts was observed in both doses and was reversible upon treatment discontinuation.
- Both doses showed an improvement in disease activity, as measured by mSLEDAI-2K, which persisted long after the treatment and was higher with 4 mg.
- The 4 mg is the dose is currently being tested in the ongoing phase 3 (OPUS) program.

The results of the Japanese study (ID-064A203) are consistent with the findings from the global Phase 2 trials (AC-064A201 & ID-064A202). Together, these studies provide a robust and comprehensive set of Phase 2 efficacy and safety data.