EULAR Presentation
May 2024

Pharmacodynamic effects of the selective $S1P_1$ receptor modulator cenerimod on the blood transcriptome of patients with SLE

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Idorsia Pharmaceuticals Ltd. and Viatris Innovation GmbH

Conflict of Interest declaration

Daniel Strasser is an employee of Idorsia Pharmaceuticals Ltd.

SLE - a molecularly heterogeneous disease

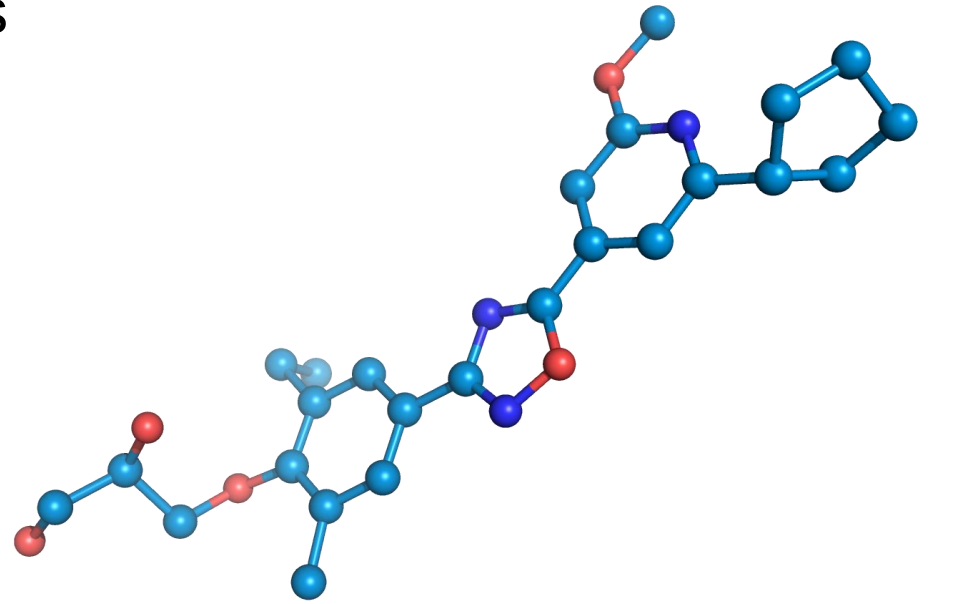
- SLE is a clinically and molecularly heterogeous autoimmune disease.
- The IFN-1 molecular endotype is recognized as an important SLE patient subgroup.
- IFN-1 high patients present with an increased incidence of clinical manifestations such as arthritis[1], and increased risk to develop lupus nephritis[2].
- The IFN-1 high patient endotype associates with high expression of other pathogenic inflammatory pathways such as the IFN-γ pathway[3].

References: [1]Northcott M, Lupus Science and Medicine 2022;9:e000625; [2]Kim CH Mol Diagn 2015;17(2):118-27; [3]Strasser DS, Arthritis Rheumatol. 2022;74(suppl 9):1981-2
Abbreviations: SLE, systemic lupus erythematosus; IFN-1, type-1-interferon.

Cenerimod: Next generation highly selective $S1P_1$ receptor modulator with a novel MoA for SLE

S1P via the $S1P_1$ receptor regulates key pathogenic processes in SLE[1]

- T and B cell egress from lymphoid organs
- Inflammatory response
- Antigen transport into lymphoid organs

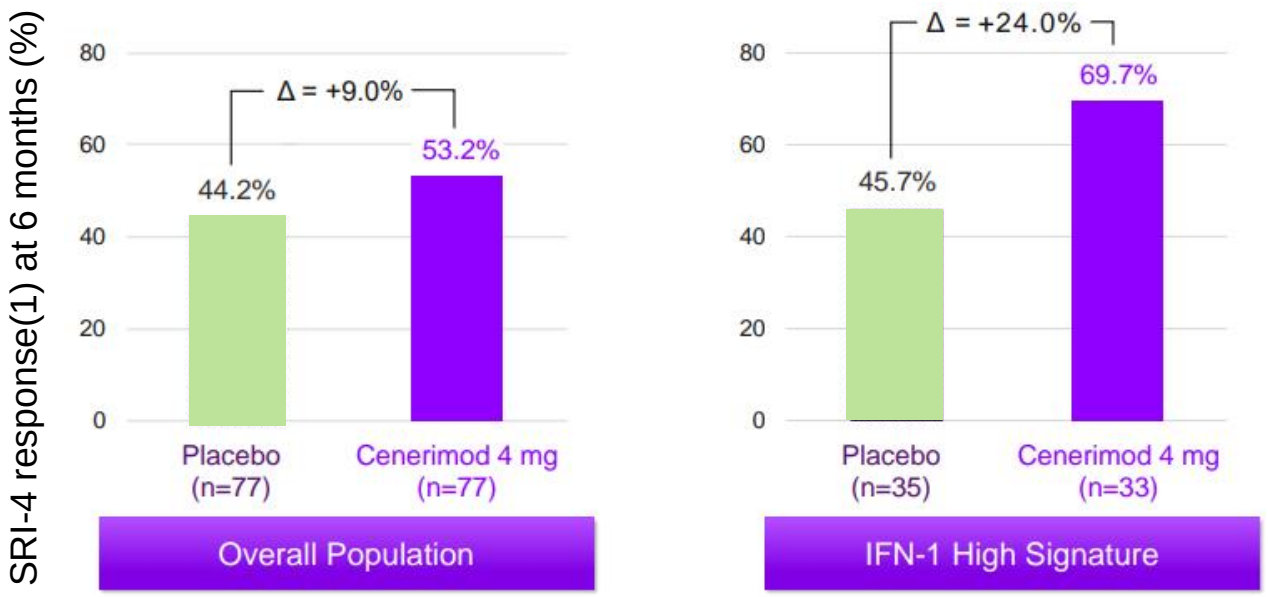


References: [1]Burg N, Nat Rev Immunol. 2022. PMID: 35508810

Abbreviations: MoA, mechanism of action; SLE, systemic lupus erythematosus; $S1P_1$, sphingosine-1-phosphate receptor 1.

Phase 2b Clinical Study (CARE)

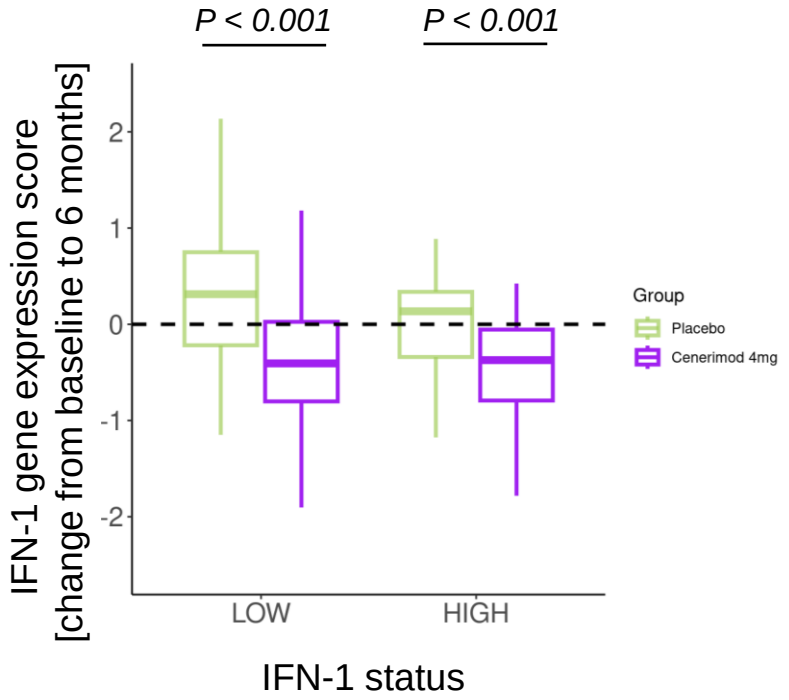
Cenerimod 4 mg improved clinical score in patients with SLE



Full Analysis Set

(1) SRI-4 response is defined as a response of all three components: mSLEDAI-2K (reduction from baseline ≥4), Physicians Global Assessment (increase from baseline ≤0.3), BILAG-2004 (no new BILAG A organ domain score and ≤1 new BILAG B organ domain score)

Cenerimod decreased IFN-1 gene expression in IFN-1 high and low patients



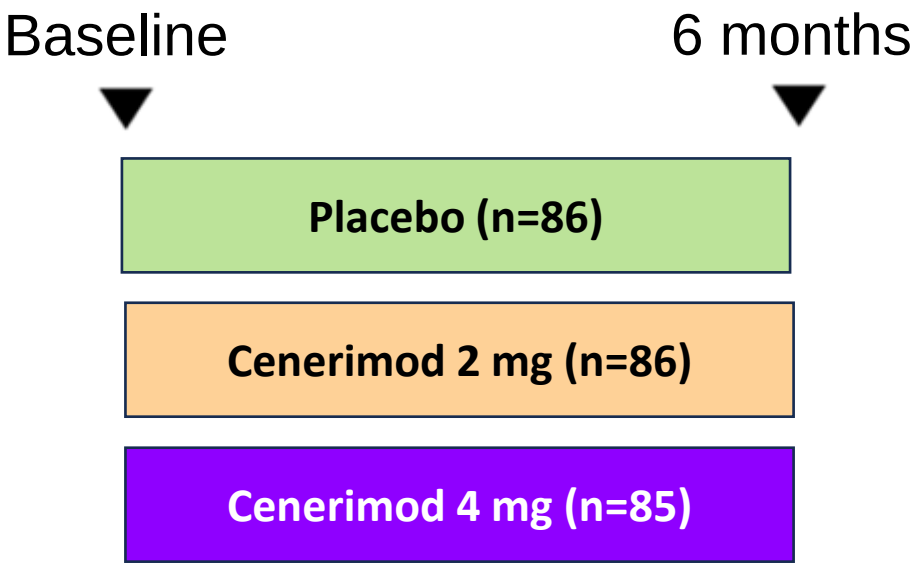
References: Askanase A, Arthritis Rheumatol. 2022;74(suppl 9):3293-7; Strasser DS, Arthritis Rheumatol. 2022;74(suppl 9):1981-2

Objective

Explore the pharmacodynamic effect of 2 mg and 4 mg cenerimod in the whole blood transcriptome in samples from the phase 2b clinical trial (CARE – NCT03742037) in adult subjects with moderate to severe SLE concurrently receiving background therapy.

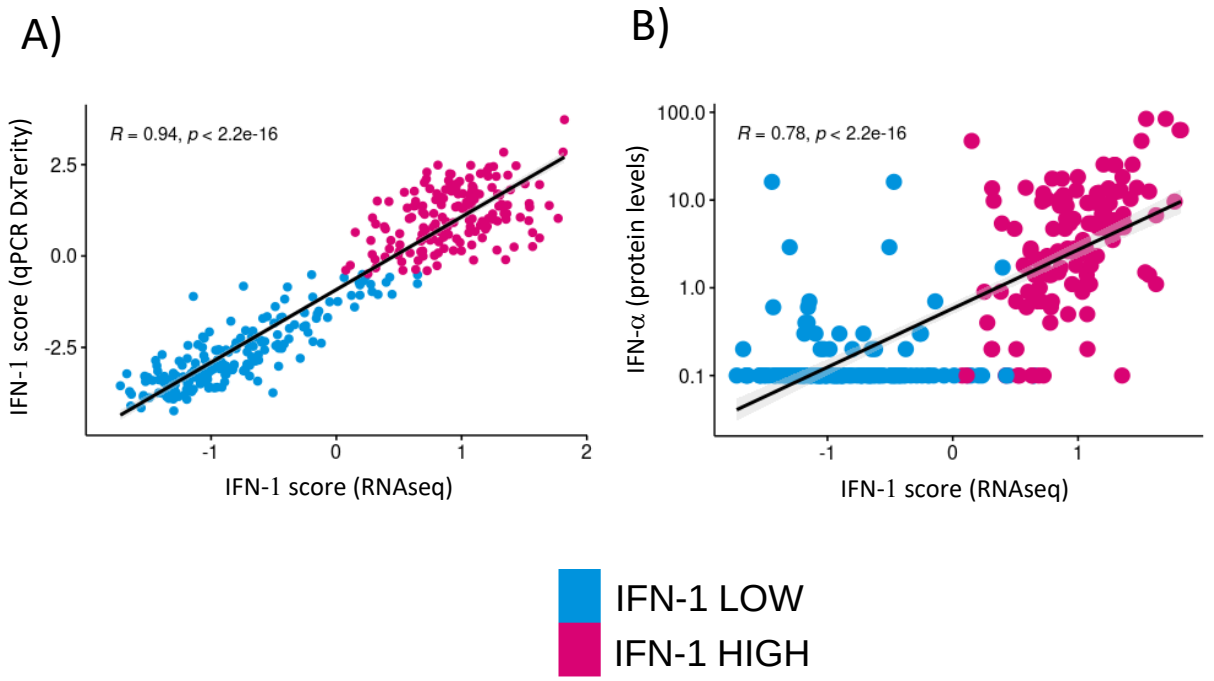
Methods

- Peripheral blood samples from patients with SLE participating in the CARE study were collected at baseline and after 6 months of treatment with cenerimod.
- Gene expression was quantified by qPCR and total RNA sequencing (RNAseq).



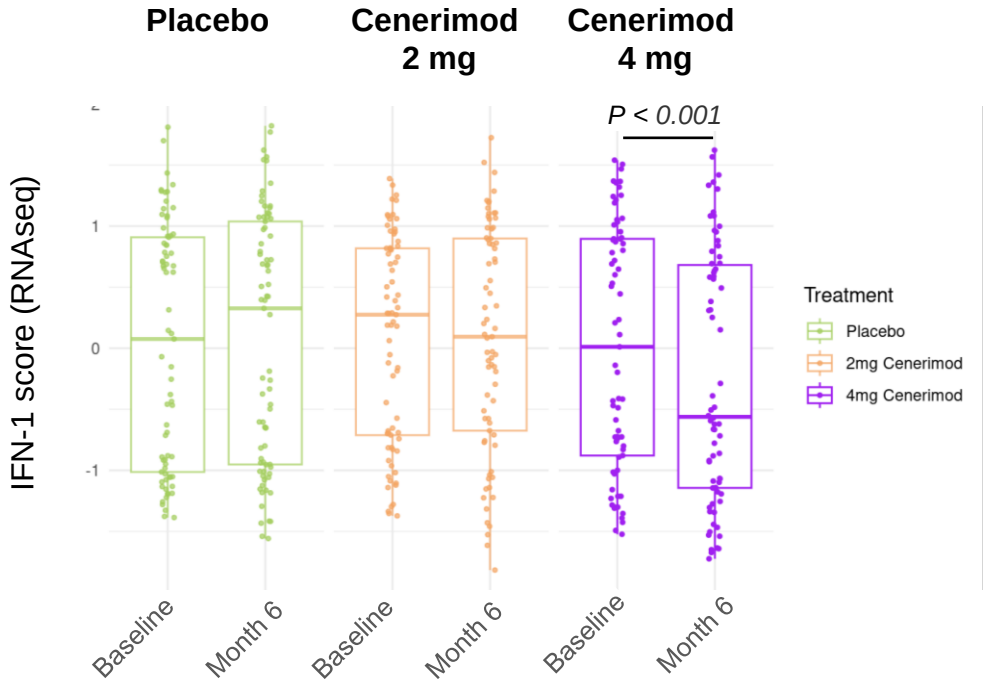
IFN-1 RNAseq score correlates with qPCR score (DxTerity) and protein IFN-α levels

IFN-1 RNAseq score correlates with qPCR score (A) and IFN-α protein levels (B)



Pearson's correlation

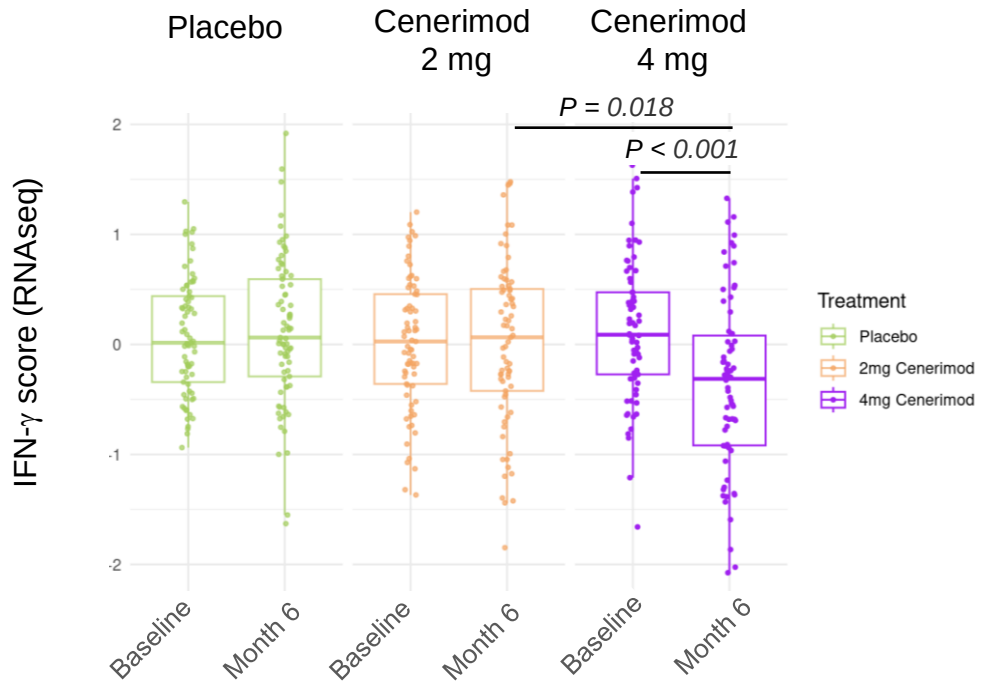
IFN-1 RNAseq score is significantly decreased in the 4 mg cenerimod dose



Linear mixed-effect model

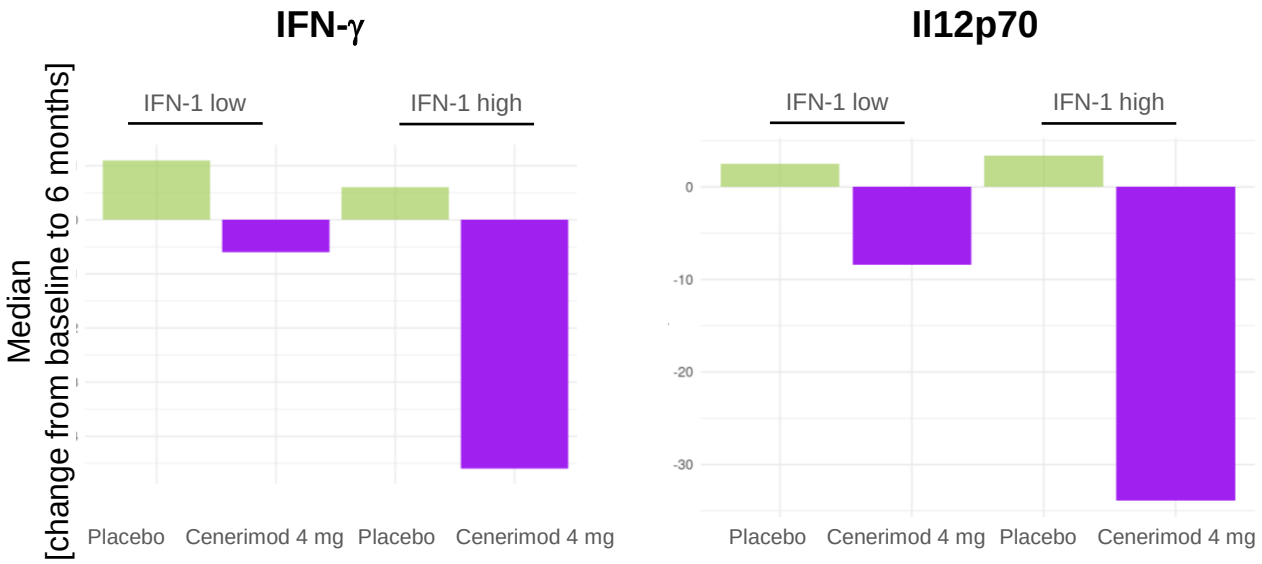
Cenerimod 4 mg reduces IFN-γ RNAseq score and IFN-γ pathway protein levels

Cenerimod 4 mg reduces the IFN-γ signature score



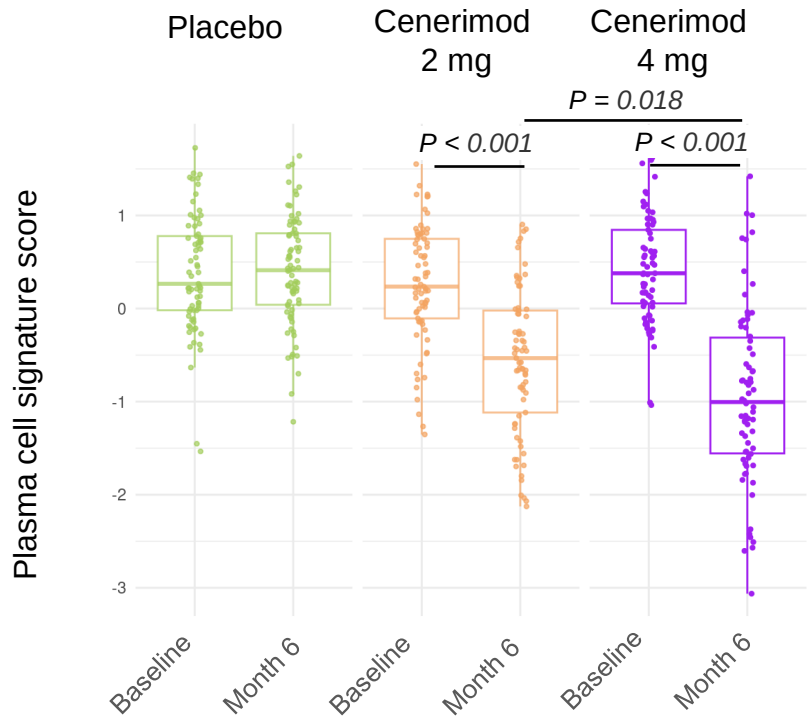
Linear mixed-effect model

Cenerimod 4 mg reduces protein IFN-γ and downstream target of IFN-γ (IL12) particularly in IFN-1 high patients



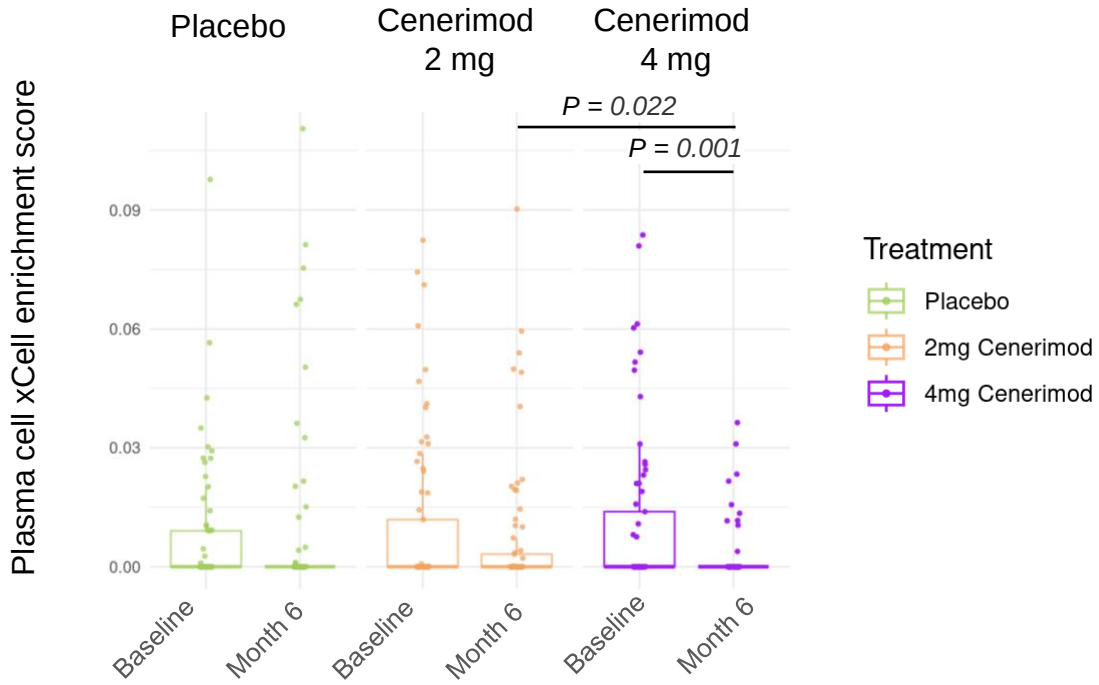
Cenerimod 4 mg shows the most pronounced reduction on plasma cells

Cenerimod 4 mg reduces the plasma cell RNAseq score to a greater extent than 2 mg cenerimod

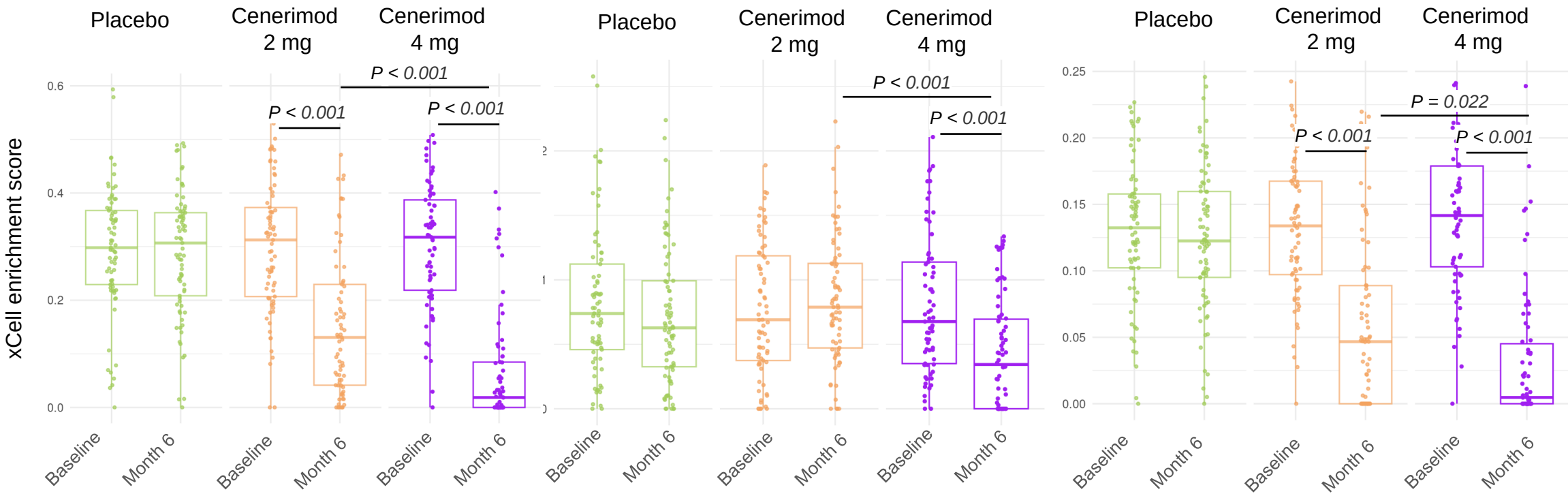


Linear mixed-effect model

Cenerimod 4 mg reduces the plasma cell inferred abundance

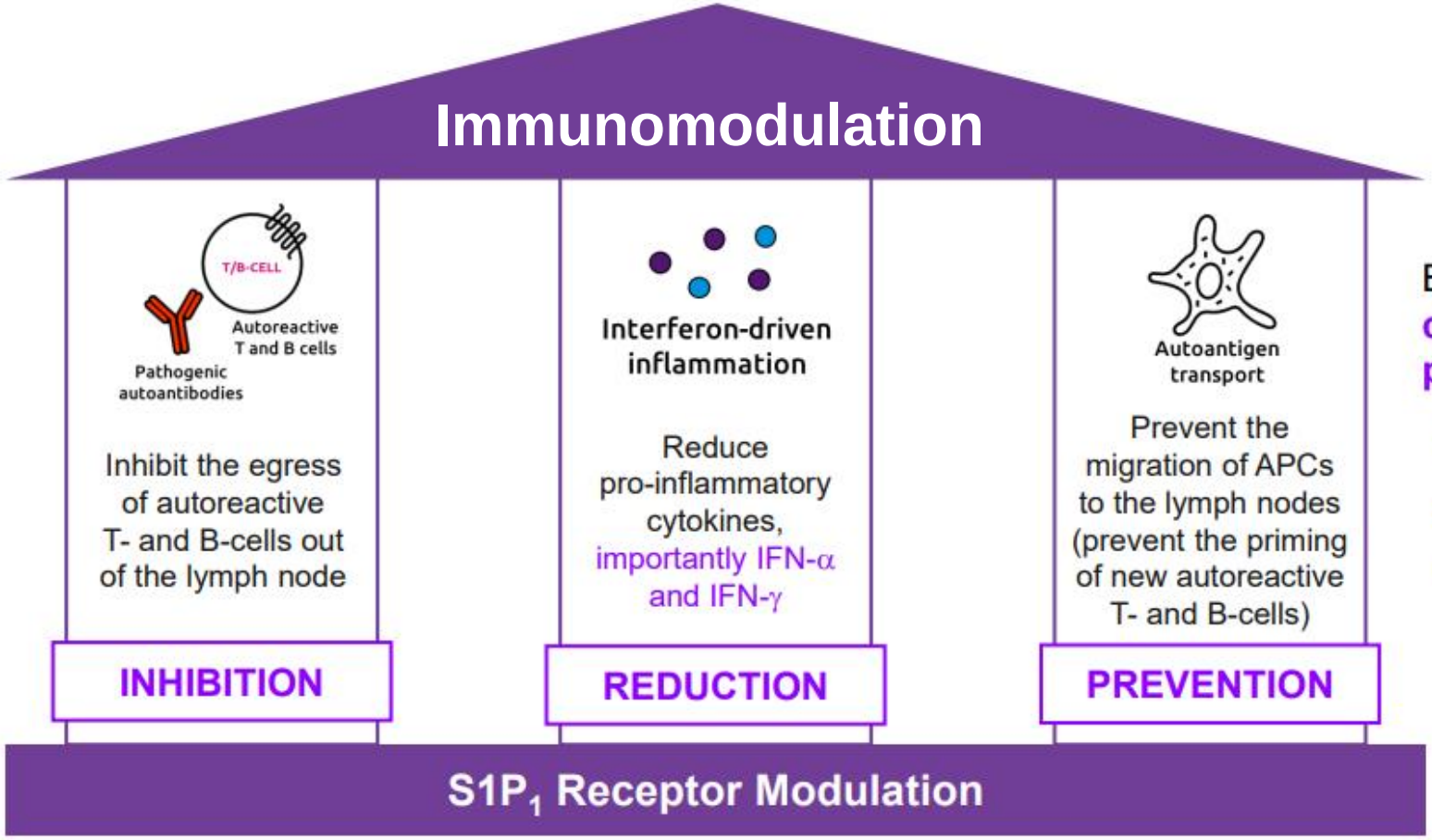


Cenerimod 4 mg shows the most pronounced reduction on inferred T cells abundance



Linear mixed-effect model

Cenerimod – Mechanism of Action



By targeting the S1P/$S1P_1$ axis, **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. PMID: 32917831; Gerossier E, Arthritis Res Ther. 2021. PMID: 34839819; Hermann V, Lupus Sci Med. 2019. PMID: 31798918; Askanase A, Arthritis Rheumatol. 2022;74(suppl 9):3293–7; Strasser DS, Arthritis Rheumatol. 2022;74(suppl 9):1981-2; Hoyler T, Lupus Science & Medicine. 2023. Abstract 2023-0588 Burg N et al. Nature Review Rheumatology 2022, 18

Conclusion

These results confirm the $S1P_1$-dependent immunomodulatory properties of cenerimod and demonstrate that the 4 mg dose consistently reduced the investigated disease-relevant pathways. The efficacy and safety of 4 mg cenerimod is under evaluation in two Phase 3 clinical studies for SLE (OPUS – NCT05648500, NCT05672576).

Acknowledgments

- CARE study patients
- Idorsia Pharmaceuticals Ltd.
- Viatris Innovation GmbH

For more information please visit:

- Poster 1408 in session poster view VIII on Saturday – Targeting Key Components of SLE pathogenesis with the multifaceted Immunomodulatory properties of cenerimod
- Booth number S14 in Hall B (Exhibition Hall)

EULAR Poster
May 2024

Targeting Key Components of SLE Pathogenesis with the Multifaceted Immunomodulatory Properties of Cenerimod, a Selective S1P$_1$ Receptor Modulator

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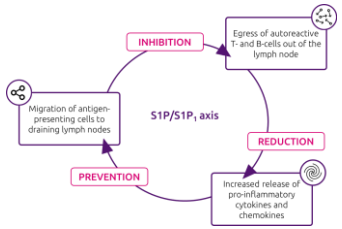
BACKGROUND

In SLE, aberrant lymphocyte activation and autoantibody production result in deposition of immune complexes and contribute to tissue damage. Cenerimod, a highly selective S1P$_1$ receptor modulator with a biased signaling, shows potential therapeutic effect in SLE through its immunomodulatory effects on lymphocyte trafficking, inflammation, and autoantigen transport. Preclinical and clinical data suggest that cenerimod may halt the vicious circle of autoimmunity, ultimately preventing organ damage in SLE.

Objectives

We combine results from preclinical and clinical studies to give a holistic view of the multifaceted immunomodulatory properties of cenerimod.



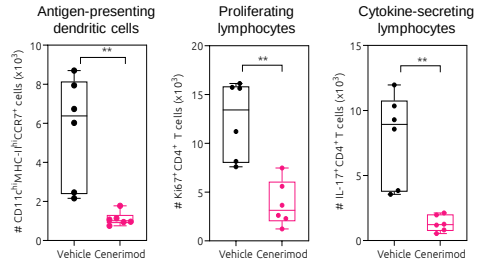
Methods

A murine model of SLE (MRL/lpr mice) and a proof-of-mechanism murine model for antigen transportation were used to evaluate the effects of cenerimod on leukocyte distribution, autoantibody titers, inflammation, and antigen transport, using flow cytometry, ELISA, and histology.[2-4] Leukocytes, autoantibodies, and inflammation biomarkers were further assessed in two phase 2 clinical studies of once-daily cenerimod (0.5, 1, 2, or 4 mg) versus placebo in patients with SLE (NCT02472795 and NCT03742037 [CARE]).[4-6] In the first phase 2 study, patients were treated for 12 weeks. In the CARE study, treatment was for 12 months; patients assigned to cenerimod 4 mg were re-randomized to placebo or cenerimod 2 mg at Month 6.

Results

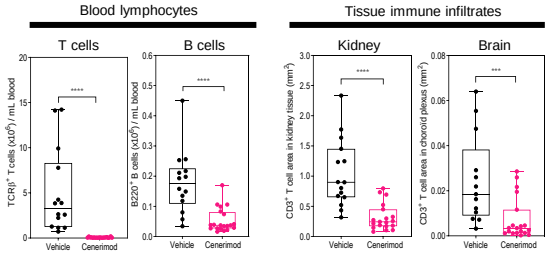
In rodent disease models, cenerimod reduced the migration of dendritic cells to the draining lymph node, which was accompanied by reduced T cell proliferation and pro-inflammatory cytokine secretion (see **section I**). Furthermore, in the MRL/lpr lupus mouse model, treatment with cenerimod led to significant disease amelioration, evidenced by a reduction of tissue-infiltrating lymphocytes, lower titers of autoantibodies, and reduced levels of inflammatory cytokines. This was associated with reduced signs of pathology in the kidneys, improved kidney function, and increased survival (see **section II – IV pre-clinical**).
In the 12-week Phase 2a clinical trial, treatment with cenerimod decreased circulating T and B lymphocytes and decreased autoantibody levels. These findings were confirmed in the Phase 2b CARE study, with reduction of several pro-inflammatory cytokines and improved clinical indices of disease activity (see **section II – IV clinical**).

I pre-clinical: Prevention of antigen transport, associated with a reduction of activated T cells in a mouse RA model



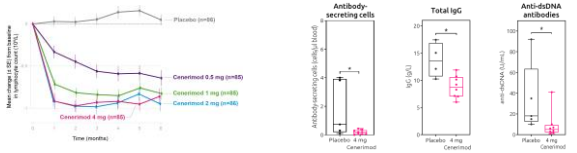
*Data presented as whisker plot with median, min to max **p<0.01 (Mann-Whitney test)*

II pre-clinical: Inhibition of lymphocyte migration in blood and peripheral organs in the MRL/lpr SLE model



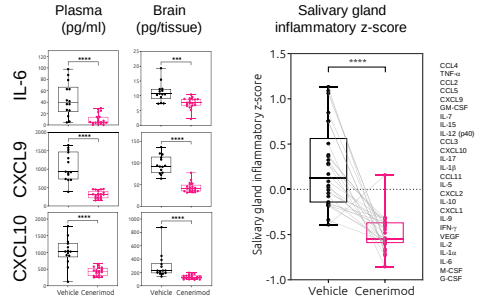
*All data presented as whisker plot with median, min to max. ***p<0.001; ****p<0.0001 (Mann-Whitney test)*

II clinical: Inhibition of lymphocyte migration and reduction of antibody-secreting cells in Phase 2a & Phase 2b clinical trials.



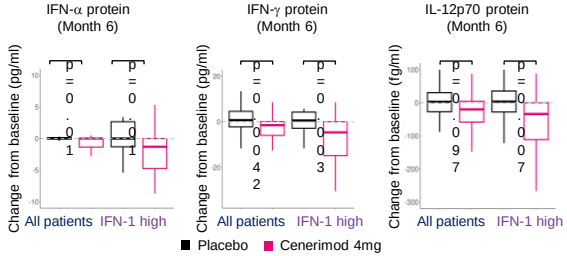
*Data presented as whisker plot with median, min to max *p<0.05 (Mann-Whitney test)*

III pre-clinical: Reduction of cytokine release in blood and peripheral organs in the MRL/lpr SLE model



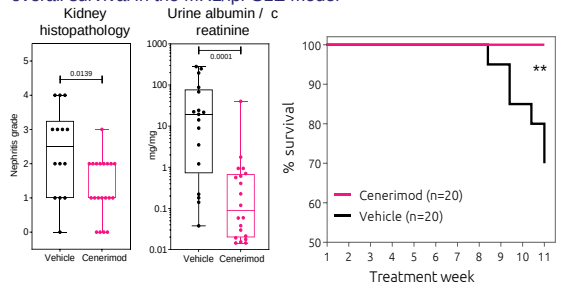
*Data presented as whisker plot with median, min to max. ***p<0.001; ****p<0.0001 (Mann-Whitney test)*

III clinical: Reduction of cytokine release in blood of patients with active SLE in a Phase 2b clinical study [CARE]



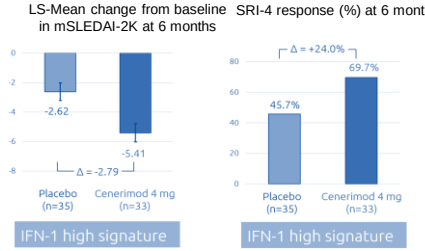
Data presented as whisker plot with median, p value as indicated .(Mann-Whitney test). IFN-1 status based on *IFI27*, *RSAD2*, *HERC5*, and *IFIT1* gene expression at baseline

IV pre-clinical: Efficacy by conferring kidney protection and increased overall survival in the MRL/lpr SLE model



*Data presented as whisker plot with median, min to max.(Mann-Whitney test). Comparison of survival curves analyzed as log rank test, **p<0.01 (Mantel-Cox)*

IV clinical: Efficacy in reducing disease activity in patients with active SLE in a Phase 2b clinical study [CARE]



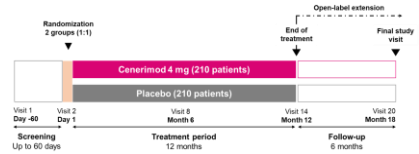
Data presented as bas graph ± SEM, Δ change from baseline as indicated.
IFN-1 status based on *IFI27*, *RSAD2*, *HERC5*, and *IFIT1* gene expression at baseline

Conclusion

Both preclinical and clinical research provide evidence that cenerimod is a promising immunomodulatory drug candidate that addresses three critical aspects of SLE pathogenesis: migration of autoreactive lymphocytes, release of pro-inflammatory cytokines and chemokines, and continuous autoimmune priming. The S1P$_1$ receptor modulator cenerimod may effectively interrupt this pathogenic circle of SLE autoimmunity.

The ongoing OPUS Phase 3 program (NCT05648500, NCT05672576) is designed to further investigate the safety and efficacy of cenerimod at a dose of 4 mg for the treatment of SLE in adults.

Clinical trial design of the OPUS research studies
(OPUS-1: NCT05648500 & OPUS-2: NCT05672576)



References
1. Hoyler T et al. Arthritis Rheumatol 2023;75(Suppl. 9). Copyright © 2023 John Wiley & Sons Inc. *Reproduced with permission of John Wiley & Sons Inc.*
2. Hoyler T et al. Abstract LO-016. LUPUS KCR meeting 2023.
3. Gerossier E et al. Arthritis Res Ther 2021;23(1):289.
4. Strasser DS et al. RMD Open 2020;6(2):e001261.
5. Hermann V et al. Lupus Sci Med 2019;6(1):e000354.
6. Askanase A et al. Arthritis Rheumatol 2022;74(suppl 9):3293–7.

Disclaimer
- This abstract was presented at the 2023 ACR meeting.[1]
- All authors are current or previous employees of Idorsia Pharmaceuticals Ltd. Views expressed in this poster are those of the author(s) and do not necessarily reflect the position of Idorsia Pharmaceuticals Ltd.
- All experimental procedures were conducted in accordance with the Swiss animal welfare policy and were approved by the Baselland veterinary office.
- The development of Cenerimod, previously funded by Idorsia, has now transitioned to Viatris.

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