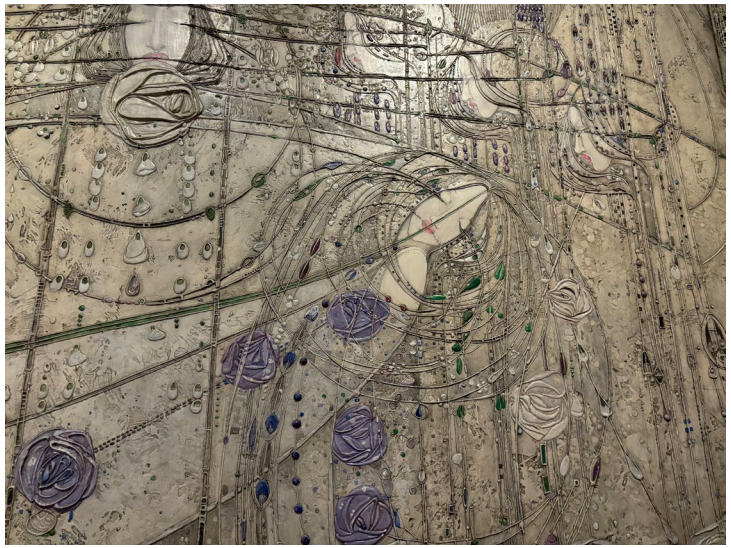
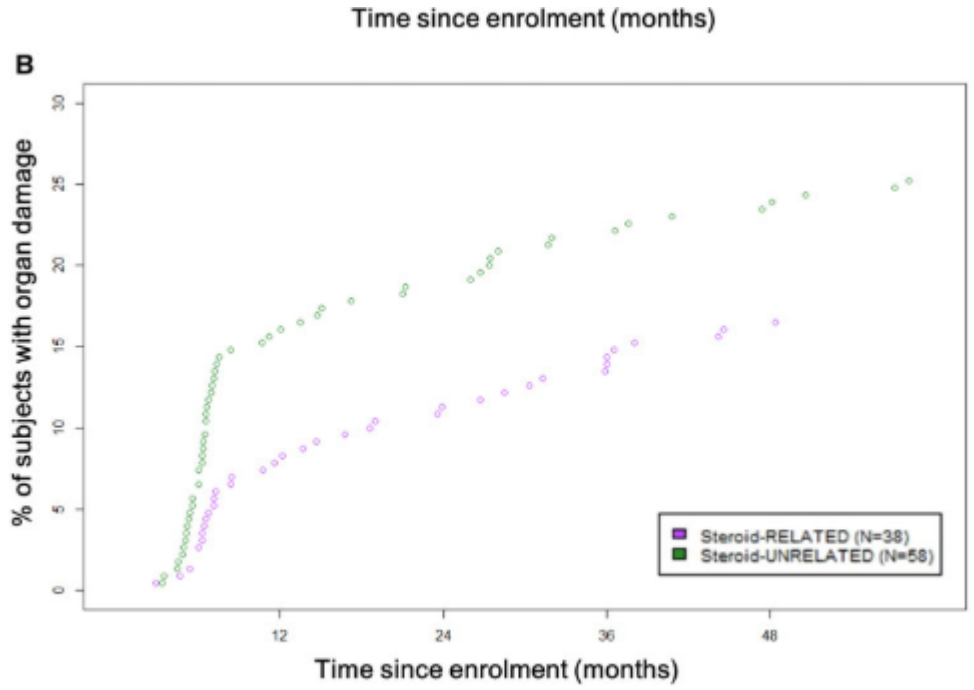
EULAR Focus SLE/Sjögren

Thomas Daikeler

USB



Steroide sind assoziiert mit Damage



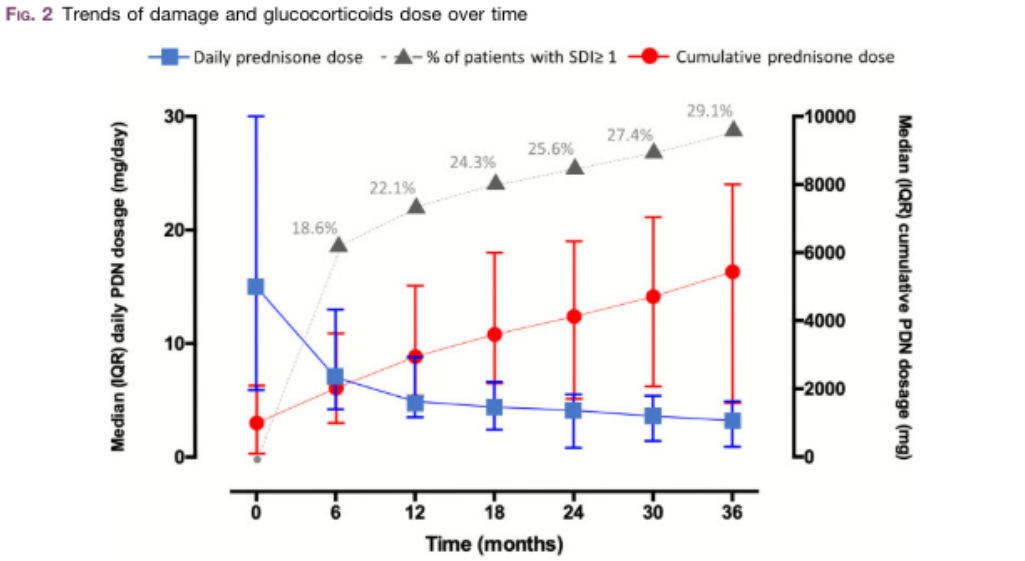


FIG. 2 Trends of damage and glucocorticoids dose over time

Trends of the median daily prednisone dose (square, blue line), median cumulative prednisone dose (circle, red line) and percentage of patients with at least one SDI item of damage (triangle, grey line) over follow-up. SDI; SLICC/ACR Damage Index.

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Lupusnephritis neudiagnostiziert
Propensity score matched

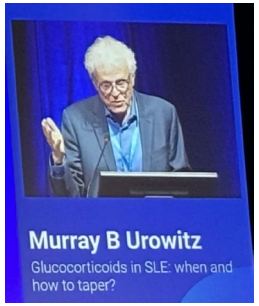

Table 1. Baseline characteristics of the patients (propensity score matched)*

Characteristic	Medium prednisone (≤30 mg/day) (n = 103)	High prednisone (≥40 mg/day) (n = 103)	*P*
Age, mean ± SD years	34.0 ± 10.5	33.5 ± 11.7	0.751
Female sex	84 (81.6)	86 (83.5)	0.715
White	54 (52.4)	56 (54.4)	0.773
Black	14 (13.6)	21 (20.4)	0.209
Chinese	19 (18.4)	12 (11.7)	0.144
Others	16 (15.5)	14 (13.6)	0.695
Treatment initiation after January 2003	68 (66.0)	62 (60.2)	0.376
SLEDAI-2K score, mean ± SD	13.9 ± 6.2	15.0 ± 7.0	0.165
SLEDAI-2K renal score, mean ± SD	8.6 ± 4.2	8.4 ± 4.2	0.726
SDI score, mean ± SD	0.4 ± 0.8	0.4 ± 1.0	0.818
Disease duration, mean ± SD years	6.0 ± 5.9	5.4 ± 5.4	0.435
Class II	3 (2.9)	6 (5.8)	0.317
Class III	18 (17.5)	17 (16.5)	0.853
Class IV	34 (33.0)	43 (41.7)	0.189
Class V	38 (36.9)	28 (27.2)	0.114
Class IV/V	10 (9.7)	9 (8.7)	0.808
Activity index score, mean ± SD	4.8 ± 3.8	6.0 ± 4.4	0.045
Chronicity index score, mean ± SD	2.6 ± 2.3	2.3 ± 2.5	0.476
Hypertension†	49 (47.6)	52 (50.5)	0.662
Systolic BP (mm Hg), mean ± SD	126.8 ± 19.9	131.6 ± 18.0	0.078
Diastolic BP (mm Hg), mean ± SD	79.7 ± 13.1	80.5 ± 10.8	0.646
Diabetes mellitus	5 (4.9)	1 (1.0)	0.102
Body mass index, mean ± SD kg/m^2	23.6 ± 5.7	24.9 ± 5.9	0.072
Serum creatinine, mean ± SD mmol/liter	87.7 ± 40.0	91.0 ± 38.9	0.544
eGFR, mean ± SD ml/minute/1.73m^2	88.5 ± 33.9	88.0 ± 38.4	0.966
eGFR <60 ml/minute/1.73m^2	21 (20.4)	29 (28.2)	0.194
Proteinuria, mean ± SD gm/24 hours	2.8 ± 2.2	2.7 ± 2.4	0.943
Low complement (C3/C4)	74 (71.8)	63 (61.2)	0.093
Anti-dsDNA positive	61 (59.2)	65 (63.1)	0.555
Prednisone dose, mean ± SD mg/day	24.2 ± 4.6	48.6 ± 12.3	<0.0001
Prednisone dose, median (range)	20 (20–30)	40 (40–100)	<0.001
IV methylprednisolone	3 (2.9)	4 (3.9)	0.705
No. of pulses, mean ± SD	3.0 ± 0.0	3.0 ± 0.0	1.000
Mean dose of pulses, mean ± SD mg of methylprednisolone	500 ± 0	587.5 ± 283.9	0.620
Azathioprine	47 (45.6)	49 (47.6)	0.773
Azathioprine dose, mean ± SD mg/day	105.3 ± 40.4	98.9 ± 40.4	0.425
Mycophenolate mofetil	52 (50.5)	46 (44.7)	0.376
Mycophenolate dose, mean ± SD mg/day	2,189.4 ± 684.9	2,075.1 ± 700.3	0.515
Cyclophosphamide‡	7 (6.8)	14 (13.6)	0.127
Antimalarials	62 (60.2)	59 (57.3)	0.674
ACE inhibitors/ARBs	43 (41.7)	44 (42.7)	0.886
Other antihypertensives	20 (19.4)	40 (38.8)	0.002

* Values are the number (%) unless indicated otherwise. ACE = angiotensin-converting enzyme; anti-dsDNA = anti–double-stranded DNA; ARB = angiotensin receptor blocker; BP = blood pressure; eGFR = estimated glomerular filtration rate; IV = intravenous; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.
† Defined as BP ≥130/80 mmHg.
‡ All patients received the Euro-lupus cyclophosphamide protocol (6 intravenous biweekly pulses of 500 mg each).

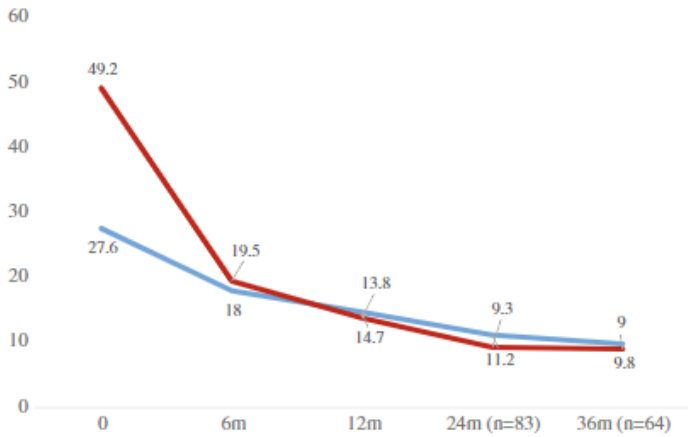

Figure 1. Mean daily prednisone dose at baseline, 6, 12, 24, and 36 months for low-to-medium prednisone (≤30 mg/day) group (blue) and high-dose prednisone (≥40 mg/day) group (red). Differences were not statistically significant at all time points except for the baseline ($P < 0.001$).

Arthritis care research 2022 Sep;74(9):1451-1458. doi: 10.1002/acr.24592

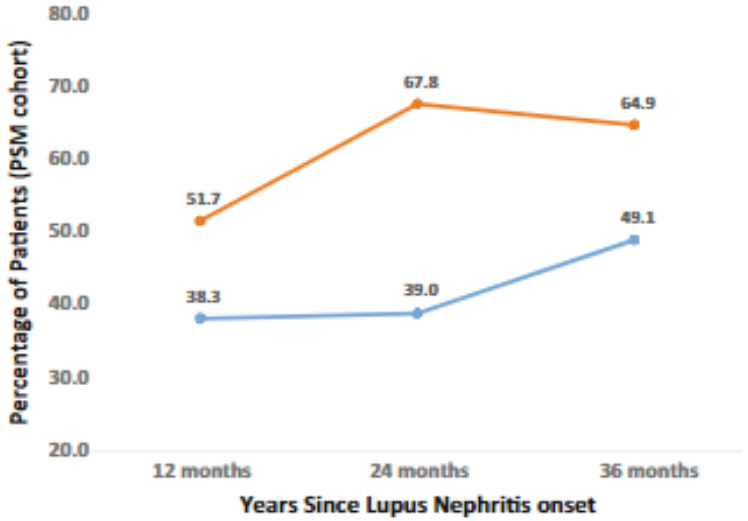

Figure 2. Rates of complete renal response (%) in the low-medium prednisone (≤30 mg/day) subgroup (blue; n = 60) and the high-dose prednisone (≥40 mg/day) subgroup (orange; n = 60) at 12, 24, and 36 months after the initiation of remission induction treatment (n = 120). Statistically significant differences were observed at 24 ($P = 0.002$) and 36 months ($P = 0.025$). PSM = propensity score matching. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24592/abstract.

Table 3. Yearly cumulative glucocorticoid dose and glucocorticoid-related damage accrual over time*

	Medium prednisone (≤30 mg/day)	High prednisone (≥40 mg/day)	*P*
At 12 months, no.	103	103	
Cumulative prednisone dose, mean ± SD gm	6.8 ± 3.0	8.5 ± 3.7	0.001
Prednisone dose at 12 months, mean ± SD	14.7 ± 10.5	13.8 ± 9.8	0.486
Patients discontinuing prednisone at 12 months	0 (0)	1 (0.8)	NA
Cataract (new)	1 (1.0)	1 (1.0)	1.000
Osteoporosis (new)	0 (0.0)	2 (1.9)	NA
Osteonecrosis (new)	3 (2.9)	0 (0.0)	NA
Diabetes mellitus (new)	2 (1.9)	1 (1.0)	0.317
At 24 months, no.	83	83	
Cumulative prednisone dose in 12–24 months, mean ± SD gm	5.9 ± 3.7	5.7 ± 4.2	0.743
Prednisone dose at 24 months, mean ± SD	11.2 ± 9.7	9.3 ± 8.7	0.171
Patients discontinuing prednisone at 24 months	6 (7.2)	7 (8.4)	0.763
Cataract (new)	4 (4.8)	4 (4.8)	1.000
Osteoporosis (new)	0 (0.0)	2 (2.4)	NA
Osteonecrosis (new)	5 (6.0)	3 (3.6)	0.479
Diabetes mellitus (new)	2 (2.4)	2 (2.4)	1.000
At 36 months, no.	64	64	
Cumulative prednisone dose in 24–36 months, mean ± SD gm	4.1 ± 3.3	3.4 ± 3.4	0.427
Prednisone dose at 36 months, mean ± SD	9.8 ± 7.8	9.0 ± 8.9	0.653
Patients discontinuing prednisone at 36 months	4 (6.3)	12 (18.8)	0.011
Cataract (new)	7 (10.9)	4 (6.3)	0.366
Osteoporosis (new)	1 (1.6)	2 (3.1)	0.564
Osteonecrosis (new)	5 (7.8)	5 (7.8)	1.000
Diabetes mellitus (new)	3 (4.7)	2 (3.1)	0.564

* Values are the number (%) unless indicated otherwise. NA = not applicable.

Wann sollte wir die Steroide stoppen?

- For the purpose of the present study, UTLC patients with **first prolonged clinical remission for a continuous period of 2 years**
- retrieved from the database. Remission was defined based on a clinical SLE Disease Activity Index 2000 (**SLEDAI-2K) of 0** that remained stable over those 2 years. Isolated serologic activity (abnormal levels of dsDNA antibodies and/or low levels of complement C3/C4 was allowed. **Patients should be receiving prednisone (5 mg/day)** at the beginning of the observation period and antimalarials

https://doi.org/10.1002/acr2.11267

Absetzschema

- • Week 1: usual dose (5 mg/day) for 6 days and reduced dose
- (4 mg/day) for Day 7.
- • Week 2: usual dose (5 mg/day) for 5 days and reduced dose
- (4 mg/day) for 2 days.
- • Week 3: usual dose (5 mg/day) for 4 days and reduced dose
- (4 mg/day) for 3 days, and so on.

Results

Table 1. Demographic, clinical, serological, and therapeutic characteristics of the patients at baseline

Variable	Maintenance Group (n = 102)	Withdrawal Group (n = 102)	SMD	Variance Ratio	*P* Value
Female sex	92 (90.2)	89 (87.3)	-	-	0.884
Black	12 (11.8)	8 (7.8)	-	0.88	0.317
Age, years	44.1 ± 15.4	41.7 ± 12.9	0.17	1.07	0.242
Disease duration, years	12.8 ± 10	11.7 ± 7.9	0.12	1.1	0.292
Duration of clinical remission, years	3.6 ± 2.6	3.6 ± 2.2	0.01	0.7	0.967
SLEDAI-2K	1.7 ± 1.5	1.6 ± 1.5	0.08	0.91	0.577
Adjusted mean SLEDAI-2K for the first 5 years since enrollment	3.5 ± 1.9	3.1 ± 1.9	0.23	1.05	0.075
History of lupus nephritis[a]	37 (36.3)	41 (40.2)	-	0.99	0.572
History of CNS involvement[b]	34 (33.3)	28 (27.5)	-	0.93	0.396
Low C3/C4	42 (41.2)	41 (40.2)	-	1	0.866
Anti-dsDNA (+)	45 (44.1)	40 (39.2)	-	1.04	0.484
SDI	1.2 ± 1.4	1.0 ± 1.5	0.13	0.68	0.352
Cumulative glucocorticoid dose,[c] g	30.6 ± 24.4	25.5 ± 22.6	0.22	1.17	0.062
Antimalarials	67 (65.7)	67 (65.7)	-	0.88	1.000
Immunosuppressives	51 (50)	44 (43.1)	-	0.98	0.25

Categorical variables are presented as n (%), continuous variables are presented as mean ± SD.
Abbreviation: SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SMD, standardized mean difference.
[a] Based on renal biopsy demonstrating lupus nephritis or abnormal proteinuria (>0.5g/day) in two consecutive visits treated with glucocorticosteroids and immunosuppressives by the attending physician.
[b] Based on any central nervous system involvement treated with glucocorticosteroids and/or immunosuppressives by the attending physician.
[c] From first clinic visit up to the index date (in prednisone equivalent).

Table 2. Flare rates at 12 and 24 months and damage accrual at 24 months

	Maintenance Group (n = 102)	Withdrawal Group (n = 102)	*P* Value
Flares at 12 months			
Flare (first definition)[a]	30 (29.4)	18 (17.6)	0.023
Flare (second definition)[b]	14 (13.7)	11 (10.8)	0.467
Flare (third definition)[c]	12 (11.8)	7 (6.9)	0.197
Flares at 24 months			
Flare (first definition)[a]	51 (50)	34 (33.3)	0.01
Flare (second definition)[b]	28 (27.5)	15 (14.7)	0.024
Flare (third definition)[c]	27 (26.5)	13 (12.7)	0.013
Damage accrual at 24 months			
Related to glucocorticosteroids	12 (11.8)	3 (2.9)	0.02
Not related to glucocorticosteroids	7 (6.9)	4 (3.9)	0.317
Increase in SDI	18 (17.6)	7 (6.9)	0.022

Abbreviation: SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SMD, standardized mean difference.
Data are given as n (%).
[a] Any increase in clinical SLEDAI-2K (excluding serology).
[b] Any increase in clinical SLEDAI-2K plus treatment escalation (for glucocorticosteroids, antimalarials or immunosuppressives).
[c] Any increase ≥4 in clinical SLEDAI-2K.

Flare rates in patients with shorter clinical remission=2 konsekutive Visiten mit Remission
Keine Unterschiede in der Relapse rate

Steroide

- Initial höherdosierte Steroide (40mg) sind mit weniger flares verbunden, höherer Wahrscheinlichkeit Steroide stoppen zu können
- In stabiler Remission können die Steroide ausgeschlichen werden.

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Efficacy and safety of nipocalimab, an anti-FcRn monoclonal antibody, in primary Sjögren's disease: results from a phase 2, multicenter, randomized, placebo-controlled, double-blind study (DAHLIAS)

Jacques-Eric Gottenberg,[1] Kathy Sivils,[2] Kim Campbell,[2] Jada Idokogi,[2]
Kim Hung Lo,[2] Sophia G Liva,[2] Harman Dhatt,[3] Jonathan J Hubbard,[2] Ghaith Noaiseh[4]

[1]Department of Rheumatology, Strasbourg University Hospital, National Centre for Rare Systemic Autoimmune Diseases, and Immunology, Immunopathology and Therapeutic Chemistry, Institute of Molecular and Cellular Biology, Strasbourg University, Strasbourg, France; [2]Janssen Research & Development, LLC, a Johnson & Johnson Company, Spring House, PA, USA; [3]Janssen Global Services, LLC, a Johnson & Johnson Company, Raritan, NJ, USA; [4]Division of Allergy, Clinical Immunology and Rheumatology, Department of Medicine, University of Kansas, Kansas City, KS, USA.

Sjögren's Disease

Chronic, systemic, autoimmune disease

Characterized by:

- Presence of autoantibodies
- Lymphocytic infiltration of exocrine glandular tissues
- Systemic organ and tissue injury[1]

Dysregulated humoral immunity implicated

- Involving aberrant B-lymphocyte activity
- Leading to abnormally elevated IgG and IgG autoantibody levels, particularly anti-Ro and anti-La[1]

Substantial disease burden[2,3] and increased mortality

- ~1.5-fold higher all-cause mortality[4]
- Common symptoms include mucosal dryness, fatigue, and pain

IgG, immunoglobulin G.

1. Nocturne G, Mariette X. *Nat Rev Rheumatol*. 2013;9(9):544-556. 2. Mariette X, Criswell LA. *N Engl J Med*. 2018;378(10):931-939. 3. Beydon M, et al. *Nat Rev Rheumatol*. 2024;20(3):158-169. 4. Huang H, et al. *Rheumatol (Oxford)*. 2021;60(9):4029-4038.

Nipocalimab Inhibits FcRn to Decrease Circulating IgG and IgG Autoantibodies

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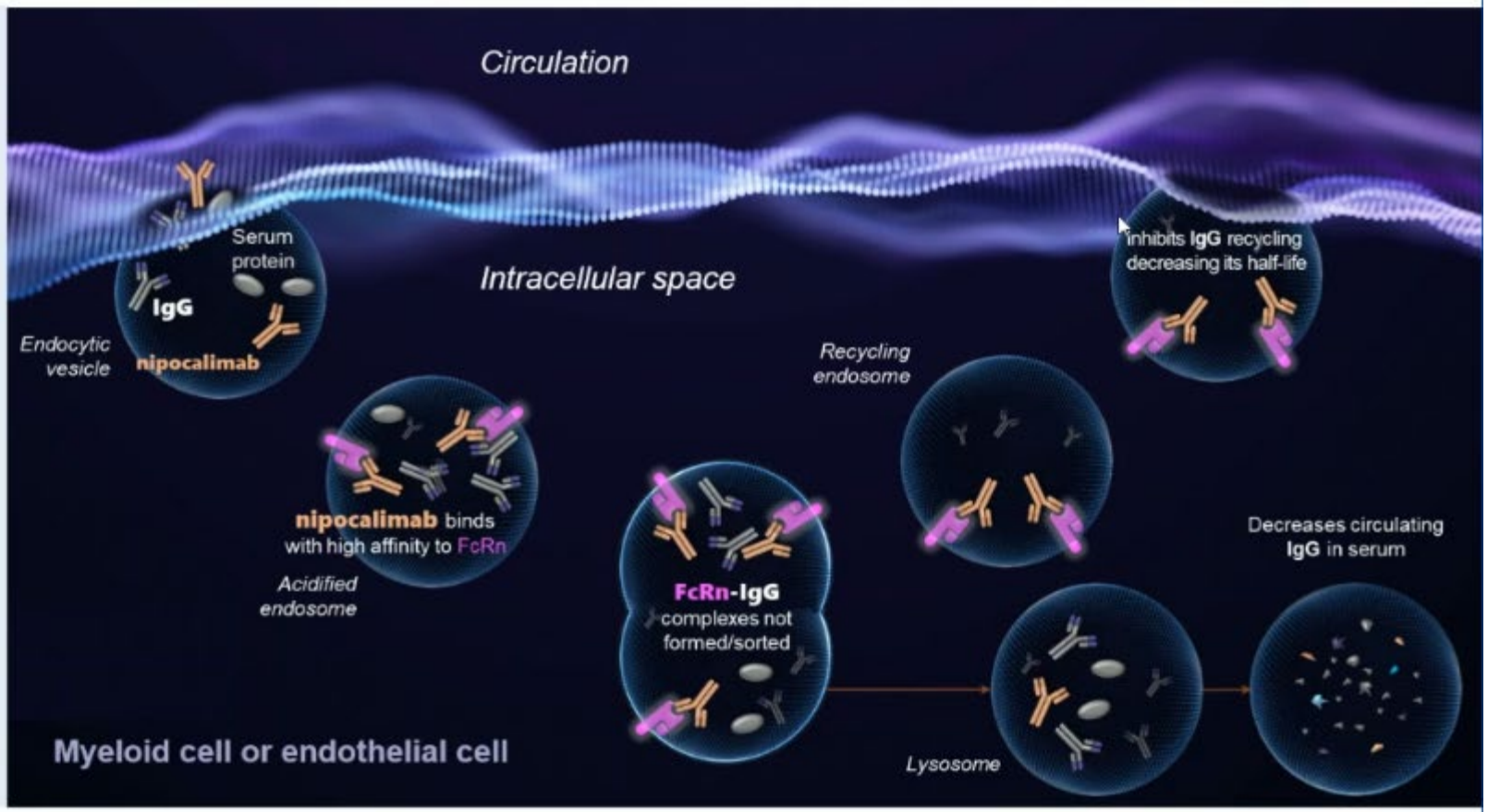
What is the neonatal crystallizable fragment receptor (FcRn)?[1-3]

- A transmembrane protein present throughout life
- Located mostly inside vesicles in many cells including endothelial and immune cells
- Reduces clearance of IgG via binding and recycling

What is nipocalimab?

- A fully human IgG1 monoclonal antibody that binds with high affinity to the IgG binding site of FcRn
- An FcRn blocker that decreases levels of IgG and autoantibodies without broad immunosuppression
- Robust efficacy has been established in generalized myasthenia gravis and hemolytic disease of the fetus and newborn[4,5]



FcRn, neonatal crystallizable fragment receptor.

1. Blumberg LJ, et al. *Sci Adv*. 2019;5(12):eaax9586. 2. Roopenian DC, et al. *Nat Rev Immunol*. 2007;7(9):715-25. 3. Peter HH, et al. *J Allergy Clin Immunol*. 2020;146(3):479-491. 4. Antozzi C, et al. *Neurology*. 2024;102(2):e207937. 5. Moise KJ, et al. Presented at: 20th World Congress in Fetal Medicine; June 25-29, 2023; Valencia, Spain.

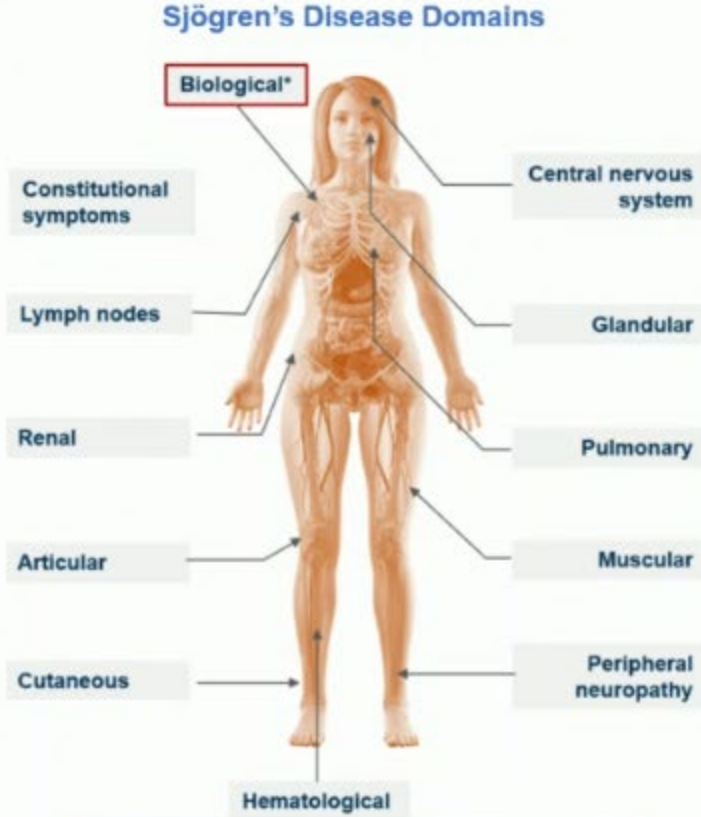
Clinical Assessment Scales in Sjögren's Disease[1]

EULAR Sjögren's Syndrome *Patient Reported* Index (ESSPRI)	EULAR Sjögren's Syndrome *Disease Activity* Index (ESSDAI)	Clinical ESSDAI (ClinESSDAI)
• 3 domains (weight: 1) • 3 items (VAS 0–10)	• 12 domains (weight: 1–6) • 44 items (0–3)	• 11 domains (weight 1–7) • 40 items (0–3)
• Mean score range 0–10	• Sum score range: 0–123	• Sum score range: 0–135
• Unsatisfactory symptom state = ≥5/10	• Disease activity: Low <5; Moderate ≥5 to ≤13; High ≥14	• Disease activity: Low <5; Moderate ≥5 to ≤13; High ≥14
• MCII: ≥1-point or ≥15% improvement	• MCII: ≥3-point improvement	• MCII: ≥3-point improvement

Composite endpoints to define responders

STAR (≥5 points)
- ClinESSDAI (3 points) + ESSPRI (3) + Tear production (1) + Saliva production (1) + IgG or rheumatoid factor reduction (1)

CRESS
- Same domains as STAR but different scoring rules: improvement in ≥3 domains



*Includes IgG values; omitted from ClinESSDAI.

Disease activity: The functional or structural changes in an organ related to inflammatory burden of the disease and are reversible under treatment. **CRESS**, Composite of Relevant Endpoints for Sjögren's Syndrome; **MCII**, Minimal Clinically Important Improvement; **STAR**, Sjögren's Tool for Assessing Response; **VAS**, visual analogue scale.

1. Parisis D, et al. *J Clin Med*. 2020;9(7):2299. doi:10.3390/jcm9072299.

DAHLIAS Study

First study of an FcRn blocker in Sjögren's disease (SjD)

Objective:
To evaluate the efficacy and safety of nipocalimab in patients with primary SjD

Study design:
Phase 2, multicenter, randomized, placebo-controlled, double-blind study

Participants: Adults aged 18-75 years with moderately-to-severely active primary SjD (total ClinESSDAI ≥6) who were seropositive for anti-Ro60 and/or anti-Ro52 IgG antibodies

Treatment Groups (N=163)
Placebo
Nipocalimab 5 mg/kg
Nipocalimab 15 mg/kg

Primary Endpoint
Change from baseline in ClinESSDAI score at Week 24

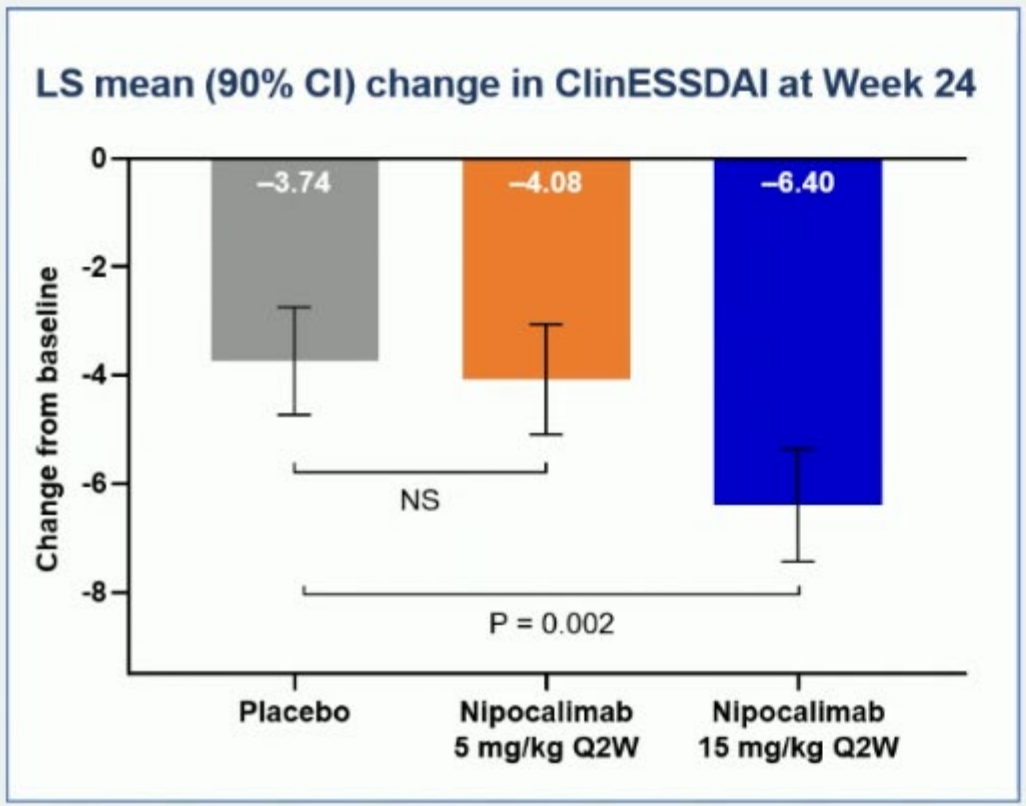
The DAHLIAS study was pre-specified to use a 2-sided alpha level of 0.10 without multiplicity control.
SjD, Sjögren's disease.

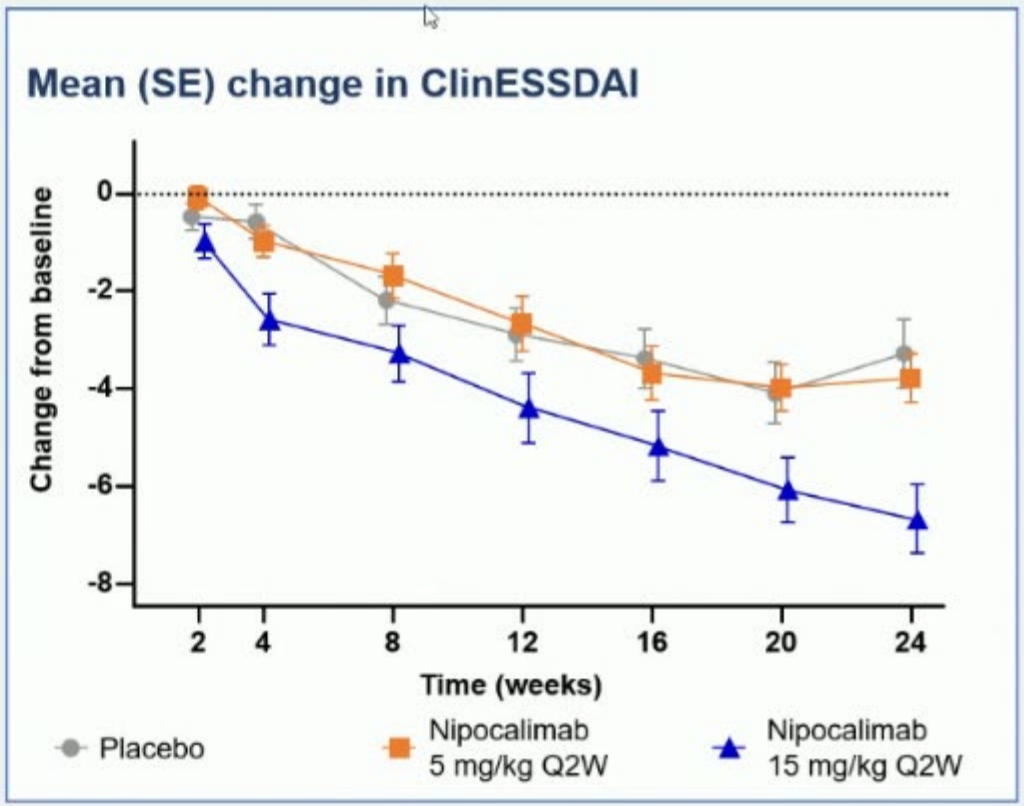
Demographic and Baseline Disease Characteristics

Characteristic	Placebo (N=56)	Nipocalimab 5 mg/kg Q2W (N=53)	Nipocalimab 15 mg/kg Q2W (N=54)	All patients (N=163)
Age, years, median (range)	46.5 (23–73)	49.0 (20–72)	48.5 (24–72)	48.0 (20–73)
Female	92.9%	92.5%	92.6%	92.6%
White	89.3%	92.5%	90.7%	90.8%
Time since diagnosis, years, median (range)	4.0 (0.6–34.0)	3.7 (0.6–27.9)	4.3 (0.6–18.2)	4.0 (0.6–34.0)
ClinESSDAI score, mean (SD)	10.0 (3.8)	9.4 (3.1)	10.2 (3.6)	9.9 (3.5)
ESSPRI score, mean (SD)	7.0 (1.3)	7.0 (1.3)	7.2 (1.2)	7.1 (1.2)
Total IgG levels,[a] g/L, median (range)	14.8 (7.7–40.5)	14.8 (4.6–35.2)	15.5 (7.6–49.6)	14.9 (4.6–49.6)
Autoantibody positivity, N	55	52	53	160
Anti-Ro60	98.2%	98.1%	98.1%	98.1%
Anti-La	74.5%	76.9%	64.2%	71.9%
Anti-Ro52	78.2%	86.5%	77.4%	80.6%
RF	78.6%	71.7%	63.0%	71.2%

Q2W, administered once every 2 weeks; **RF**, rheumatoid factor; **SD**, standard deviation.
[a]Measured at a central laboratory. Reference range 6.03-16.13 g/L.

Primary Endpoint: Change From Baseline in ClinESSDAI at Week 24





ClinESSDAI, clinical EULAR Sjögren's Syndrome Disease Activity Index; **LS**, least square; **SE**, standard error.

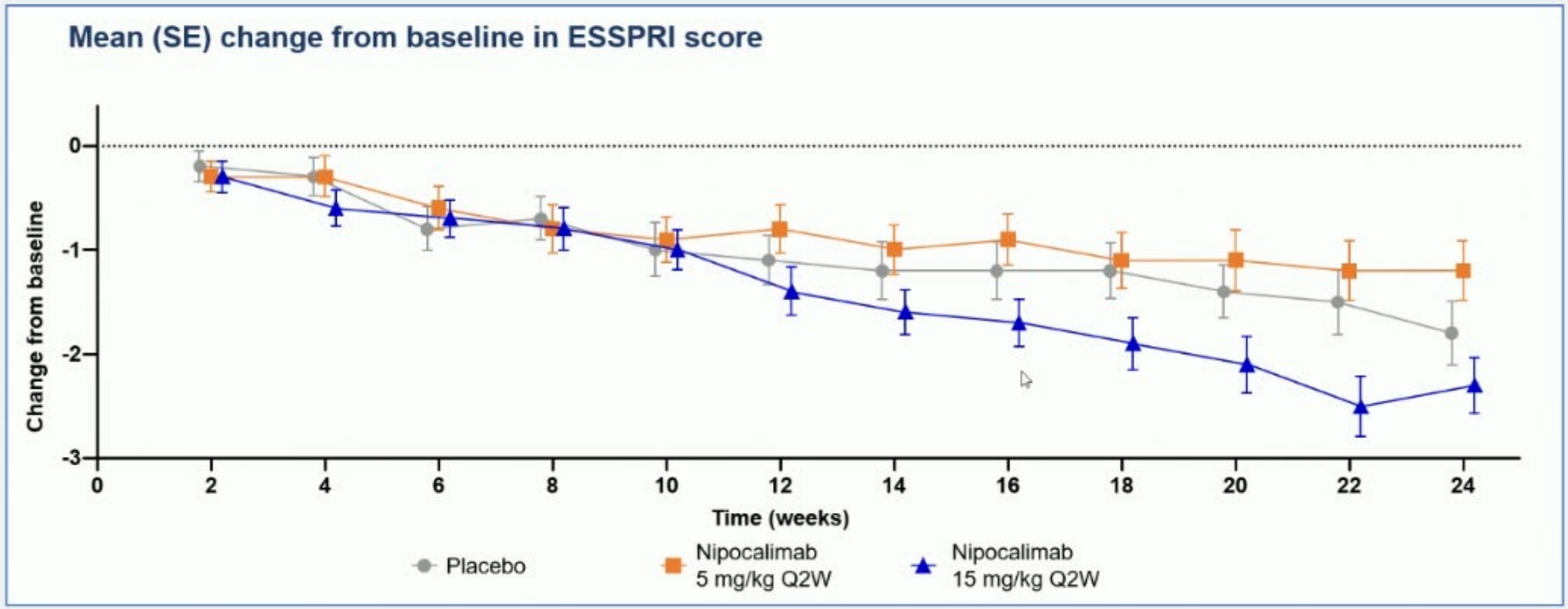
Other Secondary and Supportive Endpoints

Endpoint – Change from Baseline at Week 24	LS Mean Difference (90% CI): Nipocalimab vs Placebo[a]		Nominal P-value Nipocalimab 15 mg/kg Q2W vs Placebo
	5 mg/kg Q2W (N=53)	15 mg/kg Q2W (N=54)	
PhGA	–2.26 (–8.50, 3.99)	**–14.50** (–20.81, –8.19)	**<0.001**
ESSDAI	–0.52 (–1.67, 0.63)	**–1.79** (–2.94, –0.63)	**0.012**
ESSPRI	0.62 (0.01, 1.23)	–0.41 (–1.03, 0.20)	0.268

Endpoint – Responder Rate at Week 24	Difference in Proportions [% (90% CI)]: Nipocalimab vs Placebo[b]		Nominal P-value Nipocalimab 15 mg/kg Q2W vs Placebo
	5 mg/kg Q2W (N=53)	15 mg/kg Q2W (N=54)	
ESSDAI-3	9.5 (–5.8, 24.8)	16.1 (0.8, 31.4)	0.172
STAR	11.7 (–3.9, 27.2)	**23.7** (8.4, 38.9)	**0.017**
CRESS	25.5 (11.5, 39.5)	**30.3** (16.3, 44.3)	**0.001**
DAL[c]	18.9 (3.6, 34.2)	**19.8** (4.5, 35.0)	**0.046**

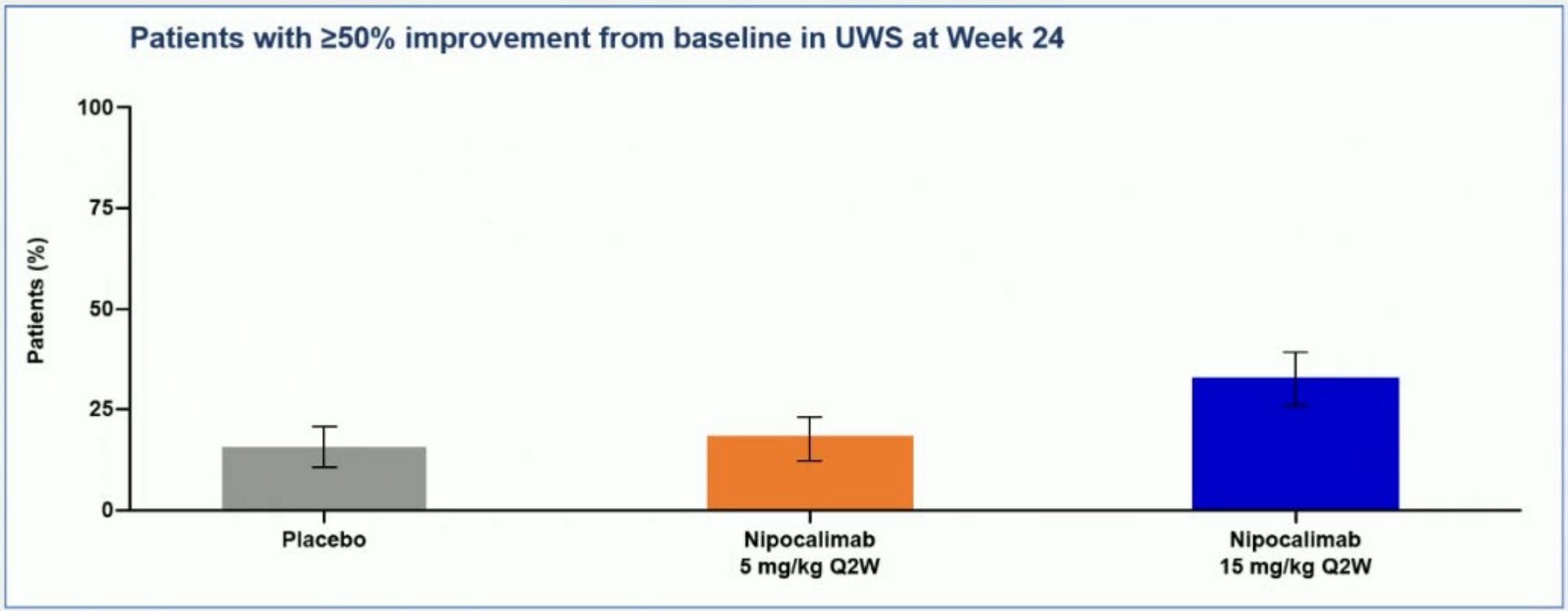
CI, confidence interval; **CRESS**, Composite of Relevant Endpoints for Sjögren's Syndrome; **DAL**, Disease Activity Level; **ESSDAI**, European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; **ESSPRI**, European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; **PhGA**, Physician Global Assessment of Disease Activity; **STAR**, Sjögren's Tool for Assessing Response.
[a]Compared with placebo group using a Mixed Effects Repeated Measures model with baseline score, study treatment, visit, region, baseline steroid use, baseline anti-malarial use, and an interaction of treatment and visit as terms in the model. For continuous endpoints, participants with an intercurrent event per protocol were considered to have missing data thereafter. [b]Values are percentages. Statistically compared with placebo group using a Cochran-Mantel-Haenszel test with region, baseline steroid use, and baseline anti-malarial use as stratification factors. For binary composite endpoints, participants with intercurrent events were considered non-responders after the event. [c]DAL response is a reduction from baseline in disease activity level by at least 1 level in at least 1 ClinESSDAI domain (eg, articular, hematological, cutaneous, constitutional, etc.)

Secondary Endpoint: ESSPRI



ESSPRI, European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; **SE**, standard error.

Unstimulated Whole Salivary Flow Rate



UWS, unstimulated whole salivary flow rate.

Biomarkers: IgG and Autoantibody Levels

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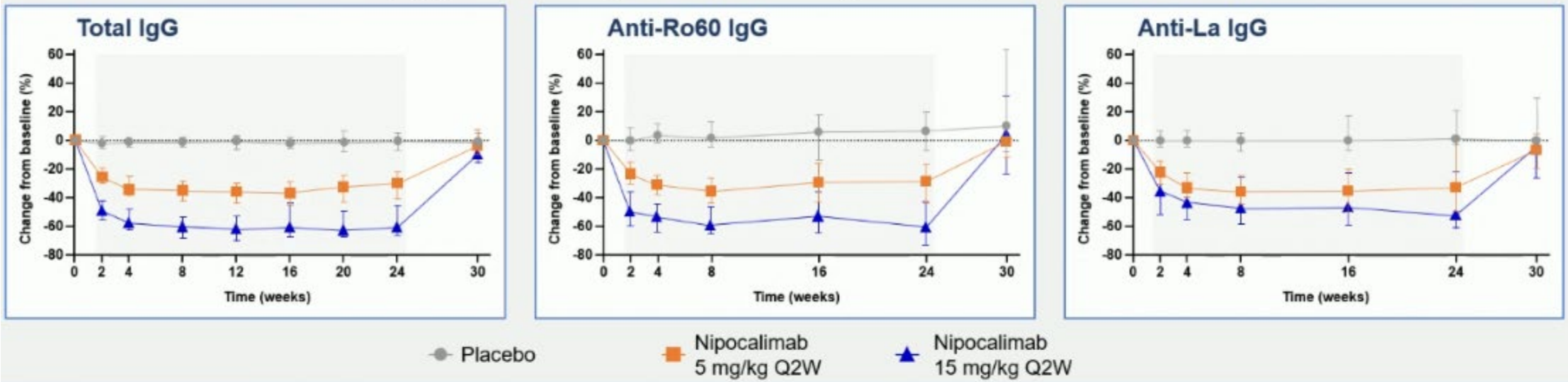
VIENNA
12–15 JUNE 2024

Median (IQR) Percent Change from Baseline in IgG Antibody Levels Over Time[a]



- **77% maximum reduction in total IgG** (PK/PD simulations)
  - Pre-dose (minimum) median reduction of 61% in total IgG at Week 24
- Consistent reductions in SjD-associated anti-Ro60, -Ro52, and -La IgG autoantibodies

IQR, interquartile range; **PD**, pharmacodynamic; **PK**, pharmacokinetic.
[a]Shaded areas represent pre-dose measurements of minimum IgG reduction.

Nipocalimab Safety and Tolerability

Participants with ≥1 AE, n (%)	Placebo (N=56)	Nipocalimab		
		5 mg/kg Q2W (N=53)	15 mg/kg Q2W (N=54)	Combined (N=107)
AEs	35 (62.5)	42 (79.2)	43 (79.6)	85 (79.4)
Serious AEs	3 (5.4)	4 (7.5)	4 (7.4)	8 (7.5)
Infections and infestations	24 (42.9)	32 (60.4)	28 (51.9)	38 (56.1)
Severe infections[a]	1 (1.8)	2 (3.8)	1 (1.9)	3 (2.8)
Opportunistic infections	0	0	0	0
Infusion reactions	2 (3.6)	6 (11.3)	1 (1.9)	7 (6.5)
Hypersensitivity reactions	3 (5.4)	6 (11.3)	7 (13.0)	13 (12.1)
MACE[b]	2 (3.6)	0	0	0

- In the nipocalimab 15 mg/kg group, mean changes from baseline at Week 24 in albumin (–6.9%), low-density lipoprotein cholesterol (6.6%), and total cholesterol (8.3%) were not clinically significant
- Severe hypoalbuminemia (<20 g/L) was not observed; no deaths were reported
- Consistent with findings from patients with myasthenia gravis, rheumatoid arthritis, and hemolytic disease of the fetus and newborn

AE, adverse event; **IV**, intravenous; **MACE**, major adverse cardiovascular event.

[a]Infections that are severe or require IV anti-infective or operative/invasive intervention, as assessed by the investigator. [b]Cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Conclusions

The DAHLIAS study established proof of concept for nipocalimab in Sjögren's disease

- Nipocalimab 15 mg/kg led to significant improvement versus placebo in ClinESSDAI (P=0.002) and demonstrated similar trends in other key efficacy endpoints
- Nipocalimab treatment was well-tolerated with no new safety signals observed

Findings established the clinical benefits of reducing IgG autoantibody levels for the treatment of Sjögren's disease

Findings support the further clinical evaluation of nipocalimab, a novel FcRn blocker, in Sjögren's disease and other autoantibody-associated rheumatic diseases

09:00 - 10:00 Oral Abstract Sessions: Late-Breaking Abstracts 2

Chairs: Christian Dejaco, Caroline Ospelt

A Single-Center Phase 2 Open-Label Trial Evaluating the Safety and Efficacy of Daratumumab in Systemic Lupus Erythematosus

Tobias Alexander[1,2], Lennard Ostendorf[1,2], Jan Zernicke[1], Jens Klotsche[2], Udo Schneider[1], Robin Biesen[1], Robin Kempkens[2], Qingyu Cheng[2], Laleh Khodadadi[2], Gabriela Guerra[2], Frederik Heinrich[2], Pawel Durek[2], Gerd Burmester[1], Farzin Mashreghi[1], Gerhard Krönke[1,2] and Falk Hiepe[1,2]

[1] Charité – Universitätsmedizin Berlin, Germany
[2] German Rheumatism Research Center, a Leibniz Institute, Berlin, Germany

Tobias Alexander

Safety and Efficacy of Daratumumab in Systemic Lupus Erythematosus - A Single-Center Phase 2 Open-Label Trial

A Single-Center Trial Evaluating of Daratumuma Erythematosus

Tobias Alexander[1,2], Lennard Ostend
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Gerd Burmester[1], Farzin Mashreghi[1],

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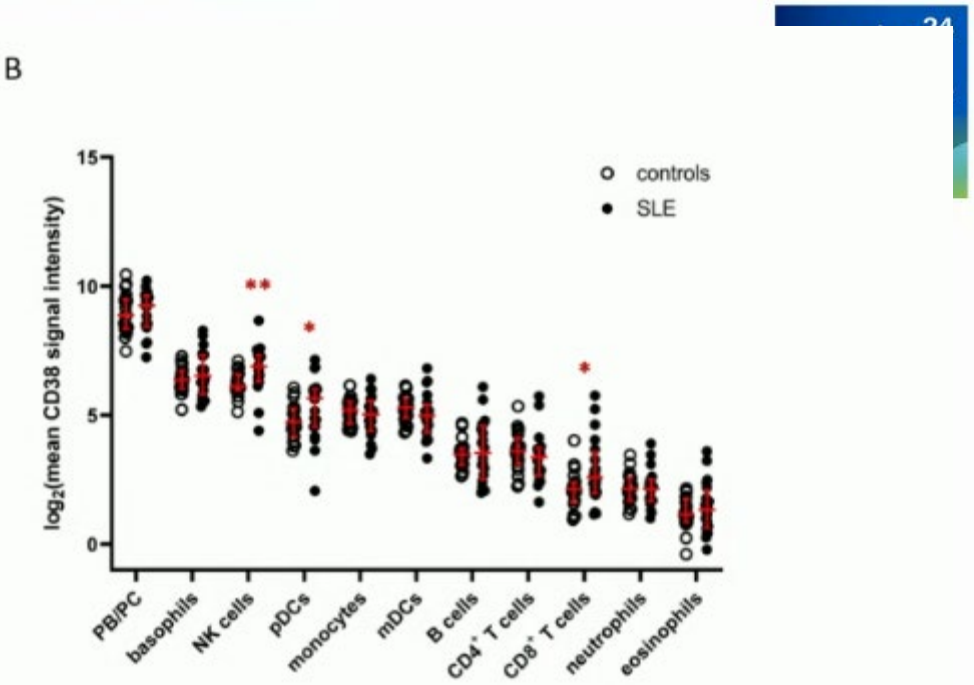


Tobias Alexander

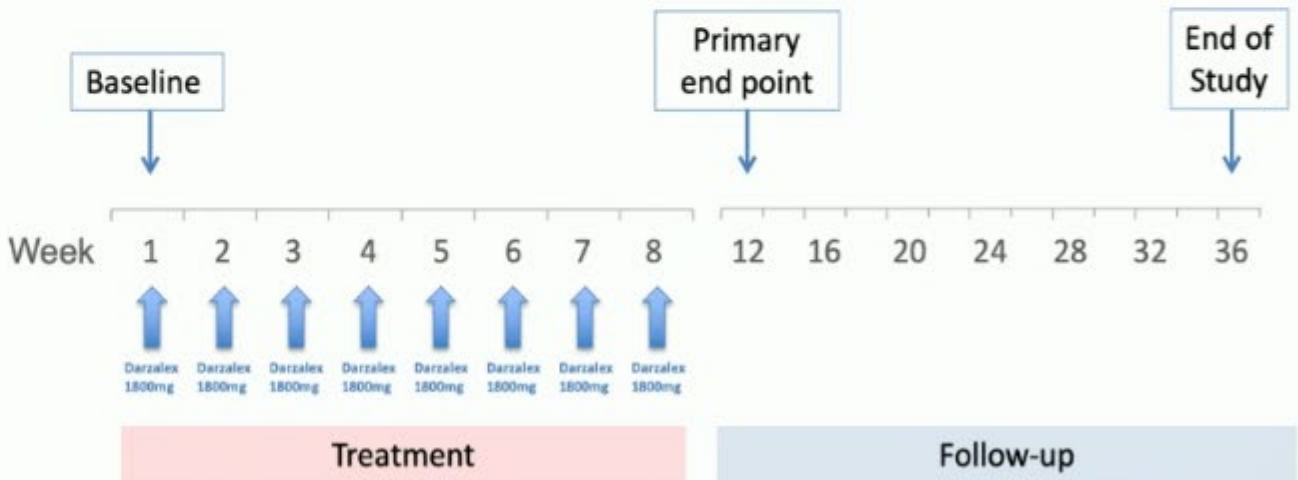
Safety and Efficacy of Daratumumab in Systemic Lupus Erythematosus - A Single-Center Phase 2 Open-Label Trial

Study design

Design:
This was a phase 2, investigator-initiated, open-label, single-center, proof-of-concept study (DARALUP).

Primary endpoint:
Reduction of Anti-dsDNA antibodies at Week 12, i.e. 4 weeks after the last daratumumab injection.

Inclusion:
- Age 18 - 60 years
- SLE according to 2019 EULAR/ACR classification criteria
- SLEDAI-2K ≥ 4 for clinical features
- Insufficient response to ≥ 2 DMARD
- Anti-dsDNA antibody positive

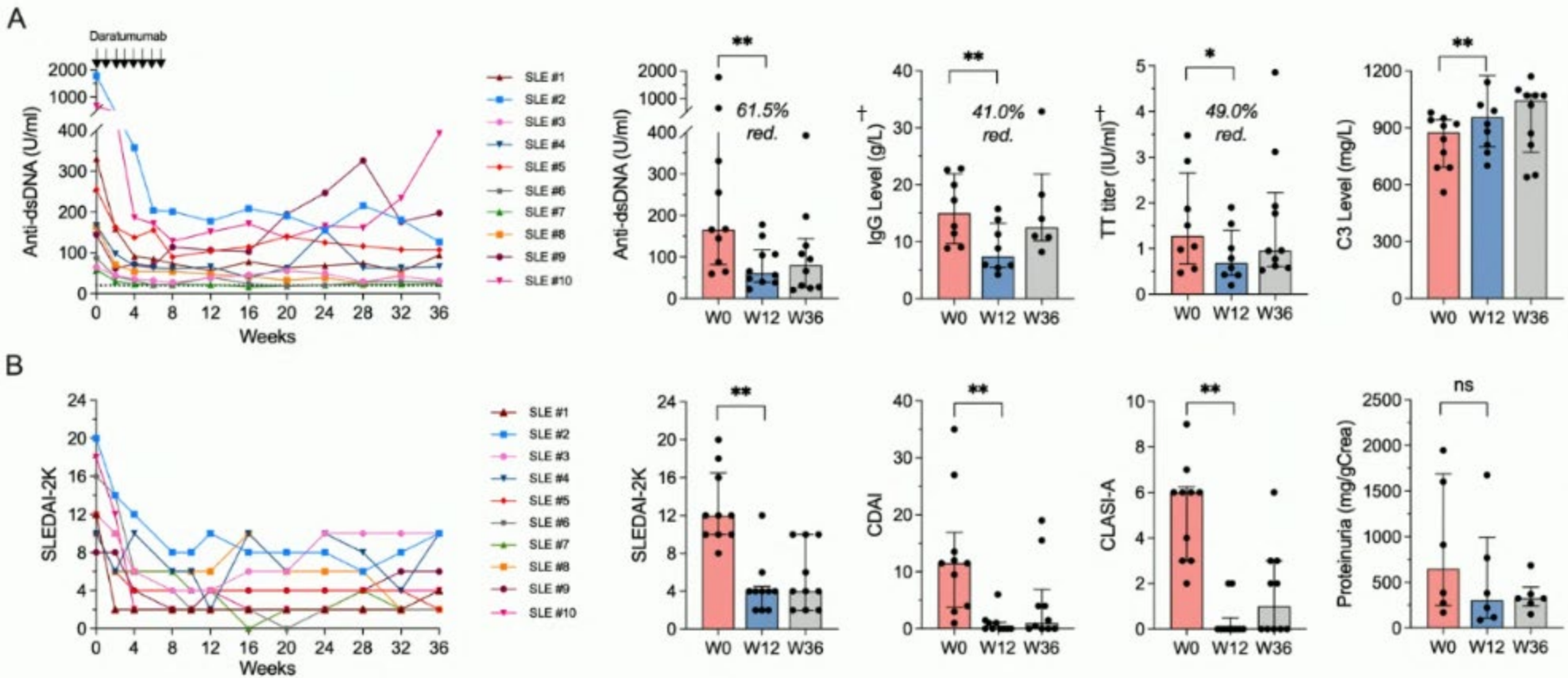


Baseline Demographics and Disease Characteristics

Pat.	Age/Sex	Race	SLEDAI-2K baseline	Organ manifestations	Previous therapies*	Failed previous DMARD	Continued DMARD
1	38/f	Caucasian	12	Arthritis, skin, alopecia, pleuritis, fever	9	HCQ, AZA, MTX, **BEL**, MMF, CsA, CYC, BAR, IVIG	HCQ, Pred 5mg
2	24/f	Caucasian	20	Renal (LN V), arthritis, skin, alopecia, hematologic, pleuritis, hematologic, fever	2	HCQ, MFA	HCQ, MFA, Pred 7.5mg
3	40/f	Caucasian	12	Renal (LN V), arthritis, skin, alopecia, hematologic, pericarditis	5	HCQ, AZA, MMF, MFA, **BEL**	MFA, Pred 5mg
4	32/f	Caucasian	10	Renal (LN II), arthritis, skin, alopecia, hematologic	8	HCQ, AZA, MTX, **BEL**, BAR, **RTX**, IVIG, CYC	HCQ, Pred 12.5mg
5	35/f	Black	10	Renal (LN IV/V), arthritis, alopecia, rash, hematologic	3	HCQ, AZA, MMF	HCQ, MMF, Pred 5mg
6	27/f	Caucasian	16	Renal (LN IV), CNS, rash, alopecia, hematologic, arthritis	8	HCQ, MTX, AZA, CYC, MMF, **RTX, BEL**, IVIG	HCQ, Pred 5mg
7	43/f	Caucasian	10	Renal (no biopsy), arthritis, rash, alopecia, hematologic,	7	HCQ, AZA, MTX, CsA, CYC, MMF, **BEL**	Pred 9mg
8	41/f	Caucasian	12	Renal (LN IV), rash, ulcer, alopecia, arthritis, hematologic	6	HCQ, AZA, MTX, CYC, MMF, **BEL**	MMF, HCQ, Pred 5mg
9	38/f	Black	8	Renal (LN II), rash, alopecia, hematologic, arthritis	2	HCQ, AZA	HCQ, AZA, Pred 7.5mg
10	42/f	Caucasian	18	Renal (LN IV), arthritis, alopecia, pleuritis, hematologic	3	HCQ, AZA, MMF	HCQ, MMF, Pred 10mg

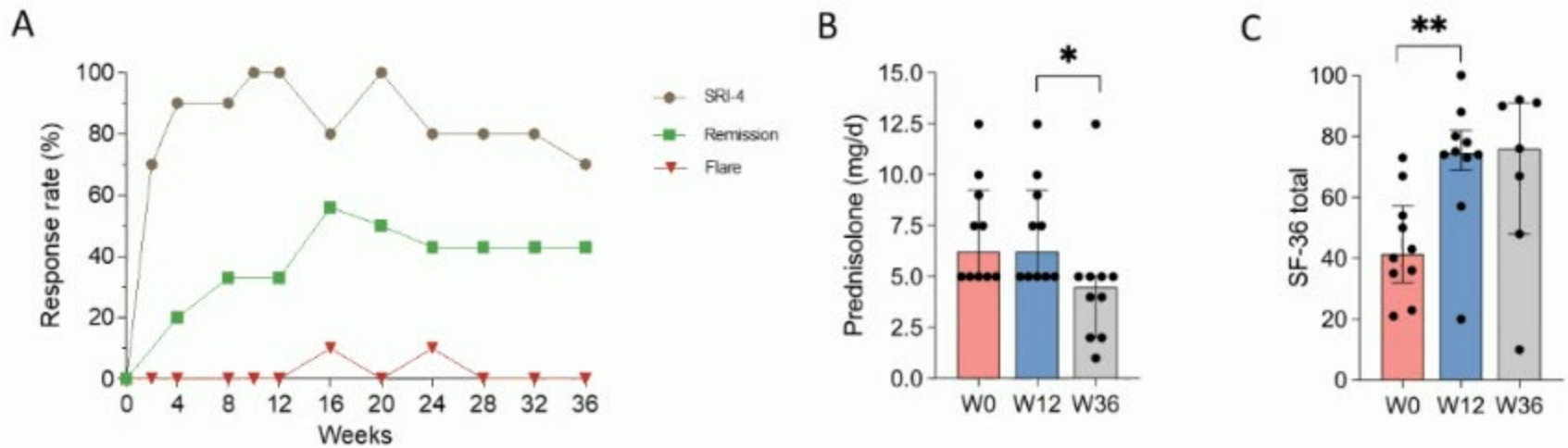
AZA, azathioprine; BAR, baricitinib; BEL, belimumab; CYC, cyclophosphamide; CsA, cyclosporine A; HCQ, hydroxychloroquine, IVIG, intravenous immunoglobulins; LN, lupus nephritis; MFA, mycophenolic acid; MMF, mycophenolate mofetil; MTX, methotrexate; Pred, prednisolone; RTX, rituximab. * Including continued DMARDs, excluding glucocorticoids.

Clinical and Serologic Responses

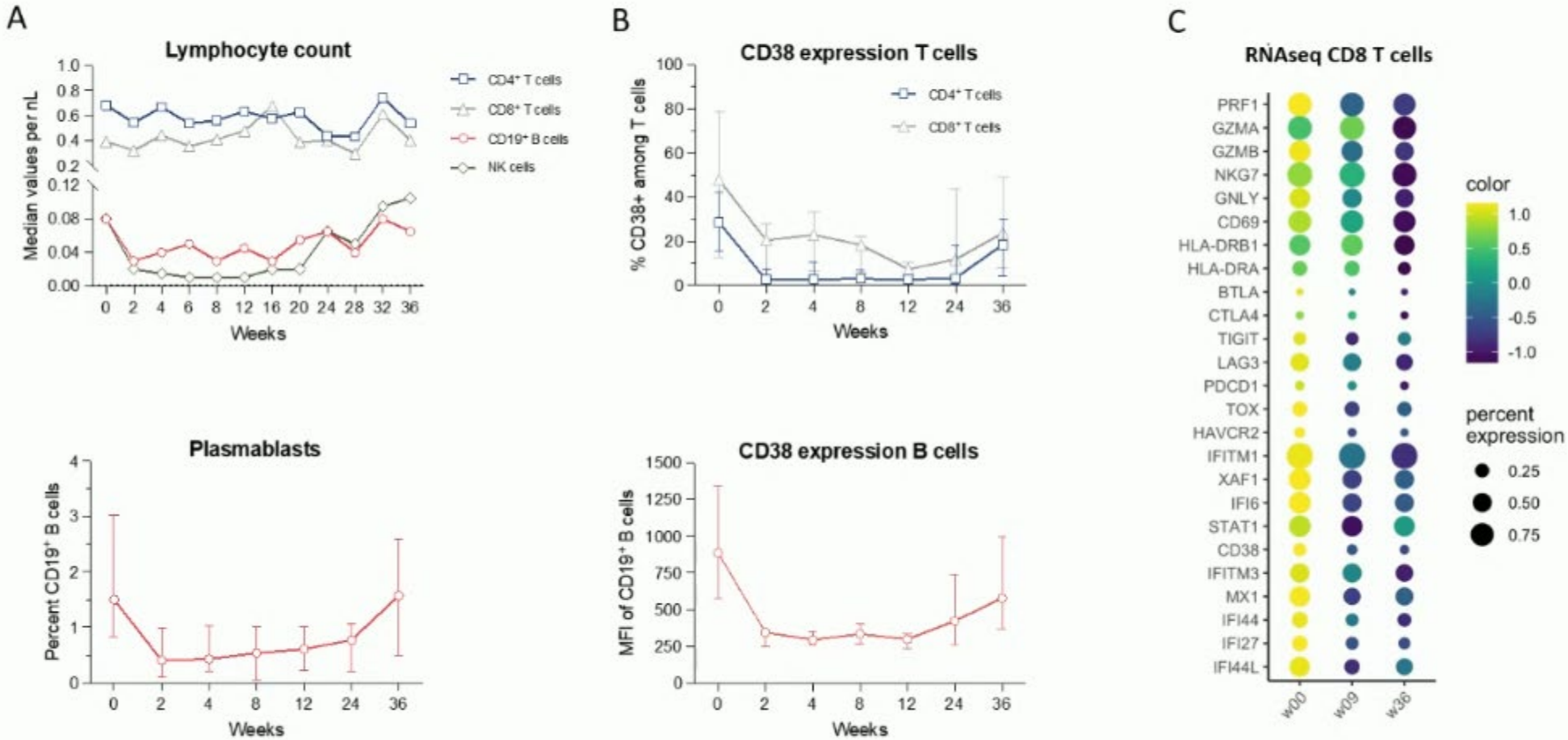


IgG, immunoglobulin G; TT, tetanus toxoid; C3, complement factor C3; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000, CDAI, Clinical Disese Activity Index; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index. † Excluding two patients who received IVIG before week 12.

Clinical Responses



Immune responses



Lymphocyte counts have been determined in clinical routine laboratory. Flow cytometry was performed on cryopreserved PBMC using an anti-CD38 antibody that also binds in the presence of daratumumab. RNAseq (RNA sequencing) was performed on FACS-sorted CD8 memory T cells (excluding CD45RA$^+$ CCR7$^+$ naive T cells).

Safety and Tolerability

Event	Number of patients	Percent of patients
TEAEs	**10**	**100**
SAEs	0	0
Hematologic	**5**	**50**
Immunoglobulin G <5 g/L	5	50
General	**7**	**70**
Injection site reaction	4	40
Fatigue	3	30
Infections and infestations	**8**	**80**
Nasopharyngitis	5	50
COVID-19	3	30
Gastroenteritis	3	30
Bronchitis	2	20
Herpes zoster	2	20
Bacteriuria	1	10
Oral herpes	1	10
Sinusitis	1	10
Upper respiratory tract infection	1	10
Urinary tract infection	1	10
Gastroentestinal	**6**	**60**
Nausea	4	40
Diarrhea	3	30
Abdominal pain	2	20
Muskuloskeletal	**2**	**20**
Back pain	2	20
Nervous System Disorders	**4**	**40**
Headache	4	40

TEAEs, treatment-emergent adverse events; SAE, severe adverse events.

Summary and Conclusion

- Daratumumab produced **strong, rapid and durable** clinical improvements, with efficacy in all major organ sites
- Targeting CD38 induced therapeutically relevant **reductions of pathogenic anti-dsDNA** antibodies with a **favorable safety profile,** but caution is required for hypogammaglobulinemia and infections
- In addition to **depleting plasma cells**, daratumumab had a **modulatory effect on T cells**, resulting in a **deep disease modification,** but not in treatment-free remissions
- These data confirm the **central role of plasma cells** in the pathogenesis of SLE and justify the **further development** of CD38-targeting antibodies or other plasma cell directed agents in SLE