ClinESSDAI Versus ESSDAI for Assessing Treatment Effects in Sjögren's Disease: Findings From the Phase 2 DAHLIAS Trial of the FcRn Blocker Nipocalimab

Raphaele Seror,[1,*] Federico Zazzetti,[2] Jonathan J Hubbard,[2] Soumya D Chakravarty,[3,4] Kim Campbell,[2] Angelina Villasis-Keever,[5] Roy van Heesbeen,[6] Tom Thomas,[2] Kathy Sivils,[2] Sara S McCoy[7]

[1]Service d'Immuno-Rhumatologie, Hôpital Universitaire Bicêtre, Université Paris-Saclay, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France; [2]Johnson & Johnson, Spring House, PA, USA; [3]Johnson & Johnson, Horsham, PA, USA; [4]Drexel University College of Medicine, Philadelphia, PA, USA; [5]Johnson & Johnson, Raritan, NJ, USA; [6]Johnson & Johnson, Leiden, The Netherlands; [7]University of Wisconsin, Madison, WI, USA

*Presenting author.

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Key Takeaways

- In DAHLIAS, the nipocalimab 15 mg/kg IV Q2W group met the primary endpoint of change from baseline in ClinESSDAI score at Week 24 in participants with moderate-to-severe, active SjD, showing significantly greater reduction compared with placebo[6]
- Directionally consistent improvements were also observed when disease activity was assessed using ESSDAI; however, the treatment difference versus placebo was attenuated
- Modification of ESSDAI to exclude the scoring rule that assigned moderate biological domain activity for a "recent decrease in IgG level (<5 g/L)" (mESSDAI) demonstrated that ESSDAI-based assessments were influenced by treatment-related reductions in IgG with nipocalimab
- This analysis confirms that the ESSDAI biological domain scoring may be affected by therapies that reduce circulating IgG levels through their mechanism of action, such as nipocalimab
- By excluding this domain, the ClinESSDAI provides a clinically focused measure of systemic disease activity independent of drug-related pharmacodynamic effects
- Broader adoption of the ClinESSDAI for therapies that directly influence IgG biology in research/clinical settings could enhance consistency and reliability of disease activity assessments, avoid biomarker-related confounding of ESSDAI scoring, and improve clinical interpretation of SjD activity

Background

- Sjögren's disease (SjD) is a chronic, systemic autoimmune disorder characterized by the presence of increased immunoglobulin G (IgG) autoantibodies and lymphocytic infiltration of exocrine glands, leading to dryness symptoms[1]
- Current therapeutic strategies, including corticosteroids, immunosuppressants, and B-cell–depleting therapies (eg, rituximab), aim to mitigate inflammation and reduce damage driven by pathogenic IgG autoantibodies and IgG immune complexes[2,3]
- The European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI; 12 domains) and its clinical version excluding the biological domain, Clinical ESSDAI (ClinESSDAI; 11 domains), are the most widely recognized validated outcome measures for assessing systemic disease activity in SjD trials
- For therapies that target IgG, use of ESSDAI has potential methodological limitations since its biological domain contains IgG-based criteria that may introduce mechanistic bias when a therapy directly changes these biomarkers; for example, the domain assigns moderate activity for a recent decrease in IgG level to <5 g/L, a scoring rule that can be triggered directly by a drug's pharmacodynamic effect rather than by true clinical change[4,5]
  - ClinESSDAI excludes the biological domain of ESSDAI, thus avoiding potential confounding[4,5]
- Nipocalimab is a fully human IgG monoclonal antibody that selectively blocks the neonatal Fc receptor (FcRn), thereby preventing endogenous IgG recycling and mechanistically reducing circulating IgG, including pathogenic IgG autoantibodies and circulating immune complexes observed in multiple IgG autoantibody–mediated diseases, such as SjD[6,7]
- The phase 2 DAHLIAS study of nipocalimab used the ClinESSDAI and ESSDAI as primary and secondary study endpoints, respectively, and demonstrated a significant reduction in ClinESSDAI score with the 15 mg/kg dose at 24 weeks[6]
  - However, it was unclear how these measures of systemic disease activity were influenced by changes in circulating IgG levels that result from nipocalimab's mechanism of action

Objective

This analysis evaluated how measures of systemic disease activity used in the phase 2 DAHLIAS study of nipocalimab in adults with SjD were influenced by changes in circulating IgG levels that result from nipocalimab's mechanism of action

Methods

Study Design

- DAHLIAS (ClinicalTrials.gov identifier: NCT04968912) was a phase 2, double-blind, multicenter trial that enrolled adults (18-75 years of age) with moderate-to-severe, active SjD (ClinESSDAI score of ≥6) who met American College of Rheumatology and EULAR 2016 classification criteria and were seropositive for anti-Ro60 and/or anti-Ro52 IgG autoantibodies
- Participants were randomly assigned 1:1:1 to receive intravenous (IV) nipocalimab 5 mg/kg or 15 mg/kg or placebo every 2 weeks (Q2W) for 22 weeks

Assessments

- Changes from baseline at Week 24 and the proportion of participants achieving ≥3- and ≥4-point improvements in ESSDAI, ClinESSDAI, and modified ESSDAI (mESSDAI), which removes the scoring rule that assigns moderate biological domain activity based on a "recent decrease in IgG level (<5 g/L)" (**Table 1**), were evaluated
- Changes from baseline at Week 24 in ClinESSDAI, ESSDAI, and the ESSDAI biological domain among participants with available Week 24 IgG levels <5 g/L versus ≥5 g/L were also assessed

TABLE 1: Comparison of ESSDAI, ClinESSDAI, and mESSDAI domain structure scoring

Domain (activity level)	Domain weight		
	ESSDAI	ClinESSDAI	mESSDAI
Constitutional (0-2): Fever, night sweats, weight loss	3	4	3
Lymphadenopathy (0-3): Lymphadenopathy, B-cell malignancy	4	4	4
Glandular (0-2): Glandular swelling	2	2	2
Articular (0-3): Arthralgias, synovitis	2	3	2
Cutaneous (0-3): Erythema multiforme, cutaneous vasculitis	3	3	3
Pulmonary (0-3): Persistent cough, interstitial lung disease	5	6	5
Renal (0-3): Renal tubular acidosis, renal involvement	5	6	5
Muscular (0-3): Myositis (muscular pain or weakness)	6	7	6
PNS (0-3): Demyelinating/small fiber neuropathy	5	5	5
CNS (0-3): CNS events with abnormalities on MRI	5	5	5
Hematological (0-3): Cytopenia, anemia, thrombocytopenia	2	2	2
Biological (0-2): Clonal component, hypocomplementemia, hypergammaglobulinemia, cryoglobulinemia, IgG level (low activity: IgG 16-20 g/L; moderate activity: IgG >20 g/L)	1	NA	1 Excluding "recent decrease in IgG level (<5 g/L)"
Total score	0-123	0-135	0-123

Pink shading indicates a difference in domain weight or composition of ClinESSDAI or mESSDAI versus ESSDAI.
ClinESSDAI=Clinical EULAR Sjögren's Syndrome Disease Activity Index; **CNS**=central nervous system; **ESSDAI**=EULAR Sjögren's Syndrome Disease Activity Index; **EULAR**=European Alliance of Associations for Rheumatology; **IgG**=immunoglobulin G; **mESSDAI**=modified EULAR Sjögren's Syndrome Disease Activity Index; **NA**=not available; **PNS**=peripheral nervous system.

Statistical Analysis

- The primary endpoint, change from baseline in ClinESSDAI score at Week 24, was evaluated at the prespecified 2-sided alpha level of 0.1 without formal adjustment for multiple comparisons; statistical significance was not prespecified for other assessments, and *P* values are nominal
- For continuous outcomes, least-squares (LS) means, LS mean differences, confidence intervals (CIs), and *P* values were analyzed using a longitudinal mixed-effects repeated-measures model that included baseline score, treatment, visit, region, baseline steroid and antimalarial use, and treatment-by-visit interaction as independent variables
  - Intercurrent events were handled using a hypothetical strategy, in which data at and after the event were treated as missing without imputation, while all available pre-event longitudinal data contributed to LS mean estimates
- For binary outcomes, treatment differences and their CIs were based on unstratified Wald statistics, and *P* values were based on a Cochran-Mantel-Haenszel test with region, baseline steroid use, and baseline antimalarial use as stratification factors
  - Intercurrent events were handled using a composite strategy, in which data after the event were treated as nonresponses

Results

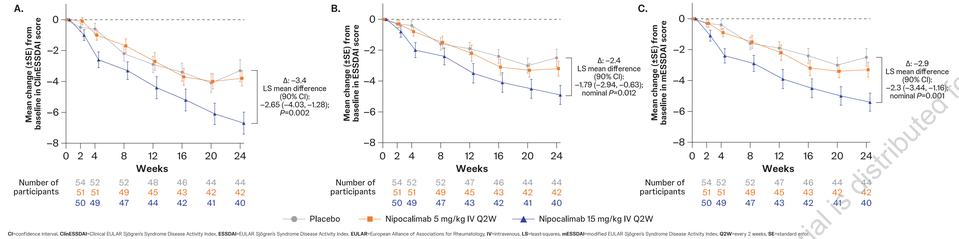
Participants

- In total, 163 participants were randomized and included in the efficacy analyses (nipocalimab 5 mg/kg IV Q2W, n=53; nipocalimab 15 mg/kg IV Q2W, n=54; placebo, n=56)
- Baseline characteristics were generally balanced across treatment groups[6]
  - Mean (standard deviation [SD]) age was 48.1 (12.12) years, and 151 (93%) participants were female
  - Mean (SD) baseline ClinESSDAI score was 9.9 (3.49), and mean (SD) baseline ESSDAI score was 8.9 (3.44)

Change From Baseline in ESSDAI and Its Variants at Week 24

- A significantly greater improvement in ClinESSDAI score at Week 24 was observed with nipocalimab 15 mg/kg versus placebo (**Figure 1A**)
- A greater reduction in ESSDAI score at Week 24 was observed with nipocalimab 15 mg/kg compared with placebo, although the magnitude of improvement was smaller than that observed with ClinESSDAI (**Figure 1B**)
- A greater improvement in mESSDAI score at Week 24 was observed with nipocalimab 15 mg/kg versus placebo, although the relative magnitude of improvement was smaller than that observed with ClinESSDAI but larger than that observed with ESSDAI (**Figure 1C**)

FIGURE 1: Change from baseline through Week 24 in (A) ClinESSDAI, (B) ESSDAI, and (C) mESSDAI

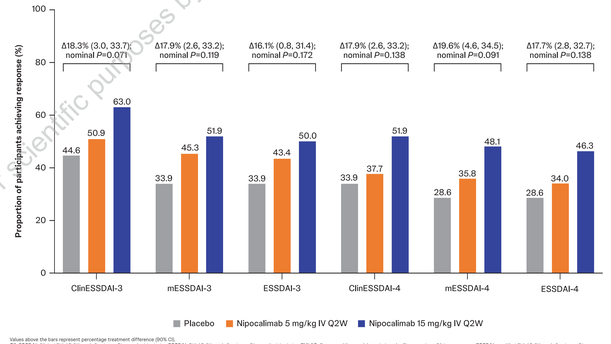


CI=confidence interval; **ClinESSDAI**=Clinical EULAR Sjögren's Syndrome Disease Activity Index; **ESSDAI**=EULAR Sjögren's Syndrome Disease Activity Index; **EULAR**=European Alliance of Associations for Rheumatology; **IV**=intravenous; **LS**=least-squares; **mESSDAI**=modified EULAR Sjögren's Syndrome Disease Activity Index; **Q2W**=every 2 weeks; **SE**=standard error.

Achievement of ≥3-Point and ≥4-Point Improvements in ESSDAI and Its Variants at Week 24

- Numerically higher response rates for a ≥3-point improvement at Week 24 for ClinESSDAI, ESSDAI, and mESSDAI were observed with nipocalimab 15 mg/kg versus placebo, with the greatest treatment effects for ClinESSDAI, followed by mESSDAI and ESSDAI (**Figure 2**)
- A similar treatment effect was observed for ≥4-point improvements in ESSDAI and its variants at Week 24

FIGURE 2: Proportion of participants achieving ≥3-point and ≥4-point improvements in ClinESSDAI, ESSDAI, and mESSDAI

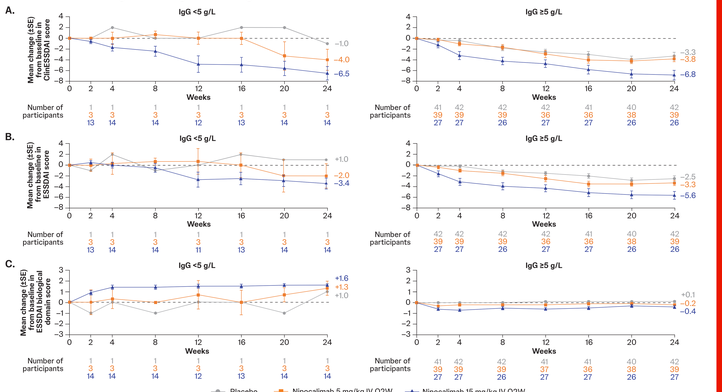


Values above the bars represent percentage treatment difference (90% CI).
ClinESSDAI=Clinical EULAR Sjögren's Syndrome Disease Activity Index; **ESSDAI**=EULAR Sjögren's Syndrome Disease Activity Index; **EULAR**=European Alliance of Associations for Rheumatology; **IV**=intravenous; **mESSDAI**=modified EULAR Sjögren's Syndrome Disease Activity Index; **Q2W**=every 2 weeks.

ClinESSDAI, ESSDAI, and ESSDAI Biological Domain Score Changes Stratified by IgG Level at Week 24

- At Week 24, nipocalimab 15 mg/kg resulted in a median pre-dose (trough) IgG reduction of 61%, and 14 (34.1%) participants had IgG <5 g/L compared with 3 (7.1%) participants with nipocalimab 5 mg/kg and 1 (2.3%) with placebo
- Within the nipocalimab 15 mg/kg group, improvement from baseline in ClinESSDAI score through Week 24 was similar between those with Week 24 IgG <5 g/L and ≥5 g/L (**Figure 3A**)
- For total ESSDAI score, greater improvement from baseline through Week 24 was observed among participants with Week 24 IgG ≥5 g/L versus with IgG <5 g/L (**Figure 3B**)
- By contrast, for the ESSDAI biological domain, improvement from baseline was observed among participants with IgG ≥5 g/L at Week 24, whereas the scores in participants with IgG <5 g/L at Week 24 increased (**Figure 3C**)
  - This increase artifactually suggests worsening disease activity rather than true clinical worsening since the ClinESSDAI scores in these same participants demonstrated disease improvement, which is also consistent with the patient-reported outcome endpoints[6]

FIGURE 3: Change from baseline through Week 24 in (A) ClinESSDAI, (B) ESSDAI, and (C) the ESSDAI biological domain scores among participants with available Week 24 IgG levels <5 g/L versus ≥5 g/L



ClinESSDAI=Clinical EULAR Sjögren's Syndrome Disease Activity Index; **ESSDAI**=EULAR Sjögren's Syndrome Disease Activity Index; **EULAR**=European Alliance of Associations for Rheumatology; **IgG**=immunoglobulin G; **IV**=intravenous; **Q2W**=every 2 weeks; **SE**=standard error.

This material is distributed for scientific purposes by Johnson & Johnson Innovative Medicine and is not for promotional use.

PRESENTED AT: The American College of Rheumatology (ACR) Convergence; November 6-11, 2026; Orlando, FL, USA. **REFERENCES: 1.** Baldini C, et al. *Nat Rev Rheumatol*. 2024;20(8):473-491. **2.** Parisis D, et al. *J Clin Med*. 2020;9(7):2299. **3.** Zhan Q, et al. *Front Immunol*. 2023;14:1127417. **4.** Seror R, et al. *RMD Open*. 2015;1(1):e000022. **5.** Seror R, et al. *Ann Rheum Dis*. 2016;75(11):1945-1950. **6.** Noaiseh G, et al. *Lancet*. 2025;406(10518):2435-2438. **7.** Antozzi C, et al. *Lancet Neurol*. 2025;24(2):105-116. **ACKNOWLEDGMENTS:** This research was sponsored by Johnson & Johnson. Writing and editorial assistance were provided by Russell Craddock, PhD, of Lumanity Communications Inc., and funded by Johnson & Johnson. **DISCLOSURES: RS** has nothing to declare. **FZ**, **JJH**, **SDC**, **KC**, **AV-K**, **RvH**, **TT**, and **KS** are employees of and may own stock/stock options in Johnson & Johnson. **SSM** is a consultant for Amgen, Argenx, Artiva, Johnson & Johnson, Novartis, Otsuka, Veloxis, and Vor Bio; and is the founder of Quench Therapeutics.