Efficacy and Safety of Nipocalimab in Primary Sjogren's Disease: Results From a Phase 2, Randomized, Double-blind DAHLIAS Study

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Key Takeaway

In adults with active Sjögren's disease, treatment with nipocalimab 15 mg/kg for 24 weeks led to reduced IgG autoantibody levels and improved clinical and patient-reported outcomes compared to placebo

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 score and demonstrated similar trends in other key efficacy endpoints**
  - **Nipocalimab treatment was well tolerated, with no new safety signals observed**
- **These findings established the clinical benefits of reducing IgG autoantibody levels for the treatment of Sjögren's disease**
- **These findings support further clinical evaluation of nipocalimab, a novel FcRn blocker, in Sjögren's disease and other autoantibody-associated rheumatic diseases**

Background

- Sjögren's disease (SjD) is a chronic, systemic autoimmune disease characterized by the presence of autoantibodies, lymphocytic infiltration of exocrine glandular tissues, and systemic organ and tissue injury[1]
- Dysregulated humoral immunity involving aberrant B-lymphocyte activity leading to abnormally elevated levels of immunoglobulin (Ig) G and IgG autoantibodies, particularly anti-Ro and anti-La autoantibodies, has been implicated in SjD[1]
- SjD is associated with substantial disease burden, with symptoms that include mucosal dryness, fatigue, and pain,[2,3] and ~1.5-fold higher all-cause mortality[4]
- Neonatal crystallizable fragment receptor (FcRn) is a transmembrane protein that is involved with IgG recycling and transcytosis as well as innate and adaptive immune function[5]
- Nipocalimab is a fully human IgG1 monoclonal antibody that binds with high affinity to the IgG binding site of the FcRn
- As an FcRn blocker, nipocalimab decreases levels of IgG and IgG autoantibodies without broad immunosuppression
- The efficacy of nipocalimab has been established in generalized myasthenia gravis and hemolytic disease of the fetus and newborn[6,7]

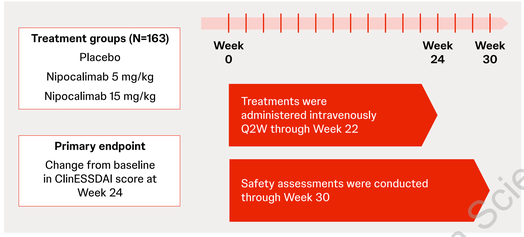
Objective

- **To evaluate the efficacy and safety of nipocalimab in patients with SjD**

Methods

- A phase 2, multicenter, randomized, placebo-controlled, double-blind study (DAHLIAS; ClinicalTrials.gov Identifier: NCT04968912) was conducted in adults aged 18 to 75 years with moderately to severely active SjD (total Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index [ClinESSDAI] score ≥6) who were seropositive for anti-Ro60 and/or anti-Ro52 IgG autoantibodies (**Figure 1**)
  - ClinESSDAI is a variant of the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) clinical assessment scale that does not include the biological domain (including IgG) of SjD[8]

FIGURE 1: Study design



ClinESSDAI=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; Q2W=Every 2 weeks.

- Participants were randomized 1:1:1 to receive intravenous (IV) nipocalimab at 5 or 15 mg/kg or placebo every 2 weeks through Week 22 and protocol-permitted background standard of care
- The primary endpoint was change from baseline in ClinESSDAI score at Week 24
- Secondary and supportive endpoints included:
  - Change from baseline at Week 24 in Physician Global Assessment of Disease Activity (PhGA), ESSDAI score, and European League Against Rheumatism Sjögren's Syndrome Patient Reported Index (ESSPRI) score
  - Responder rate at Week 24 for improvement of ≥3 points from baseline in ESSDAI score (ESSDAI-3), disease response according to the Sjögren's Tool for Assessing Response (STAR), improvement from baseline in ≥3 of 5 Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) categories, and improvement in disease activity level (DAL) by ≥1 level in ≥1 ClinESSDAI or ESSDAI domain
  - Proportion of participants with ≥50% improvement from baseline in unstimulated whole salivary flow rate (UWS) at Week 24
  - IgG, anti-Ro60 IgG, and anti-La IgG levels
- Safety assessments were conducted through Week 30

Results

- In total, 163 participants were enrolled (**Table 1**)
  - Demographic and baseline disease characteristics were comparable among groups

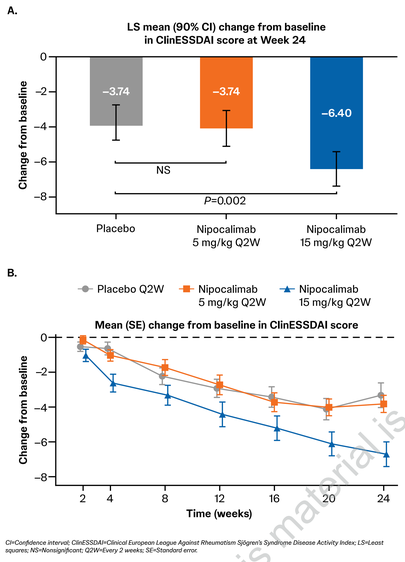
TABLE 1: Demographic and baseline disease characteristics

Characteristic	Placebo (N=56)	Nipocalimab 5 mg/kg Q2W (n=53)	Nipocalimab 15 mg/kg Q2W (n=54)	All participants (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

[a]Measured at a central laboratory. Reference range was 6.03 to 16.13 g/L. ClinESSDAI=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; IgG=Immunoglobulin G; Q2W=Every 2 weeks; RF=Rheumatoid factor; SD=Standard deviation.

- The nipocalimab 15 mg/kg group met the primary endpoint versus placebo (least squares mean difference, −2.65; 90% CI, −4.03, −1.28; *P*=0.002; **Figure 2**)

FIGURE 2: Change from baseline in ClinESSDAI score



CI=Confidence interval; ClinESSDAI=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; LS=Least squares; NS=Nonsignificant; Q2W=Every 2 weeks; SE=Standard error.

- Similar improvements in the nipocalimab 15 mg/kg group versus placebo were observed in most secondary and supportive endpoints (**Tables 2** and **3**)

TABLE 2: Change from baseline at Week 24 in selected secondary and supportive endpoints

Endpoint	LS mean difference (90% CI): nipocalimab vs placebo[a] 5 mg/kg Q2W (n=53)	LS mean difference (90% CI): nipocalimab vs placebo[a] 15 mg/kg Q2W (n=54)	Nominal *P* value: nipocalimab 15 mg/kg Q2W vs placebo
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

[a]Comparisons with the placebo group used a mixed-effects repeated-measures model with baseline score, study treatment, visit, region, baseline steroid use, baseline antimalarial 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. CI=Confidence interval; ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; LS=Least squares; PhGA=Physician Global Assessment of Disease Activity; Q2W=Every 2 weeks.

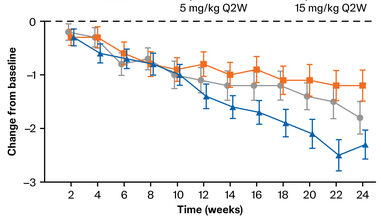
TABLE 3: Responder rate at Week 24 for selected secondary and supportive endpoints

Endpoint	Difference in proportions % (90% CI): nipocalimab vs placebo[a] 5 mg/kg Q2W (n=53)	Difference in proportions % (90% CI): nipocalimab vs placebo[a] 15 mg/kg Q2W (n=54)	Nominal *P* value: nipocalimab 15 mg/kg Q2W vs placebo
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[b]	18.9 (3.6, 34.2)	19.8 (4.5, 35.0)	0.046

[a]Values are percentages. Statistical comparisons with the placebo group used a Cochran-Mantel-Haenszel test with region, baseline steroid use, and baseline antimalarial use as stratification factors. For binary composite endpoints, participants with intercurrent events were considered nonresponders after the event. [b]DAL response is a reduction from baseline in DAL by ≥1 level in ≥1 ClinESSDAI domain (eg, articular, hematological, cutaneous, constitutional). CI=Confidence interval; ClinESSDAI=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome; DAL=Disease activity level; ESSDAI-3=Improvement of ≥3 points from baseline in European League Against Rheumatism Sjögren's Syndrome Disease Activity Index score; Q2W=Every 2 weeks; STAR=Sjögren's Tool for Assessing Response.

- Nipocalimab 15 mg/kg treatment resulted in greater reductions from baseline in ESSPRI score from Weeks 12 through 24 compared to placebo (**Figure 3**)

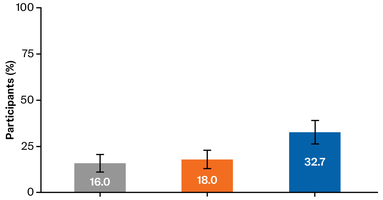
FIGURE 3: Mean (SE) change from baseline in ESSPRI score



ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; Q2W=every 2 weeks; SE=standard error.

- The proportion of participants with ≥50% improvement from baseline in UWS at Week 24 in the nipocalimab 15 mg/kg group was more than double that of the placebo group (**Figure 4**)

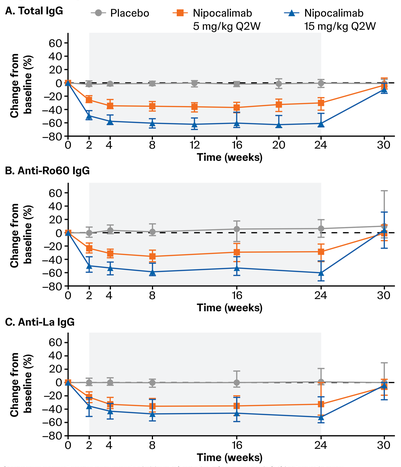
FIGURE 4: Proportion (SE) of participants with ≥50% improvement from baseline in UWS at Week 24



Q2W=Every 2 weeks; SE=Standard error; UWS=Unstimulated whole salivary flow rate.

- Significant nipocalimab dose-dependent reductions from baseline in total IgG antibody and IgG autoantibody levels were observed (**Figure 5**)
  - There was a **77% maximum reduction** in total IgG, as determined by pharmacokinetic/pharmacodynamic simulations
  - There was a median predose (minimum) observed reduction of 61% in total IgG at Week 24
  - Consistent reductions in SjD-associated anti-Ro60, anti-Ro52, and anti-La IgG autoantibodies were observed

FIGURE 5: Median (IQR) minimum observed percent change from baseline in IgG antibody levels over time



Shaded areas represent predose measurements of minimum IgG reduction. IgG=Immunoglobulin G; IQR=Interquartile range; Q2W=every 2 weeks.

- Serious adverse events (AEs) were reported in 7.5%, 7.4%, and 5.4% of participants in the nipocalimab 5 mg/kg, nipocalimab 15 mg/kg, and placebo groups, respectively (**Table 4**)
  - One participant in the nipocalimab 5 mg/kg group experienced a serious AE reported by the preferred term "anaphylactic reaction," which presented as tachycardia, hypertension, dyspnea, and urticaria during the 10th administration of study treatment
- Severe infections or infections requiring IV anti-infectives occurred in 3.8%, 1.9%, and 1.8% of participants in the nipocalimab 5 mg/kg, nipocalimab 15 mg/kg, and placebo groups, respectively, without a clear correlation with IgG nadir; none were deemed related to study treatment

TABLE 4: AEs and serious AEs

Participants with ≥1 AE, n (%)	Placebo (N=56)	Nipocalimab 5 mg/kg Q2W (n=53)	Nipocalimab 15 mg/kg Q2W (n=54)	Nipocalimab 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)	60 (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

[a]Infections that were severe or required IV anti-infective or operative/invasive intervention, as assessed by the investigator. [b]Cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. AE=Adverse event; IV=Intravenous; MACE=Major adverse cardiovascular events; Q2W=Every 2 weeks.

- 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
- The safety profile of nipocalimab was consistent with findings from patients with myasthenia gravis, rheumatoid arthritis, and hemolytic disease of the fetus and newborn[6,7]

PRESENTED AT: Congress of Clinical Rheumatology-West (CCR-W); San Diego, CA, USA; September 26-29, 2024. **REFERENCES: 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. *Rheumatology (Oxford).* 2021;60(9):4029-4038. **5.** Pyzik M, et al. *Nat Rev Immunol.* 2023;23(7):415-432. **6.** Antozzi C, et al. *Neurology.* 2024;102(2):e207937. **7.** Moise KJ, et al. *N Engl J Med.* 2024;391(6):526-537. **8.** Parisis D, et al. *J Clin Med.* 2020;9(7):2299. **ACKNOWLEDGEMENTS:** The authors would like to thank all study participants, investigators, study site staff, and ICON for their contributions to the study. Valuable advice was provided by Raphaele Seror, MD, PhD; Simon Bowman, MBBS, PhD; Fai Ng, MB, BChir, PhD; Hal Scofield, MD; Daniel Wallace, MD; and Robert Hoffman, DO. This study was sponsored by Janssen Research & Development, LLC. Medical writing support was provided by Catherine Bautista, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC. **DISCLOSURES; JEG:** has consulted for AbbVie, Janssen, BMS, UCB, MSD, Novartis, Pfizer, Gilead, Galapagos, Eli Lilly, and Sanofi. **KS, KC, JI, KL, SGL, JS, HD,** and **JJH:** employees of Janssen Research and Development, LLC; may own stock/stock options in Johnson & Johnson. **GN:** advisory board member of Janssen and Novartis. Previously presented at APLAR 2024; Suntec, Singapore; August 21-25, 2024.