Pharmacodynamic Effects of Nipocalimab on Disease Biomarkers in Patients With Moderate-to-Severe Active Sjögren's Disease: Results From a Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study

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Key Takeaways

- **Nipocalimab substantially and reversibly reduced total IgG, IgG autoantibodies, and circulating immune complexes, consistent with its mechanism of action, with clear differences by dose in adults with active SjD**
- **Furthermore, substantial reductions in RF and ESR were observed with nipocalimab 15 mg/kg**
- **These findings suggest that autoantibodies and circulating immune complexes may play an important role in SjD and support the hypothesis that reducing their levels through FcRn blockade may provide clinical benefits for patients with SjD**

Background

Sjögren's disease (SjD) is a chronic, systemic autoimmune disease characterized by the presence of autoantibodies, immune cell infiltration of exocrine tissues, and systemic organ and tissue injury[1]

Abnormally elevated levels of immunoglobulin (Ig) G and IgG autoantibodies, particularly anti-Ro60/SSA, anti-Ro52/TRIM21, and anti-La/SSB autoantibodies, have been implicated in SjD[1]

Neonatal fragment crystallizable receptor (FcRn) is a transmembrane protein that is involved with IgG recycling and transcytosis, as well as innate and adaptive immune function[2]

Nipocalimab is a fully human IgG1 monoclonal antibody that selectively binds to the IgG binding site of the FcRn with high affinity[3,4]

- As an FcRn blocker, nipocalimab decreases levels of IgG antibodies, including autoantibodies, without broad immunosuppression

The efficacy of nipocalimab has been demonstrated in clinical studies of alloantibody- and autoantibody-mediated diseases, including generalized myasthenia gravis and hemolytic disease of the fetus and newborn[5,6]

In a phase 2 proof-of-concept study (DAHLIAS), nipocalimab demonstrated significant improvements in clinical endpoints in participants with SjD at Week 24[7]

Objectives

To evaluate the pharmacodynamic effects of nipocalimab treatment on key disease biomarkers in participants with SjD from the DAHLIAS study

Methods

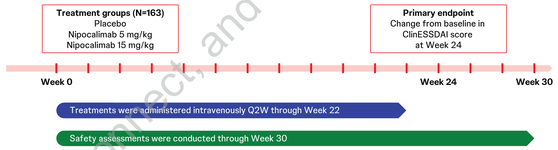
Study Design

- A phase 2, multicenter, randomized, double-blind, placebo-controlled 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
- Participants were randomized 1:1:1 to receive intravenous nipocalimab at doses of 5 or 15 mg/kg or placebo every 2 weeks through Week 22 in addition to protocol-permitted background standard of care (**Figure 1**)
- The study consisted of 3 periods: a screening period of up to 6 weeks, a 24-week treatment period, and a 6-week follow-up period (8 weeks after administration of the last study intervention)

Assessments

- Blood samples were collected from participants at Weeks 0, 2, 4, 8, 12, 16, 20, 24, and 30 to measure the serum levels of IgG, including total IgG, IgG subclasses, anti-Ro60, anti-La, and anti-Ro52; C3d-bound circulating immune complexes (C3d-CIC); IgM; IgA; and clinically relevant biomarkers, including rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR)

Figure 1: Study design



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

Results

A total of 163 participants were enrolled in the study; demographic and baseline characteristics are shown in Table 1

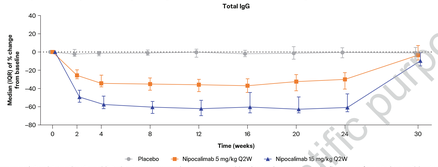
Table 1: Demographic and baseline characteristics

Characteristic	Placebo (n=56)	Nipocalimab 5 mg/kg Q2W (n=53)	Nipocalimab 15 mg/kg Q2W (n=54)
Age, years, median (range)	46.5 (23–73)	49.0 (20–72)	48.5 (24–72)
Female, %	92.9	92.5	92.6
White, %	89.3	92.5	90.7
Time since diagnosis, years, median (range)	4.0 (0.6–34.0)	3.7 (0.6–27.9)	4.3 (0.6–18.2)
ClinESSDAI score, mean (SD)	10.0 (3.8)	9.4 (3.1)	10.2 (3.6)
ESSPRI score, mean (SD)	7.0 (1.3)	7.0 (1.3)	7.2 (1.2)
Total IgG, g/L, median (range)	14.8 (7.7–40.5)	14.8 (4.6–35.2)	15.5 (7.6–49.6)
IgG subclass levels, g/L, median (range)			
IgG1	10.4 (3.8–31.5)	10.2 (2.5–27.1)	11.2 (4.2–34.9)
IgG2	2.7 (0.6–7.5)	2.7 (0.8–8.1)	2.8 (0.6–6.3)
IgG3	0.4 (0.1–1.4)	0.4 (0.1–1.6)	0.4 (0.1–1.4)
IgG4	0.3 (0–3.1)	0.3 (0–3.3)	0.3 (0–2.4)
IgM, g/L, median (range)	1.0 (0.4–4.3)	1.1 (0.3–3.8)	1.2 (0.2–8.1)
IgA, g/L, median (range)	2.5 (1.0–5.9)	2.5 (0.8–5.9)	3.0 (0.3–8.0)
Autoantibody levels			
Anti-Ro60, CU, median (range)	22,479.3 (61.3–147,552.0)	17,710.9 (47.1–142,384.0)	18,366.3 (46.4–362,768.0)
Anti-La, CU, median (range)	254.8 (27.8–41,424.0)	187.7 (20.4–65,728.0)	336.6 (22.9–32,760.0)
Anti-Ro52, CU, median (range)	5,937.4 (37.6–74,624.0)	3,650.1 (46.1–78,448.0)	2,330.7 (34.1–77,896.0)
RF, IU/mL, median (range)	28.3 (10.0–649.8)	24.2 (10.0–127.8)	22.7 (10.0–551.0)
Autoantibody positivity,[a] %			
Anti-Ro60	98.2	98.1	98.1
Anti-La	74.5	76.9	64.2
Anti-Ro52	78.2	86.5	77.4
RF	78.6	71.7	63.0
C3d-CIC, mgEq/L, median (IQR)	10.8 (7.6–13.8)	8.6 (6.3–12.4)	9.9 (7.5–15.6)
ESR, mm/h, median (range)	30.5 (2.0–122.0)	32.0 (2.0–118.0)	33.5 (3.0–120.0)

[a]All participants were seropositive at screening; each treatment group had 1 participant who was missing baseline values in the dataset for the anti-Ro autoantibodies. Only data from participants who were positive for anti-Ro60, anti-La, or anti-Ro52 at baseline were included in the anti-Ro60, anti-La, and anti-Ro52 analyses, respectively. **C3d-CIC**=C3d-bound circulating immune complex, **ClinESSDAI**=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index, **CU**=Chemiluminescent unit, **ESR**=Erythrocyte sedimentation rate, **ESSPRI**=European League Against Rheumatism Sjögren's Syndrome Patient Reported Index, **Ig**=Immunoglobulin, **IQR**=Interquartile range, **Q2W**=Every 2 weeks, **RF**=Rheumatoid factor, **SD**=Standard deviation

Substantial dose-dependent reductions from baseline in total IgG levels were observed with nipocalimab treatment; total IgG returned to baseline levels by Week 30 (Figure 2; Table 2)

Figure 2: Observed predose (minimum) change from baseline in total IgG levels over time



If a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Only data from participants with ≥1 valid postbaseline blood sample drawn for PD analysis were included. **Ig**=Immunoglobulin, **IQR**=Interquartile range, **PD**=Pharmacodynamic, **Q2W**=Every 2 weeks

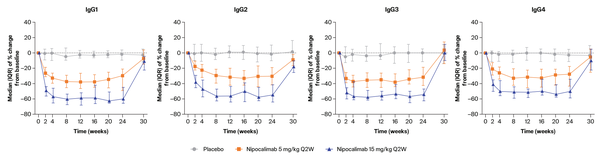
Table 2: Observed predose (minimum) percent change from baseline in clinical biomarkers at Week 24

% change from baseline, median (IQR)	Placebo (n=56)	Nipocalimab 5 mg/kg Q2W (n=53)	Nipocalimab 15 mg/kg Q2W (n=54)
Total IgG	−0.5 (−6.8, −5.0)	−30.0 (−41.0, −22.2)	−60.9 (−66.0, −45.7)
IgG subclasses			
IgG1	−1.9 (−9.4, 3.8)	−29.7 (−49.1, −21.1)	−60.0 (−65.7, −44.9)
IgG2	−1.6 (−10.2, 10.2)	−30.4 (−41.6, −19.1)	−54.7 (−64.0, −41.4)
IgG3	0 (−11.4, 5.2)	−31.7 (−42.2, −18.8)	−54.2 (−62.5, −47.1)
IgG4	−2.6 (−11.1, 4.8)	−27.6 (−43.1, −17.5)	−50.0 (−58.6, 34.1)
IgG autoantibodies			
Anti-Ro60	6.6 (−8.0, 20.3)	−29.5 (−43.4, −18.1)	−60.1 (−72.3, −42.4)
Anti-La	8.5 (−9.3, 22.7)	−32.7 (−49.0, −18.1)	−53.5 (−62.7, −36.7)
Anti-Ro52	6.1 (−6.3, 18.8)	−23.0 (−39.3, −14.1)	−50.9 (−62.7, −37.0)
C3d-CIC	5.7 (−21.7, 28.1)	−37.5 (−47.3, 0)	−55.3 (−67.5, −47.6)
IgM	2.5 (−6.5, 10.0)	−5.0 (−11.6, 2.2)	−10.5 (−22.0, −4.1)
IgA	−1.2 (−6.2, 3.7)	3.4 (−5.7, 11.4)	6.0 (−1.0, 12.2)
RF	0 (−3.4, 4.0)	−10.7 (−19.4, 0)	−15.3 (−29.0, 0)
ESR	−16.7 (−46.1, 14.0)	−17.1 (−34.8, 25.0)	−38.5 (−58.3, 0)

If a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Only data from participants with ≥1 valid postbaseline blood sample drawn for PD analysis were included. Only data from participants who were positive for anti-Ro60, anti-La, or anti-Ro52 at baseline were included in the anti-Ro60, anti-La, and anti-Ro52 analyses, respectively. **C3d-CIC**=C3d-bound circulating immune complex, **ESR**=Erythrocyte sedimentation rate, **Ig**=Immunoglobulin, **IQR**=Interquartile range, **PD**=Pharmacodynamic, **Q2W**=Every 2 weeks, **RF**=Rheumatoid factor

Decreases from baseline in IgG1, IgG2, IgG3, and IgG4 in the nipocalimab groups were consistent with those observed for total IgG levels (Figure 3; Table 2)

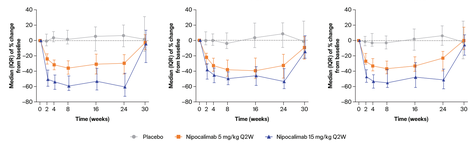
Figure 3: Observed predose (minimum) percent change from baseline in IgG subclass levels over time



The sample size was the number of participants with nonmissing values at both baseline and postbaseline time points. Only data from participants with ≥1 valid postbaseline blood sample drawn for PD analysis were included. **Ig**=Immunoglobulin, **IQR**=Interquartile range, **PD**=Pharmacodynamic, **Q2W**=Every 2 weeks

Consistent dose-dependent reductions from baseline in SjD-associated anti-Ro60, anti-La, and anti-Ro52 IgG autoantibodies were observed with nipocalimab treatment (Figure 4; Table 2)

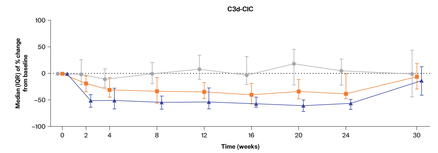
Figure 4: Observed predose (minimum) percent change from baseline in IgG autoantibody levels over time



If a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Only data from participants with ≥1 valid postbaseline blood sample drawn for PD analysis were included. Only data from participants who were positive for anti-Ro60, anti-La, or anti-Ro52 at baseline were included in the anti-Ro60, anti-La, and anti-Ro52 analyses, respectively. **Ig**=Immunoglobulin, **IQR**=Interquartile range, **PD**=Pharmacodynamic, **Q2W**=Every 2 weeks

Reductions from baseline in C3d-CIC levels were also observed in both nipocalimab groups (Figure 5; Table 2)

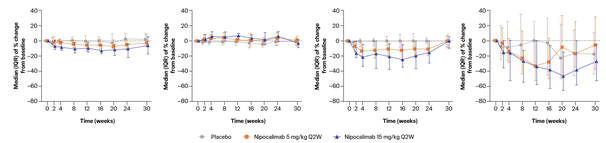
Figure 5: Observed predose (minimum) percent change from baseline in C3d-CIC levels over time



Only data from participants with elevated C3d-CIC levels were included. **C3d-CIC**=C3d-bound circulating immune complex, **IQR**=Interquartile range, **Q2W**=Every 2 weeks

Nipocalimab 15 mg/kg was associated with clinically significant changes from baseline at Week 24 in RF and ESR levels versus placebo; all biomarker changes returned to near baseline levels by Week 30 (Figure 6; Table 2)

Figure 6: Observed predose (minimum) percent change from baseline in clinical biomarker levels over time



Analyses included participants with nonmissing values at both baseline and postbaseline time points. If a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Only data from participants with ≥1 valid postbaseline blood sample drawn for PD analysis were included. **ESR**=Erythrocyte sedimentation rate, **Ig**=Immunoglobulin, **IQR**=Interquartile range, **PD**=Pharmacodynamic, **Q2W**=Every 2 weeks, **RF**=Rheumatoid factor

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