Observed and Simulated Pharmacokinetics and Pharmacodynamics of Nipocalimab, a Fully Human FcRn Blocking Monoclonal Antibody, in Adults with Sjögren's Disease: Results from a Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study

Sophia G. Liva,[1] Fudan Zheng,[1] Jocelyn H. Leu,[1] Kathy Sivils,[1] Keying Ma,[1] He Li,[1] Jacques-Eric Gottenberg,[2] Steven Leonardo,[3] Kim Hung Lo,[1] Jada Idokogi,[1] Kim Campbell,[1] Jonathan J. Hubbard[1]

[1]Johnson & Johnson, Spring House, PA, USA; [2]National Reference Center for Rare Systemic Autolmmune Diseases, Strasbourg-Hautepierre University Hospital, Strasbourg, France; [3]Johnson & Johnson, Cambridge, MA, USA

Background

Sjögren's disease (SjD) is a chronic, progressive autoimmune disease associated with substantial disease and symptom burden[1,2]

- SjD results from dysregulated immune responses and includes aberrant B-lymphocyte activity, abnormally elevated immunoglobulin G (IgG), and production of IgG, particularly anti-Ro, autoantibodies[3]
- Elevated anti-Ro autoantibodies are associated with more severe disease and an increased need for immunosuppressive therapies[4-9]

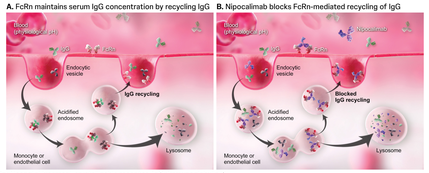
Nipocalimab, a fully human IgG1 monoclonal antibody, selectively binds with high affinity to the IgG binding site on the endogenous neonatal fragment crystallizable receptor (FcRn)[10,11]

- Through this mechanism, nipocalimab blocks IgG recycling, which results in an increase in clearance of IgG, including IgG autoantibodies (**Figure 1**)

Nipocalimab reduced IgG levels, including pathogenic antibodies, and demonstrated both safety and efficacy in several alloantibody- and autoantibody-mediated diseases, including hemolytic disease of the fetus and newborn[12] and generalized myasthenia gravis[13]

In the DAHLIAS study, nipocalimab demonstrated significantly greater improvement in clinical endpoints at Week 24 compared with placebo in participants with SjD[14]

Figure 1: Nipocalimab mechanism of action



FcRn=Neonatal fragment crystallizable receptor, IgG=Immunoglobulin G

Objectives

To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of nipocalimab in participants with SjD from the DAHLIAS study

Methods

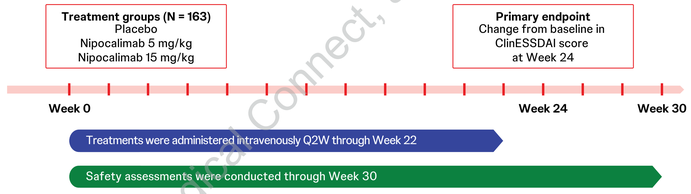
Study Design

- DAHLIAS was a phase 2, multicenter, randomized, placebo-controlled, double-blind study (ClinicalTrials.gov Identifier: NCT04968912) comparing the efficacy and safety of nipocalimab versus placebo in adult participants 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 antibodies
- Participants were randomized 1:1:1 to receive placebo, nipocalimab 5 mg/kg, or nipocalimab 15 mg/kg intravenously every 2 weeks through Week 22 (**Figure 2**)

Assessments

- Blood samples were collected from participants at Weeks 0, 2, 4, 8, 12, 16, 20, 24, and 30 to measure serum levels of nipocalimab, total IgG, and IgG autoantibodies (anti-Ro60, anti-La, and anti-Ro52) through Week 30
  - Both predose and postdose serum nipocalimab concentration samples were collected at Weeks 0, 2, 8, and 12. For all other visits, only a predose serum nipocalimab concentration sample was collected
- Population PK/PD (ie, PK-total IgG) modeling was performed using data from participants with SjD in the DAHLIAS study and healthy volunteers in four phase 1 studies
  - In total, 3667 nipocalimab concentrations, 1954 unoccupied receptors, and 4743 IgG concentration records from 366 participants were used for population PK/PD modeling
  - An indirect response model adequately described the observed total serum IgG turnover following placebo and nipocalimab doses
  - Maximal lowering of IgG autoantibodies was estimated based on the regression analysis linked to total IgG

Figure 2: Study design



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

Key Takeaways

- **Nipocalimab administration was associated with substantial reductions in both observed predose and simulated postdose total IgG and autoantibodies, including anti-Ro60, anti-La, and anti-Ro52 antibodies, with minimum IgG reductions observed at the nipocalimab nadir before each dose**
- **Total IgG and autoantibody levels returned to approximately baseline levels within 8 weeks of the last nipocalimab dose, demonstrating that nipocalimab-mediated IgG reduction is reversible upon discontinuation**
- **These results confirm nipocalimab's proposed mechanism of action and support the benefit of decreasing levels of pathogenic IgG via nipocalimab-mediated FcRn blockade as a potential new treatment for SjD**

Results

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

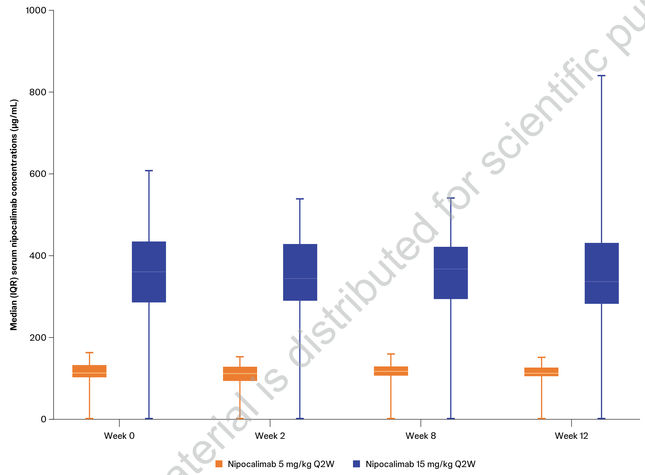
Table 1: Demographic and baseline characteristics

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 levels, g/L, median (range)	14.8 (7.7–40.5)	14.8 (4.6–35.2)	15.5 (7.6–49.6)
Autoantibody positivity, n	55	52	53
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

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

Median postdose serum nipocalimab concentrations for the nipocalimab 5 and 15 mg/kg groups ranged from 111.5 to 116.5 µg/mL and from 336.5 to 367.0 µg/mL, respectively, across Weeks 0 to 12 (Figure 3)

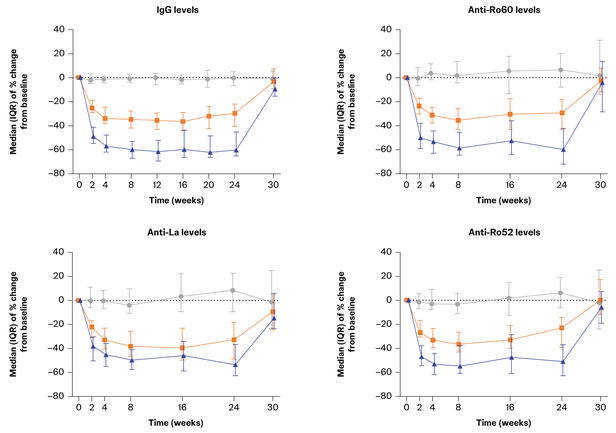
Figure 3: Median (IQR) postdose serum nipocalimab concentrations after intravenous administration[a]



[a]Data for postdose serum nipocalimab concentration were collected 45 minutes (±15 minutes) after the end of the infusion during Weeks 0, 2, 8, and 12.
IQR=Interquartile range, Q2W=Every 2 weeks

Dose-dependent reductions were observed in total IgG, anti-Ro60, anti-La, and anti-Ro52 IgG autoantibody levels across Weeks 2 to 24 of nipocalimab treatment. Total IgG and autoantibody levels returned to approximately baseline levels within 8 weeks of the final nipocalimab dose at Week 22

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



IgG=Immunoglobulin G, IQR=Interquartile range, Q2W=Every 2 weeks

PK/PD simulations indicated a median reduction in maximum total IgG at Week 24 of –64.9% and –78.2% in the nipocalimab 5 and 15 mg/kg groups, respectively. Nipocalimab administration was associated with substantial changes in observed predose (ie, minimum) reductions from baseline in total IgG and antibody levels across Weeks 2 to 24

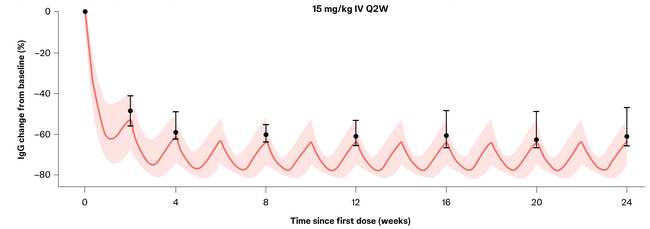
Table 2: Percent change from baseline in simulated (maximum) and observed predose (minimum) serum IgG levels at Week 24[a]

	Total IgG	Anti-Ro60 IgG	Anti-La IgG	Anti-Ro52 IgG
	Maximum percent change from baseline, median (90% PI)			
Nipocalimab 15 mg/kg	–78.2 (–81.3, –72.7)	–71.2 (–74.6, –66.5)	–59.0 (–61.6, –54.5)	–62.6 (–65.2, –58.0)
Nipocalimab 5 mg/kg	–64.9 (–72.7, –55.7)	–59.2 (–66.5, –50.6)	–48.0 (–54.5, –40.5)	–51.5 (–58.0, –43.9)
	Minimum percent change from baseline, median (Q1, Q3)			
Nipocalimab 15 mg/kg	–60.9 (–65.9, –45.7)	–60.1 (–72.3, –42.4)	–51.9 (–60.4, –21.4)	–44.3 (–59.5, 0)
Nipocalimab 5 mg/kg	–30.0 (–41.0, –22.2)	–28.5 (–43.4, –16.9)	–32.5 (–49.0, 0)	–22.1 (–38.7, –10.0)
Placebo	–0.5 (–6.8, 5.0)	6.3 (–6.8, 19.6)	1.0 (–3.3, 21.2)	4.8 (–5.1, 17.1)

[a]Includes patients with ≥1 valid postdose blood sample drawn for PD analysis.
IgG=Immunoglobulin G, PD=Pharmacodynamic, PI=Prediction interval, Q=Quartile

Figure 5 shows the overlap of simulated IgG lowering over time with observed IgG

Figure 5: Simulated IgG lowering and 90% PI over time, with observed IgG (median [IQR])



Solid line and shaded area represent median IgG lowering and 90% PI, respectively. Circles and error bars represent the median (IQR) of predose minimum IgG change from baseline levels.
IgG=Immunoglobulin G, IQR=Interquartile range, IV=Intravenous, PI=Prediction interval, Q2W=Every 2 weeks

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