Biomarker-Driven Insights to Clinical Response With Nipocalimab: A Phase 2 Randomized Trial for Sjögren's Disease

Hal Scofield,[1-3*] He Li,[4] Jacques-Eric Gottenberg,[5] David Galbraith,[4] Keying Ma,[4] Lynn Tomsho,[4] Chris Sisk,[4] Matthew J. Loza,[4] Jonathan J. Hubbard,[4] Kim Campbell,[4] Dawn Waterworth,[4] Sheng Gao,[4] Carolyn Cuff,[6] Steven Leonardo,[6] Kathy Sivils[4]

[1]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; [2]Department of Veterans Affairs Medical Center, Oklahoma City, OK, USA; [3]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [4]Johnson & Johnson, Spring House, PA, USA; [5]Strasbourg University Hospital, Strasbourg, France; [6]Johnson & Johnson, Cambridge, MA, USA

*Presenting author

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Key Takeaways

- **In DAHLIAS, nipocalimab 15 mg/kg IV Q2W reduced ClinESSDAI score and total IgG significantly in participants with SjD, with a safety profile consistent with other phase 2 studies[8–10]**
- **Biomarker analyses reinforce the mechanistic rationale for treatment with nipocalimab in SjD, with enriched response observed among participants with elevated aAbs, IFN, and IgG levels**
- **This supports the continued development of nipocalimab in SjD in the ongoing phase 3 DAFFODIL study (NCT06741969)**

Background

Sjögren's Disease (SjD) is characterized by presence of autoantibody (aAb), lymphocytic infiltration of exocrine glandular tissues, immune complex formation and interferon (IFN) production[1]

Systemic immune dysregulation involves aberrant B-lymphocyte activity and abnormally elevated immunoglobulin G (IgG) and IgG aAb levels (eg, anti-Ro, anti-La)[1]

SjD is associated with a relentless multi-organ burden, with ≥1 organ involvement in approximately 40% to 75% of patients, commonly manifested by mucosal dryness, fatigue, and pain, and an approximately 1.5-fold increase in all-cause mortality[2–7]

Objective

To evaluate whether nipocalimab's mechanism of action (MOA) and SjD pathology impact response to nipocalimab in participants with SjD in the phase 2 DAHLIAS study, using biomarker stratification approaches

Methods

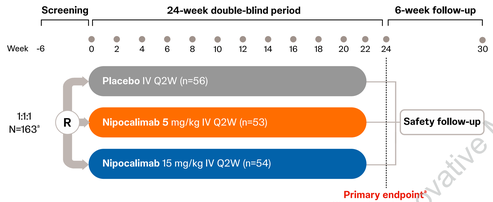
Study population
- Adults aged 18–75 years
- Moderately to severely active primary SjD (total ClinESSDAI score ≥6)
- Seropositive for anti-Ro60 and/or anti-Ro52 IgG antibodies

Primary endpoint[a]
- Change from baseline in ClinESSDAI score at Week 24

Key secondary endpoints
- ClinESSDAI-4 response[b] at Week 24

Post-hoc analyses in biomarker-based populations
- ClinESSDAI-4 response[b] at Week 24

DAHLIAS Study Design



*The DAHLIAS study was pre-specified to use a 2-sided alpha level of 0.1 without multiplicity control. [a]Defined as improvement of ≥4 points from baseline in ClinESSDAI score. **ClinESSDAI**=Clinical European Alliance of Associations for Rheumatology Sjögren's Syndrome Disease Activity Index, **IgG**=immunoglobulin G, **IV**=intravenous, **Q2W**=every 2 weeks, **R**=randomized, **SjD**=Sjögren's disease.

Participant Stratification

DAHLIAS participants were stratified using 3 approaches based on nipocalimab's MOA and SjD pathology to test their impacts on response to nipocalimab:

Baseline aAbs
Serum baseline levels of anti-Ro60, anti-Ro52, and anti-La aAbs:
- **aAb-high:** all 3 aAb levels in the top tertile

Baseline IFN scores
IFN gene signature scores derived from whole-blood RNA sequencing:
- **IFN-high:** scores >75th percentile + 1.5 × IQR of healthy controls

Baseline IgG
Total serum IgG levels at baseline:
- **IgG-high:** IgG >25% quartile of overall study population

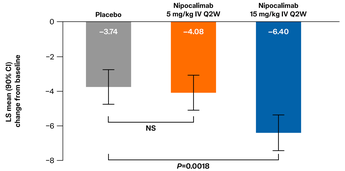
aAb=autoantibody, **IFN**=interferon, **IgG**=immunoglobulin G, **IQR**=interquartile range, **MOA**=mechanism of action, **SjD**=Sjögren's disease.

Results

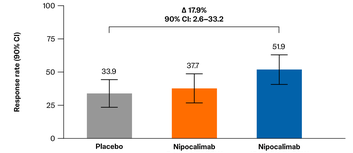
DAHLIAS primary results: Efficacy and safety

- **Safety:** Nipocalimab was well tolerated in participants with SjD, with no new safety signals observed

Primary endpoint:
Change from baseline in ClinESSDAI score at Week 24



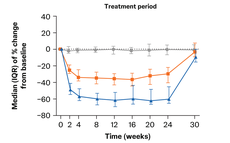
Secondary endpoint:
ClinESSDAI-4 response at Week 24



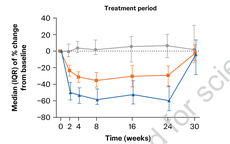
CI=confidence interval, **ClinESSDAI**=Clinical European Alliance of Associations for Rheumatology Sjögren's Syndrome Disease Activity Index, **IV**=intravenous, **LS**=least squares, **NS**=nonsignificant, **Q2W**=every 2 weeks, **SjD**=Sjögren's disease.

DAHLIAS primary results: Biomarkers

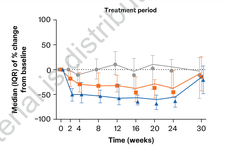
Total IgG reduction
- Observed predose (minimum) median IgG reduction of 61% at Week 24
- 77% maximum reduction in total IgG (pharmacokinetic/pharmacodynamic [PK/PD] simulations)



Anti-Ro60 IgG reduction
- Observed consistent reductions in SjD-associated anti-Ro60, anti-Ro52, and anti-La IgG aAbs during treatment



Circulating IgG immune complexes (CIC)
- Observed reductions in CICs during treatment

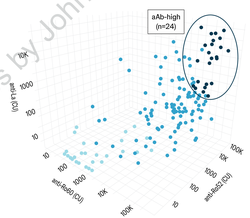


aAb=autoantibody, **IgG**=immunoglobulin G, **IQR**=interquartile range, **IV**=intravenous, **Q2W**=every 2 weeks.

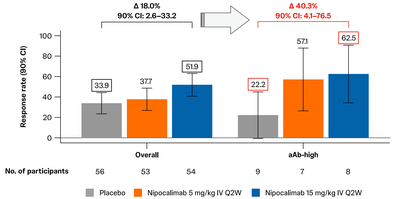
High baseline aAb level enriches responders to nipocalimab

- Enriched nipocalimab response in aAb-high population (15% of DAHLIAS participants)

Baseline aAb levels



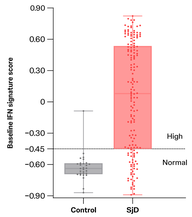
ClinESSDAI-4 responses at Week 24 in aAb-high participants



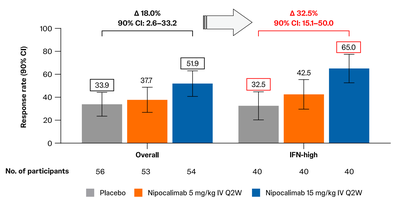
aAb=autoantibody, **CI**=confidence interval, **ClinESSDAI**=Clinical European Alliance of Associations for Rheumatology Sjögren's Syndrome Disease Activity Index, **CU**=chemiluminescent unit, **IV**=intravenous, **Q2W**=every 2 weeks.

High baseline IFN score enriches responders to nipocalimab

- Enriched nipocalimab response in IFN-high population (74% of DAHLIAS participants)



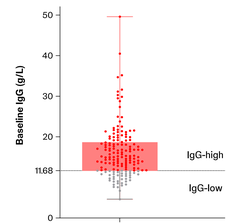
ClinESSDAI-4 responses at Week 24 in IFN-high participants



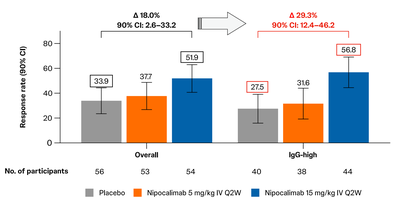
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High baseline IgG level enriches responders to nipocalimab

- Enriched nipocalimab response in IgG-high population (75% of DAHLIAS participants)



ClinESSDAI-4 responses at Week 24 in IgG-high participants



CI=confidence interval, **ClinESSDAI**=Clinical European Alliance of Associations for Rheumatology Sjögren's Syndrome Disease Activity Index, **IgG**=immunoglobulin G, **IV**=intravenous, **Q2W**=every 2 weeks.

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