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Efficacy and Safety of Nipocalimab, an Anti-FcRn Monoclonal Antibody, in Primary Sjogren's Disease: Results from a Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study (DAHLIAS)

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SESSION INFORMATION

Date: Monday, November 18, 2024

Session Type: Plenary Session

Title: Plenary III

Session Time: 9:00AM-10:30AM

Background/Purpose: Sjögren's disease (SjD) is a chronic, systemic autoimmune disease characterized by the presence of specific autoantibodies (AAb) and lymphocytic infiltration of exocrine glandular tissues. Nipocalimab, an anti-neonatal Fc receptor (FcRn) mAb, reduces circulating IgG including AAb, by selectively blocking IgG–FcRn interactions. Here, we evaluated the efficacy and safety of nipocalimab in patients (pts) with primary SjD.

Methods: A phase 2 study (DAHLIAS; NCT04968912) included adults (18-75 years) with moderately-to-severely active primary SjD (total Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index [clinESSDAI] ≥6) who were seropositive for anti-Ro60/-Ro52 IgG antibodies. Randomized pts (1:1:1) received intravenous (IV) nipocalimab 5 or 15 mg/kg, or placebo (PBO) every 2 weeks (W) through W22 and protocol-permitted background standard of care. The primary endpoint of change from baseline (BL) in clinESSDAI score at W24 was chosen to avoid mechanistic bias with IgG levels. Safety was assessed through W30.

Results: In total, 163 pts were enrolled (nipocalimab: 5 mg/kg, n=53; 15 mg/kg, n=54; PBO, n=56). BL characteristics were comparable between groups. The nipocalimab 15 mg/kg group met the primary endpoint versus (vs) PBO (least squares mean difference for 15 mg/kg: –2.65; 90% CI, –4.03, –1.28; p=0.002; for 5 mg/kg: –0.34; 90% CI, –1.71, 1.03; p=0.681; **Table 1**). Similar improvements in the 15 mg/kg nipocalimab group vs PBO were observed in most secondary/exploratory endpoints (**Table 1**), including changes from BL at W24 in Physician Global Assessment of Disease Severity and ESSDAI score, treatment response according to Sjögren's Tool for Assessing Response, Composite of

Relevant Endpoints for Sjogren's Syndrome, and disease activity level response (decrease in ≥1 clinESSDAI domain), among others. Pt-reported outcome measures numerically improved in the 15 mg/kg nipocalimab group vs PBO. Efficacy outcomes in the 5 mg/kg nipocalimab group were generally similar to PBO. Serious adverse events were reported in 7.5%, 7.4%, and 5.4% of participants with nipocalimab 5 mg/kg, 15 mg/kg, and PBO, respectively (**Table 2**). Significant nipocalimab dose-dependent reductions in IgG and AAb were observed. Severe infections/infections requiring IV anti-infectives occurred in 3.8%, 1.9%, and 1.8% of patients, respectively, without a clear correlation with IgG nadir; none were related to study treatment. At W24, changes from BL in albumin, low-density lipoprotein cholesterol, and total cholesterol were reported at –6.9%, 6.6%, and 8.3%, respectively. No opportunistic infections/severe hypoalbuminemia/deaths were reported.

Conclusion: DAHLIAS, the first study of a FcRn blocker in SjD, showed that nipocalimab led to significant improvement vs PBO in clinESSDAI and similar trends in other key efficacy endpoints at W24, and is well-tolerated. These results demonstrate the mechanistic relevance of FcRn inhibition in SjD, indicating the potential pathogenicity of IgG AAb. These findings establish proof of concept for nipocalimab in SjD and support further evaluation in pts with moderate-to-severe AAb-positive SjD.

Endpoint	PBO (n=56)	Nipocalimab 5 mg/kg (n=53)	Nipocalimab 15 mg/kg (n=54)
Primary endpoint:			
Change from baseline in clinESSDAI score, LS Mean (90% CI)	–3.74 (–4.74, –2.75)	–4.08 (–5.10, –3.07)	–6.40 (–7.43, –5.36)
LS Mean difference (90% CI)[a]		–0.34 (–1.71, 1.03)	–2.65 (–4.03, –1.28)
P value[a]		0.681	0.002
Secondary and exploratory endpoint:			
Change from baseline in PhGA score, LS Mean (90% CI)	–24.26 (–28.91, –19.61)	–26.51 (–31.27, –21.76)	–38.76 (–43.62, –33.91)
LS Mean difference (90% CI)[a]		–2.26 (–8.50, 3.99)	–14.50 (–20.81, –8.19)
Change from baseline in ESSDAI score, LS Mean (90% CI)	–2.82 (–3.67, –1.98)	–3.34 (–4.20, –2.48)	–4.61 (–5.49, –3.73)
LS Mean difference (90% CI)[a]		–0.52 (–1.67, 0.63)	–1.79 (–2.94, –0.63)
Participants who achieved ESSDAI-3 response, n (%)	19 (33.9%)	23 (43.4%)	27 (50.0%)
Difference in proportion, (90% CI)[b]		9.5% (–5.8%, 24.8%)	16.1% (0.8%, 31.4%)
Change from baseline in ESSPRI score, LS Mean (90% CI)	–1.91 (–2.36, –1.46)	–1.29 (–1.75, –0.83)	–2.32 (–2.79, –1.85)
LS Mean difference (90% CI)[a]		0.62 (0.01, 1.23)	–0.41 (–1.03, 0.20)
Participants who achieved STAR response, n (%)	22 (39.3%)	27 (50.9%)	34 (63.0%)
Difference in proportion, (90% CI)[b]		11.7% (–3.9%, 27.2%)	23.7% (8.4%, 38.9%)
Participants who achieved CRESS response, n (%)	10 (17.9%)	23 (43.4%)	26 (48.1%)
Difference in proportion, (90% CI)[b]		25.5% (11.5%, 39.5%)	30.3% (16.3%, 44.3%)
Participants who achieved DAL response[c], n (%)	19 (33.9%)	28 (52.8%)	29 (53.7%)
Difference in proportion, (90% CI)[b]		18.9% (3.6%, 34.2%)	19.8% (4.5%, 35.0%)

[a]Compared with PBO group using a Mixed Effects Repeated Measures model with baseline score, study treatment, visit, region, baseline steroid use, baseline anti-malarial use, and an interaction of treatment and visit as terms in the model. For continuous endpoints, participants that experienced an intercurrent event per protocol were considered to have missing data thereafter.
[b]Compared with PBO group using a Cochran-Mantel-Haenszel test with region, baseline steroid use, and baseline anti-malarial use as stratification factors. For binary composite endpoints, participants that experienced intercurrent events were considered non-responders after the event.
[c]DAL response is a reduction from baseline in disease activity level by at least 1 level in at least 1 clinESSDAI domain (eg, articular, hematological, cutaneous, constitutional, etc).
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; ESSPRI, European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; LS, least square; PBO, placebo; PhGA, Physician Global Assessment of Disease Severity; STAR, Sjögren's Tool for Assessing Response.

Table 1. Primary Endpoint, Key Supportive and Secondary Endpoints at Week 24

Participants with ≥1 AE, n (%)	PBO (n=56)	Nipocalimab 5 mg/kg (n=53)	Nipocalimab 15 mg/kg (n=54)	Combined nipocalimab (n=107)

AEs	35 (62.5)	42 (79.2)	43 (79.6)	85 (79.4)
Related AEs[a]	12 (21.4)	21 (39.6)	18 (33.3)	39 (36.4)
Related non-serious AEs[a]	12 (21.4)	21 (39.6)	18 (33.3)	39 (36.4)
AEs leading to death[a,b]	0	0	0	0
Serious AEs	3 (5.4)	4 (7.5)	4 (7.4)	8 (7.5)
Related serious AEs[a]	0	1 (1.9)	0	1 (0.9)
AEs leading to discontinuation of study agent	2 (3.6)	3 (5.7)	3 (5.6)	6 (5.6)
Related AEs leading to discontinuation of study agent[a]	0	2 (3.8)	1 (1.9)	3 (2.8)
Infections that are severe or require IV anti-infective or operative/invasive intervention[c]	1 (1.8)	2 (3.8)	1 (1.9)	3 (2.8)
New onset hypoalbuminaemia with albumin <20 g/L	0	0	0	0
Infusion reactions[d]	2 (3.6)	6 (11.3)	1 (1.9)	7 (6.5)
Infusion site reactions[c]	0	0	0	0
Opportunistic infections	0	0	0	0
Hypersensitivity reactions	3 (5.4)	6 (11.3)	7 (13.0)	13 (12.1)
Anaphylactic reactions or serum sickness	0	1 (1.9)	0	1 (0.9)
MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke)	2 (3.6)	0	0	0
Activation of latent virus	1 (1.8)	3 (5.7)	3 (5.6)	6 (5.6)
COVID-19 associated AEs	3 (5.4)	9 (17.0)	3 (5.6)	12 (11.2)
COVID-19 associated serious AEs	0	1 (1.9)	0	1 (0.9)

[a]An AE is assessed by the investigator as related to study agent.
[b]AEs leading to death are based on AE outcome of fatal.
[c]As assessed by the investigator.
[d]Temporally associated with infusion (during or within 1 hour after infusion).
AE, adverse event; IV, intravenous; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo.

Table 2. Number of Participants With Treatment-Emergent Adverse Events

Disclosures: J. Gottenberg: AbbVie, 2, BMS, 2, 5, Galapagos, 2, Gilead, 2, Lilly, 2, MSD, 2, Novartis, 2, Pfizer, 2, 5; **K. Sivils**: Janssen Research & Development, LLC, 3, Johnson & Johnson, 11; **K. Campbell**: Janssen Research & Development, LLC, 3, Johnson & Johnson, 11; **J. Idokogi**: Janssen Research & Development, LLC, 3, Johnson & Johnson, 11; **K. Lo**: Janssen Research & Development, LLC, 3, Johnson & Johnson, 11; **S. Liva**: Janssen Research & Development, LLC, 3, Johnson and Johnson, 11; **J. Shelton**: Janssen, 3, Johnson & Johnson, 11; **H. Dhatt**: Janssen, 3, Johnson & Johnson, 11; **J. Hubbard**: Janssen Research & Development, LLC, 3, Johnson & Johnson, 11; **G. Noaiseh**: Janssen, 1, Novartis, 1.

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