

Improvement in Executive Function Following Nipocalimab Treatment in Patients With Sjögren’s Disease: A Randomized Clinical Trial

Stefan Avey,¹ Michael Deman,² Kim Campbell,¹ Nikolay V Manyakov,² He Li,¹ Kathy Sivils,¹ Steven Leonardo,¹ Keying Ma,¹ Harman Dhatt,³ Paul Maruff,⁴ Jonathan J Hubbard,¹ Wan-Fai Ng^{5,*}

¹Johnson & Johnson, Spring House, PA, USA; ²Johnson & Johnson, Beerse, Belgium; ³Johnson & Johnson, Raritan, NJ, USA; ⁴Cogstate Ltd., Melbourne, Australia; ⁵Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

*Presenting author.

Background

- Sjögren’s disease (SjD) is a chronic, systemic, immunoglobulin G (IgG) autoantibody-mediated disease with growing evidence of cognitive function difficulties (eg, “brain fog” is a common patient-reported symptom), in addition to the commonly studied symptoms of mucosal dryness, fatigue, and chronic pain¹⁻⁴
 - While patients frequently report difficulties with attention, memory, and problem solving, the pathophysiology of these symptoms is not well understood
- Exploration of novel treatment effects using objective neuropsychological tests provides an opportunity to better understand the pathophysiology of the cognitive difficulties associated with SjD
- Nipocalimab is a fully human monoclonal antibody that binds the neonatal Fc receptor (FcRn) with high specificity and affinity to block the IgG-recycling pathway,⁵ thus lowering total IgG (including pathogenic IgG autoantibodies) without impacting other key humoral and cellular immune functions⁵⁻⁸
- In the phase 2, randomized, placebo-controlled, multicenter, double-blind DAHLIAS study of nipocalimab in adults with active, autoantibody-positive SjD, nipocalimab 15 mg/kg significantly improved clinical disease activity, reduced IgG levels, and was generally safe and well tolerated⁷

Objective

To evaluate the efficacy of nipocalimab treatment in participants with SjD on 3 aspects of cognitive function (ie, executive function): cognitive processing speed, psychomotor function, and visual attention

Methods

DAHLIAS Study Design⁷

- Eligible participants were 18 to 75 years of age; fulfilled the American College of Rheumatology (ACR) and The European Alliance of Associations for Rheumatology (EULAR) 2016 classification criteria; had moderate-to-severe, active SjD (Clinical EULAR Sjögren’s Syndrome Disease Activity Index [ClinESSDAI] score ≥6); and were seropositive for anti-Ro60 and/or anti-Ro52 IgG autoantibodies
- Participants were randomized 1:1:1 to receive intravenous (IV) infusions of either placebo, nipocalimab 5 mg/kg, or nipocalimab 15 mg/kg every 2 weeks (Q2W) through Week 22, with efficacy evaluated through Week 24

Assessments

- Participants performed digital cognitive assessments during screening and Q2W during the study
 - Participants completed 2 patient-reported outcome instruments, the Hospital Anxiety and Depression Scale (HADS), used to assess anxiety and depression, and the Short Form-36 (SF-36), used to assess health-related quality of life, during screening and every 4 weeks during the study, as depression and pain may impact cognitive performance^{9,10}
- The fatigue item of the Sjögren’s Symptoms questionnaire, a novel measure, was completed at baseline and every 4 weeks during the study to evaluate the severity of fatigue (higher scores indicate greater severity)⁷
- The cognitive testing battery included:
 - The International Digital Symbol Substitution Test – Symbols (DSST; CogState Ltd., Melbourne, Australia) measures cognitive processing speed based on the digit symbol coding paradigm, with a primary outcome measure of total number of correct responses in 120 seconds
 - Participants were presented with a legend of 9 symbols that correspond to a digit and selected the corresponding symbols for a series of numbers presented in the middle of the screen
 - The Detection Test (DET; CogState Ltd., Melbourne, Australia) measures psychomotor function using a simple reaction-time paradigm, with a primary outcome measure of reaction time (log₁₀-transformed milliseconds)
 - For each trial, participants were presented with an on-screen question (“Has the card turned over?”) and a facedown playing card and were instructed to work quickly and accurately to tap a “Yes” button when the card flipped
 - The Identification Test (IDN; CogState Ltd., Melbourne, Australia) measures visual attention using a choice reaction-time paradigm, with a primary outcome measure of reaction time (log₁₀-transformed milliseconds)
 - For each trial, participants were presented with an on-screen question (“Is the card red?”) and a facedown playing card and were instructed to work quickly and accurately to tap either “Yes” or “No” when the card flipped

Cognitive Assessment Scoring Rules

- Factors independent of cognition (eg, misunderstanding the rules and technical device errors) can introduce artifacts that do not reflect cognitive performance¹¹
- Therefore, prespecified completion and performance pass criteria were applied to the primary outcomes:
 - DSST: complete if the test interval was 120 seconds, with <11 rule break errors (eg, tapping on an incorrect area of the screen)
 - DET: complete if the number of responses was ≥27 with >75% correct responses
 - IDN: complete if the number of responses was ≥23 with >75% correct responses
- Test outcomes failing either criteria were excluded from analysis

Statistical Analysis

- Baseline performance z scoring was computed based on a cognitively unimpaired age- and sex-matched normative population using mean and standard deviation (SD) within each normative group to standardize the study data into a z score
- Change from baseline in each score was analyzed using a mixed model repeated measure (MMRM), with the baseline (Week 0) value as a covariate. Other fixed terms included were intervention group, time (study week, categorical), and time-by-intervention group
- Within-subject covariance between study weeks was estimated via an unstructured variance-covariance matrix
- Difference between active and placebo arms was reported in terms of the least squares mean change over time from baseline with 90% confidence intervals (CIs)
- MMRM interpretation used a 2-sided significance level of α = 0.10. No multiplicity adjustment was made because cognitive changes were an exploratory study end point; nominal P values are reported
- Repeated measures correlation was performed in all cases where repeated measurements within study participants were available using R package rmcrr¹²
- When adjusting for depressive symptoms and physical health, baseline and change from baseline to Week 24 in SF-36 physical component summary (PCS) and HADS–Depression subscale (HADS-D) were included as additional covariates
- In IgG subgroup analyses, participants with total serum IgG levels above the first quartile at baseline were classified as IgG-high and others were classified as IgG-low

Results

Demographic and Clinical Characteristics

- A total of 163 participants were randomized in the DAHLIAS study and 161 participants completed ≥1 cognitive assessment, 149 of whom completed ≥1 cognitive assessment at baseline (Week 0)
- Baseline demographic and clinical characteristics were well balanced across treatment arms (Table 1)

TABLE 1: Baseline demographic and clinical characteristics⁷

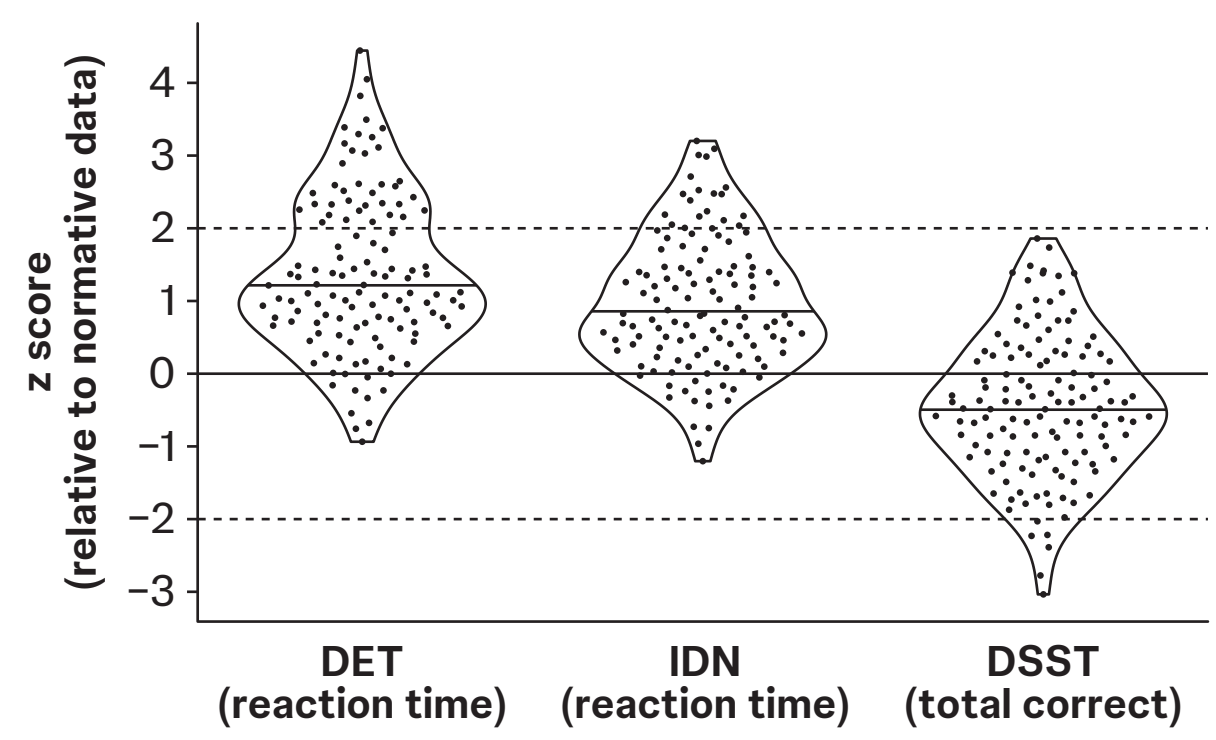
	Placebo (n = 56)	Nipocalimab 5 mg/kg Q2W (n = 53)	Nipocalimab 15 mg/kg Q2W (n = 54)	All participants (N = 163)
Age in years, median (range)	46.5 (23-73)	49.0 (20-72)	48.5 (24-72)	48.0 (20-73)
Female, %	92.9	92.5	92.6	92.6
White, %	89.3	92.5	90.7	90.8
Time since diagnosis in years, median (range)	4.0 (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 in 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, [†] %				
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

*Measured at a central laboratory. Reference range: 6.03 to 16.13 g/L.
†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.
ClinESSDAI=Clinical EULAR Sjögren’s Syndrome Disease Activity Index. EULAR=European Alliance of Associations for Rheumatology. ESSPRI=EULAR Sjögren’s Syndrome Patient Reported Index. IgG=immunoglobulin G. Q2W=every 2 weeks. RF=rheumatoid factor. SD=standard deviation.

Baseline Cognitive Performance

- At baseline, cognitive performance was compared with a cognitively unimpaired age- and sex-matched reference population
- Participants with SjD tended to have slower reaction times (median, ~1 SD slower) for the DET and IDN tests and fewer correct responses (median, ~0.5 SD fewer) on the DSST than the reference population (Figure 1)

FIGURE 1: Baseline cognitive performance

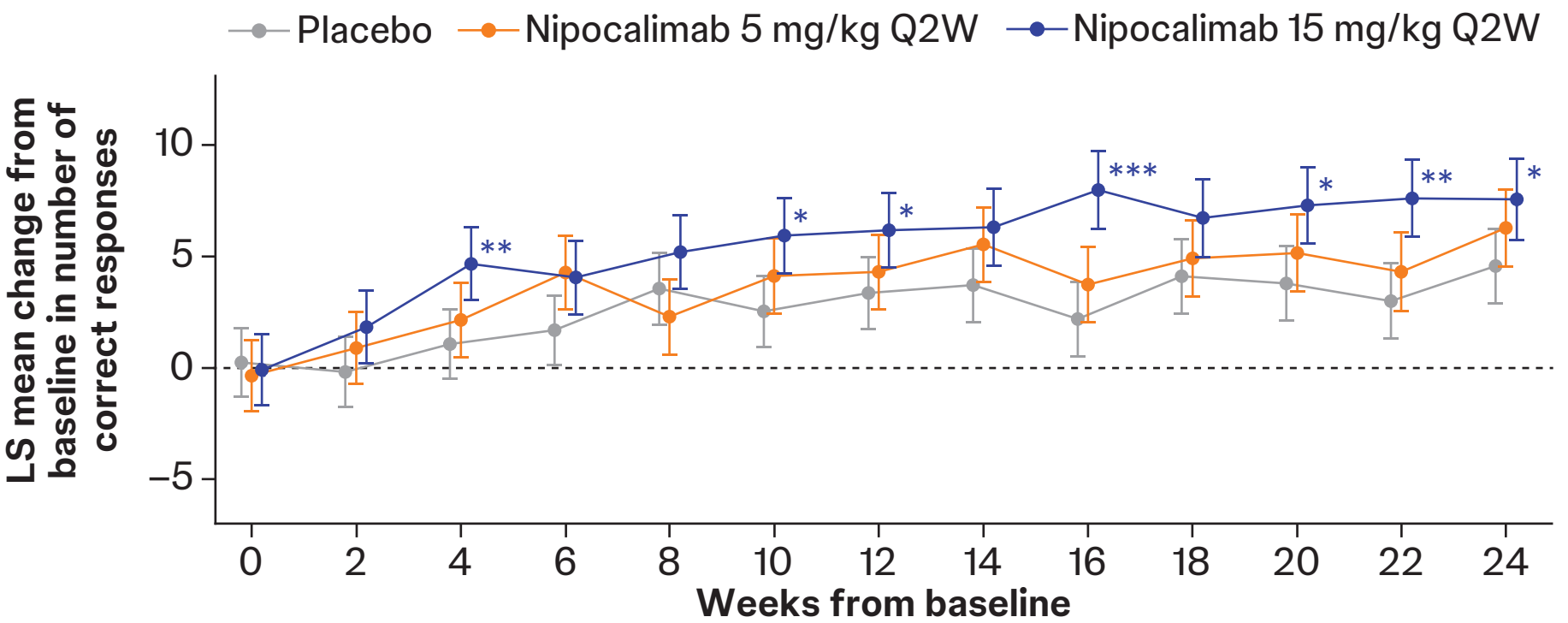


17 participants not shown; normative data unavailable for their age range. Estimates of minimum meaningful change thresholds (0.5 SD) for DET, IDN, and DSST are 0.035 log₁₀ milliseconds, 0.025 log₁₀ milliseconds, and 5 total correct scores, respectively.
DET=Detection Test. DSST=International Digital Symbol Substitution Test – Symbols. IDN=Identification Test. SD=standard deviation.

Change From Baseline in Cognitive Test Scores Over Time by Treatment Group

- A statistically significant improvement in the number of correct responses on the DSST was observed in the nipocalimab 15 mg/kg group (+7.56 [90% CI, 5.76, 9.37]) versus placebo (+4.57 [2.90, 6.24]) at Week 24 (Δ = 3.0, d = 0.26; P = 0.046; Figure 2)
- This effect remained after adjustment for baseline and change from baseline in depressive symptoms (measured by the HADS-D) and physical health (measured by the SF-36 PCS) (Δ = 3.5, d = 0.31; P = 0.018)
- No significant treatment effect was observed for DET (d = −0.15; P = 0.34) or IDN (d = −0.11; P = 0.49) at Week 24 (not adjusted for HADS-D or SF-36 PCS scores)

FIGURE 2: Change from baseline in DSST performance

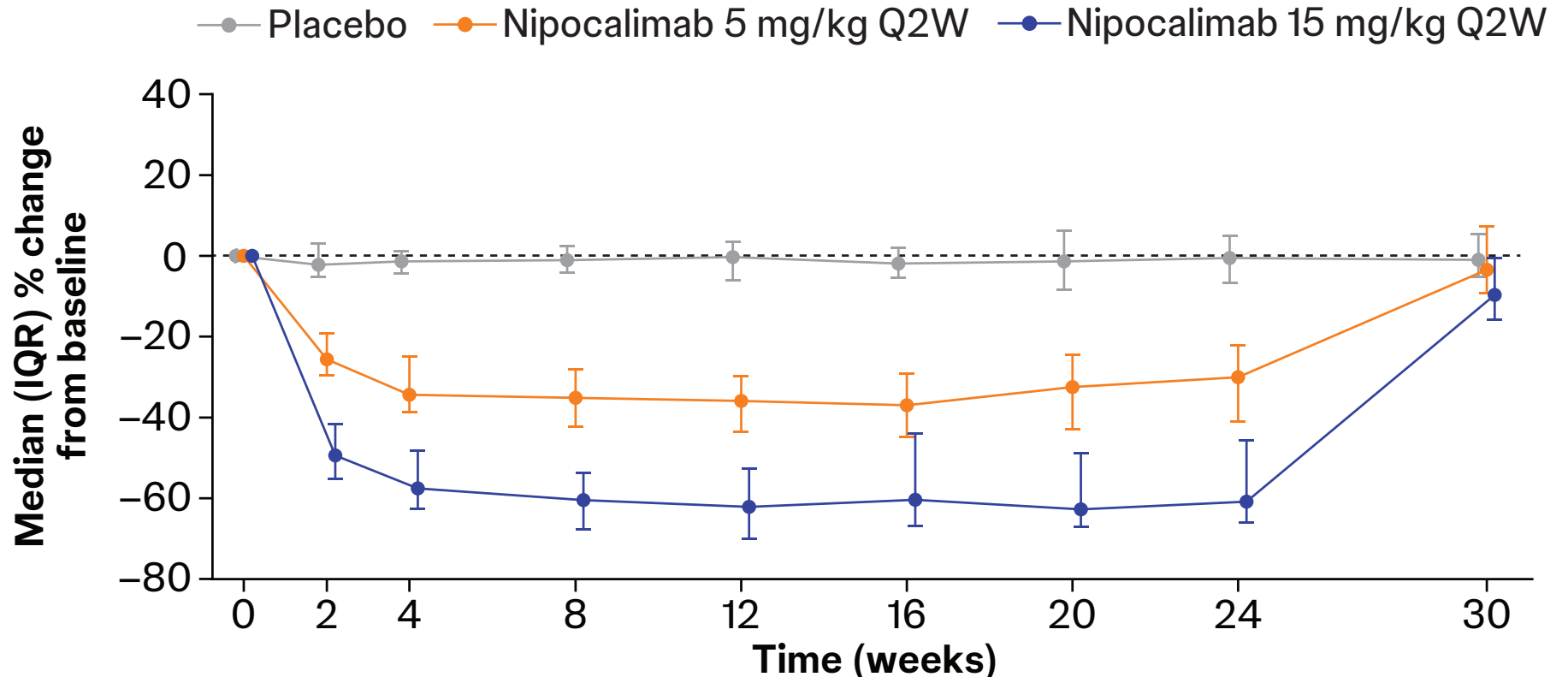


Points represent LS mean change from baseline in the number of correct responses on the DSST, and error bars represent the 90% CI. Sample size is indicated per treatment group at each time point. Asterisks represent nominally significant P values for the interaction term (Week × Treatment Group) comparing each treatment group to placebo (**P < 0.01; *P < 0.05).
CI=confidence interval. DSST=International Digital Symbol Substitution Test – Symbols. LS=least squares. Q2W=every 2 weeks.

Effects of Nipocalimab on Total IgG and Correlation With DSST Score

- Dose-dependent reductions in total IgG were observed from Weeks 2 to 24 of nipocalimab treatment (Figure 3)
- Nipocalimab treatment also coincided with reductions in baseline anti-Ro60, anti-La, and anti-Ro52 IgG autoantibody levels (data not shown)

FIGURE 3: Percent change from baseline total IgG (pre-dose, median [IQR])⁷



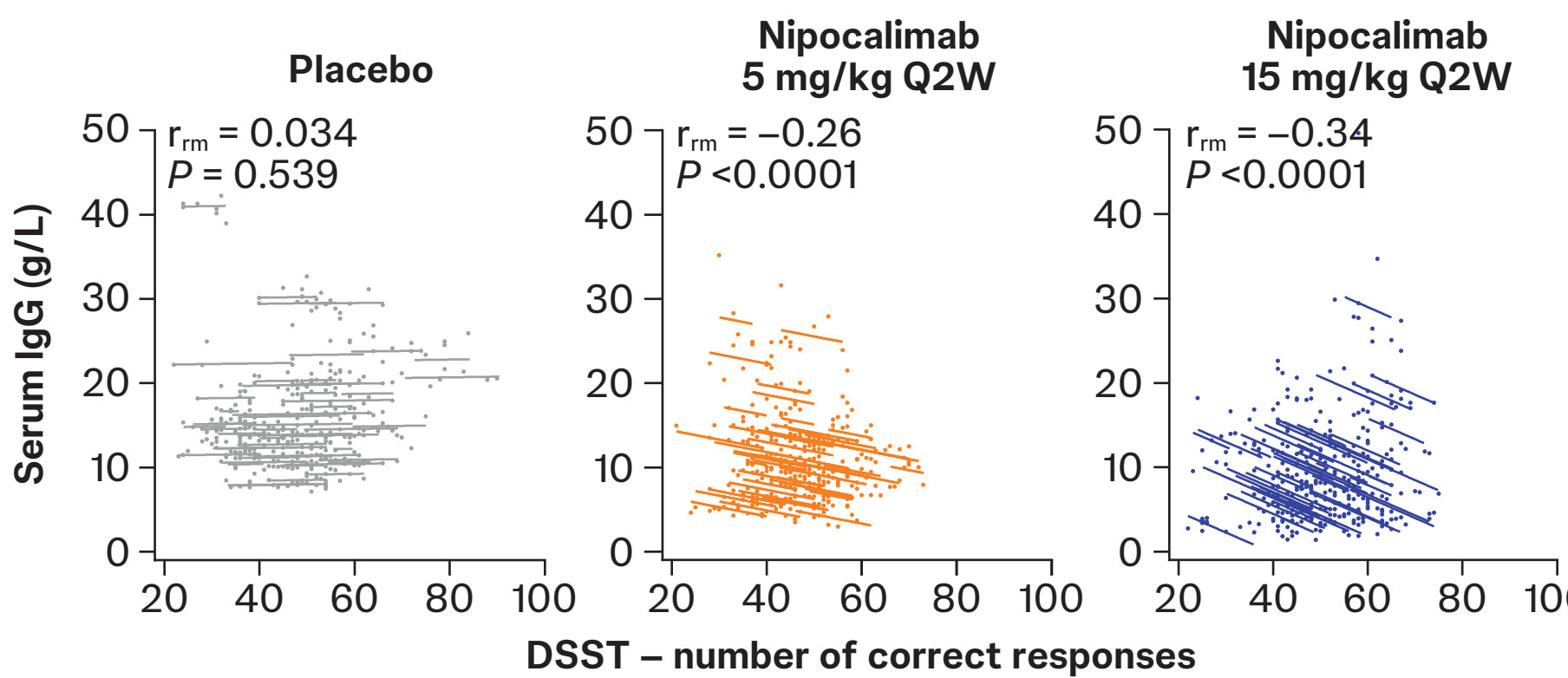
IgG=immunoglobulin G. IQR=interquartile range. Q2W=every 2 weeks.

Key Takeaways

- In participants with SjD, nipocalimab treatment resulted in dose-dependent improvements in cognitive processing speed through Week 24, as measured by the International Digital Symbol Substitution Test, an effect that could not be explained by changes in depressive symptoms, overall physical health, or changes in attention (measured by the Detection Test) or psychomotor function (measured by the Identification Test)
- Improvements in cognitive processing speed correlated with decreases in IgG levels, which suggests that nipocalimab’s mechanism of action is associated with cognitive processing speed improvements
- Baseline IgG levels predict improvements in cognitive processing speed, which suggests a potential pathophysiologic link between IgG level and executive function
- Taken together, these findings support further investigation of the potential cognitive benefits of nipocalimab treatment in patients with moderate-to-severe SjD

- At the participant level, the number of correct responses in the nipocalimab 15 mg/kg group was negatively correlated with total serum IgG concentration ($r_{\text{rm}} = -0.34$; $P < 0.0001$) through Week 24 (Figure 4)
- Change from baseline in DSST score was negatively correlated with patient-reported worst fatigue severity ($r_{\text{rm}} = -0.26$; $P < 0.0001$; data not shown)

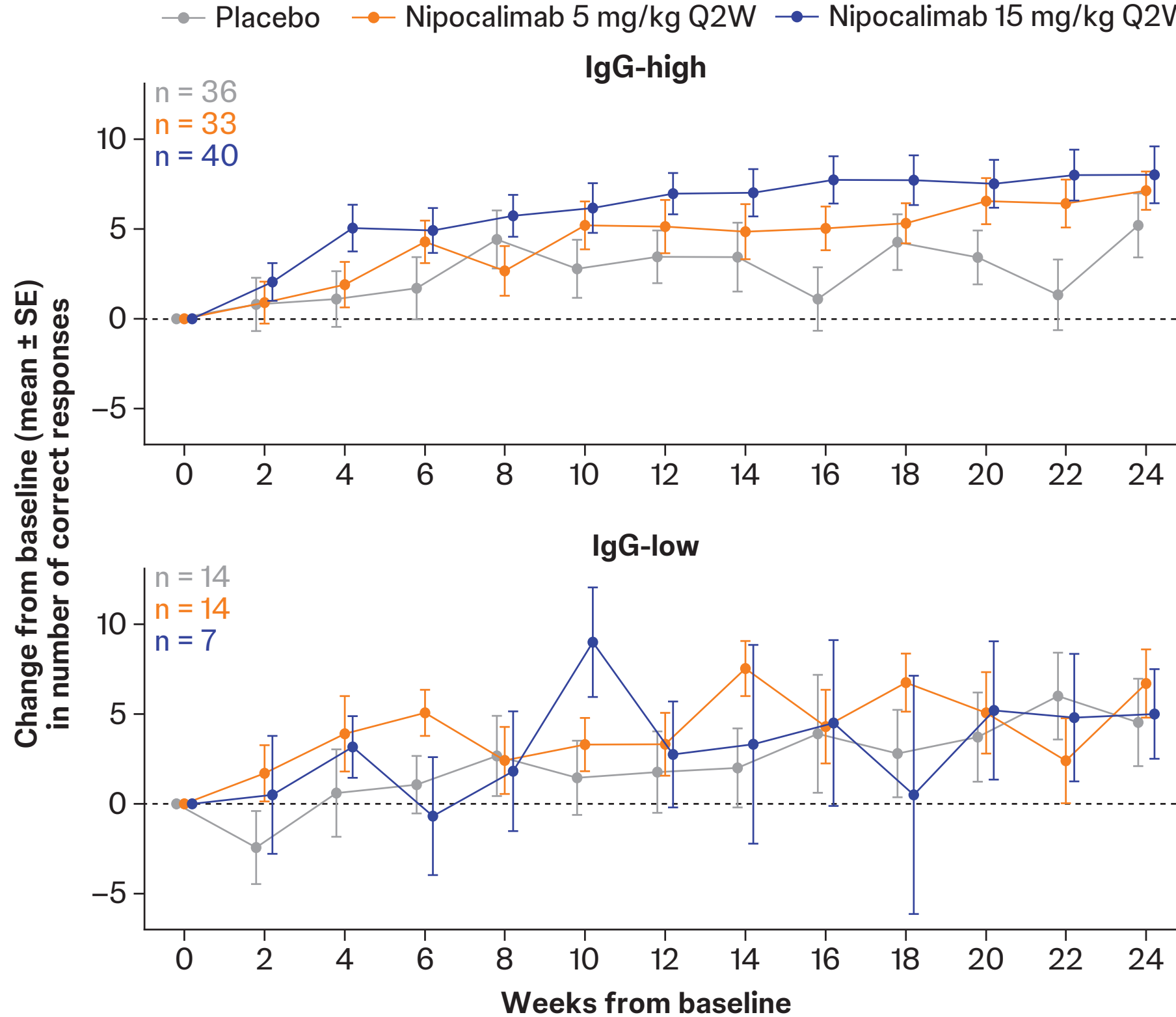
FIGURE 4: Correlation of DSST with total IgG through Week 24



DSST=International Digital Symbol Substitution Test – Symbols. IgG=immunoglobulin G. Q2W=every 2 weeks.

- When stratifying by baseline total IgG level, a dose-dependent improvement in the number of correct DSST responses was observed with nipocalimab versus placebo in the IgG-high subgroup; in contrast, no consistent treatment group differences were observed in the IgG-low subgroup (Figure 5)

FIGURE 5: Baseline IgG levels enriched for DSST improvement



Sample size is indicated per treatment group at baseline.
DSST=International Digital Symbol Substitution Test – Symbols. IgG=immunoglobulin G. Q2W=every 2 weeks. SE=standard error.