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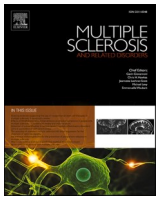

Exploratory clinical efficacy and patient-reported outcomes from NOVA: A randomized controlled study of intravenous natalizumab 6-week dosing versus continued 4-week dosing for relapsing-remitting multiple sclerosis

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ABSTRACT

Background: Natalizumab (TYSABRI®) 300 mg administered intravenously every-4-weeks (Q4W) is approved for treatment of relapsing-remitting multiple sclerosis but is associated with increased risk of progressive multifocal leukoencephalopathy (PML). Extended natalizumab dosing intervals of approximately every-6-weeks (Q6W) are associated with a lower risk of PML. Primary and secondary clinical outcomes from the NOVA randomized clinical trial (NCT03689972) suggest that effective disease control is maintained in patients who were stable during treatment with natalizumab Q4W for ≥12 months and who then switched to Q6W dosing. We compared additional exploratory clinical and patient-reported outcomes (PROs) from NOVA to assess the efficacy of Q6W dosing.

Methods: Prespecified exploratory clinical efficacy endpoints in NOVA included change from baseline in Expanded Disability Status Scale (EDSS) score, Timed 25-Foot Walk (T25FW), dominant- and nondominant-hand 9-Hole Peg Test (9HPT), and Symbol Digit Modalities Test (SDMT). Exploratory patient-reported outcome (PRO) efficacy endpoints included change from baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM), Neuro-QoL fatigue questionnaire, Multiple Sclerosis Impact Scale (MSIS-29), EuroQol 5 Dimensions (EQ-5D-5 L) index score, Clinical Global Impression (CGI)–Improvement (patient- and clinician-assessed) and CGI-Severity (clinician-assessed) rating scales. Estimated proportions of patients with confirmed EDSS improvement were based on Kaplan-Meier methods. Estimates of mean treatment differences for Q6W versus Q4W in other outcomes were assessed by least squares mean (LSM) and analyzed using a linear mixed model of repeated measures or ordinal logistic regression (CGI-scale).

Results: Exploratory clinical and patient-reported outcomes were assessed in patients who received ≥1 dose of randomly assigned study treatment and had ≥1 postbaseline efficacy assessment (Q6W group, $n = 247$, and Q4W group, $n = 242$). Estimated proportions of patients with EDSS improvement at week 72 were similar for Q6W and Q4W groups (11.7% [19/163] vs 10.8% [17/158]; HR 1.02 [95% confidence interval [CI], 0.53–1.98]; $P =$

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0.9501). At week 72, there were no significant differences between Q6W and Q4W groups in LSM change from baseline for T25FW (0.00, $P = 0.975$), 9HPT (dominant [0.22, $P = 0.533$] or nondominant [0.09, $P = 0.862$] hand), or SDMT (−1.03, $P = 0.194$). Similarly, there were no significant differences between Q6W and Q4W groups in LSM change from baseline for any PRO (TSQM, −1.00, $P = 0.410$; Neuro-QoL fatigue, 0.52, $P = 0.292$; MSIS-29 Psychological, 0.67, $P = 0.572$; MSIS-29 Physical, 0.74, $P = 0.429$; EQ-5D-5 L, 0.00, $P = 0.978$). For the EQ-5D-5 L, a higher proportion of Q6W patients than Q4W patients demonstrated worsening (≥0.5 standard deviation increase in the EQ-5D-5 L index score; $P = 0.0475$). From baseline to week 72 for Q6W versus Q4W, odds ratio (ORs) of LSM change in CGI scores did not show meaningful differences between groups (CGI-Improvement [patient]: OR [95% CI] 1.2 [0.80–1.73]; CGI-Improvement [physician]: 0.8 [0.47–1.36]; CGI-Severity [physician]: 1.0 [0.71–1.54]).

Conclusions: No significant differences were observed in change from baseline to week 72 between natalizumab Q6W and Q4W groups for all exploratory clinical or PRO-related endpoints assessed. For the EQ-5D-5 L, a higher proportion of Q6W than Q4W patients demonstrated worsening.

Abbreviations

9HPT	9-Hole Peg Test
CGI	Clinical Global Impression
CI	confidence interval
D	dominant hand
EDSS	Expanded Disability Status Scale
EQ-5D-5L	Five-Level EuroQol 5 Dimensions
HR	hazard ratio
LS	least squares
MCID	minimal clinically important differences
mITT	modified intention-to-treat
MMRM	mixed model of repeated measures
MS	multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
ND	nondominant hand
OR	odds ratio
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
Q4W	every 4 weeks
Q6W	every 6 weeks
RRMS	relapsing-remitting multiple sclerosis
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SE	standard error
T25FW	Timed 25-Foot Walk
TSQM	Treatment Satisfaction Questionnaire for Medication

1. Introduction

Intravenous natalizumab (TYASBRI®) 300 mg every 4 weeks (Q4W) is an efficacious treatment for patients with relapsing-remitting multiple sclerosis (RRMS), as documented in clinical trial data (Polman et al., 2006; Miller et al., 2007) and by real-world evidence (Butzkueven et al., 2020; Perumal et al., 2021). However, Q4W dosing of natalizumab is associated with progressive multifocal leukoencephalopathy (PML), a rare opportunistic infection of the central nervous system (Bloomgren et al., 2012; Ho et al., 2017). Retrospective analyses have demonstrated that extending dosing intervals of natalizumab to approximately every 6 weeks (Q6W) are associated with a significantly lower risk of PML (Zhovtis Ryerson et al., 2019).

NOVA (NCT03689972) is the first randomized, controlled trial to assess the efficacy and safety of intravenous natalizumab Q6W versus Q4W dosing (Foley et al., 2022). Primary and secondary radiological and clinical outcomes from NOVA suggest effective disease control in patients who switch to natalizumab Q6W dosing from Q4W. Exploratory magnetic resonance imaging outcomes also demonstrated no differences in changes in lesion volume between patients switched to Q6W and those remaining on Q4W natalizumab (Arnold et al., 2022).

Comparisons of additional clinical outcomes and patient-reported outcomes (PROs) are important for understanding the effectiveness of Q6W dosing. Ambulation has been successfully assessed in patients with multiple sclerosis (MS) using the Timed 25-Foot Walk (T25FW), which may provide a more sensitive assessment of disability progression than the Expanded Disability Status Scale (EDSS) (Koch et al., 2021; Kalinowski et al., 2022). The 9-Hole Peg Test (9HPT) has been used to document changes in manual dexterity in response to treatment (Feys et al., 2017). The Symbol Digit Modalities Test (SDMT) is an early and sensitive measure of cognitive processing speed in MS (Deloire et al., 2006), and has been associated with employment status (Strober et al., 2012).

To better understand the effectiveness of natalizumab Q6W dosing compared with Q4W dosing in patients with RRMS, we evaluated pre-specified exploratory outcomes from NOVA for ambulation, fine motor function, and cognition. Additionally, patient perceptions of efficacy of natalizumab Q6W versus Q4W dosing, quality of life, and treatment satisfaction were assessed using PRO measures.

2. Methods

2.1. Participants and study design

NOVA inclusion and exclusion criteria have been described previously (Foley et al., 2022). Briefly, patients (aged 18–60 years) with a diagnosis of RRMS who had been treated with natalizumab Q4W without relapse for ≥12 months and with EDSS scores <5.5 were randomized 1:1 to switch to natalizumab Q6W or to remain on natalizumab Q4W for a period of 72 weeks. Randomization was stratified by country/region, body weight (≤80 kg vs >80 kg), and duration of natalizumab exposure (≤3 years vs >3 years).

2.2. Assessments

2.2.1. Exploratory clinical efficacy endpoints

EDSS score was assessed at baseline, at weeks 24, 48, and 72 of assigned treatment, and at the 84-week follow-up visit. Improvement from baseline EDSS score was defined as a decrease of ≥1 point from baseline EDSS score of ≥2.0 confirmed after ≥24 weeks. Participants were assessed with T25FW, 9HPT (for dominant and nondominant hands), and SDMT at baseline and at weeks 24, 48, and 72 of treatment. Improved patient outcomes are indicated by lower times in T25FW and 9HPT and by higher scores in SDMT. Clinically meaningful changes in either direction from baseline were defined as a ≥15% change in T25FW time, ≥15% change in 9HPT time (Hobart et al., 2013; Feys et al., 2017), and a >4-point change in SDMT score (Benedict et al., 2017). Overall response score was based on 5 components (EDSS, T25FW, 9HPT-Dominant hand [9HPT-D], 9HPT-Nondominant hand [9HPT-ND], and SDMT) or 4 components (EDSS, T25FW, 9HPT-D, and 9HPT-ND). At each visit, individual components were given the following scores in relation to baseline: −1 (if the threshold was met for worsening), 0 (no changes met threshold criteria), or +1 (if the threshold was met for improvement). Overall scores ranged from −5 to +5 and −4 to +4, respectively, with

negative scores indicating worsening, 0 indicating no change, and positive scores indicating improvement.

2.2.2. Exploratory patient-reported efficacy endpoints

PRO assessments administered at randomization and at weeks 12, 24, 36, 48, and 72 of assigned treatment included: Treatment Satisfaction Questionnaire for Medication (TSQM) (Atkinson et al., 2004), Neuro-QoL fatigue questionnaire (Gershon et al., 2012), Multiple Sclerosis Impact Scale (MSIS-29) physical and psychological scales (Hobart et al., 2001), and Five-Level EuroQol 5 Dimensions (EQ-5D-5 L) index score (Herdman et al., 2011). Better patient outcomes are indicated by higher scores in TSQM and EQ-5D-5 L index and by lower scores in Neuro-QoL fatigue and MSIS-29 physical and psychological scales. Minimal clinically important differences (MCID) in improvement or worsening from baseline were defined on the basis of published estimates as the following: ≥5 points for Neuro-QoL fatigue (Norman et al., 2003; Hersh et al., 2021); ≥7.5 points in MSIS-29 physical (Phillips et al., 2014); ≥10 points in MSIS-29 psychological (Foley et al., 2017); and ≥0.5 standard deviation in EQ-5D-5 L index score (Lamu et al., 2021). Clinical Global Impression (CGI)–Improvement (patient- and physician-assessed) and CGI-Severity (physician-assessed) rating scales were assessed at baseline and at weeks 12, 24, 36, 48, and 72 of assigned treatment. Change from baseline in CGI-Improvement score was ranked as 0 (not assessed), 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), or 7 (very much worse), with a mean score of 3.0–4.0 representing minimal improvement to no change. CGI-Severity score change from baseline was ranked as ≤−2, −1, 0, 1, or ≥2, with 0 indicating no change and with negative and positive values indicating improvement and worsening, respectively.

2.3. Statistical analyses

All exploratory clinical outcomes and PROs were evaluated in the modified intention-to-treat (mITT) population, defined as all participants who received ≥1 dose of randomly assigned study treatment and had ≥1 postbaseline corresponding outcome assessment. Outcomes were adjusted for the following baseline covariates: body weight (≤80 kg vs >80 kg), duration of natalizumab exposure (≤3 years vs >3 years), and region (North America [USA and Canada], United Kingdom, Europe [Belgium, France, Germany, Italy, Netherlands, and Spain] and Israel, and Australia). Analyses of T25FW, 9HPT, SDMT, TSQM, Neuro-QoL fatigue questionnaire, MSIS-29 physical, MSIS-29 psychological, EQ-5D-5 L index, and CGI-Severity scores were also adjusted for the respective baseline scores of these outcomes.

Time to EDSS improvement was analyzed using Kaplan-Meier estimates and Cox regression models. Proportions of patients with confirmed EDSS improvement at week 72 were based on Kaplan-Meier estimates. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were computed for proportions of patients treated Q6W versus Q4W. Proportions of patients with clinically meaningful worsening in T25FW, 9HPT, or SDMT at week 72 were analyzed using a logistic regression model with treatment as the classification variable, the respective baseline scores of these parameters, and covariates in the model. Odds ratios (ORs) of Q6W versus Q4W were calculated with corresponding 95% CIs and *P* values. Estimates of mean treatment differences from baseline for Q6W versus Q4W in T25FW, 9HPT, and SDMT were analyzed at weeks 24, 48, and 72 using a linear mixed model of repeated measures (MMRM). An unstructured variance-covariance matrix structure was used in the MMRM model. Summary statistics for the change from baseline in 9HPT, T25FW, and SDMT scores by visit were calculated by treatment groups, with estimates of least squares (LS) mean treatment difference over time as well as the differences at weeks 24, 48, and 72 analyzed by the MMRM, adjusting for the respective baseline scores and covariates.

LS mean changes in TSQM, Neuro-QoL fatigue questionnaire, MSIS-29 physical, MSIS-29 psychological, and EQ-5D-5 L index scores from baseline to week 72 were analyzed using an MMRM adjusted for covariates. LS mean changes in CGI-Improvement and CGI-Severity scores over the same time period were analyzed using ordinal logistic regression adjusted for covariates. ORs and 95% CIs are reported for Q6W versus Q4W by timepoint.

3. Results

3.1. Patients

Of 499 participants randomized to receive natalizumab Q6W (*n* = 251) or Q4W (*n* = 248), 247 participants in the Q6W group and 242 participants in the Q4W group were included in the mITT population. Baseline demographics and disease characteristics were similar between treatment groups (Table 1). Mean (standard deviation [SD]) age was 40.9 (9.66) years in the Q6W group and 40.3 (9.94 years) in the Q4W group, with 70.4% (*n* = 174) and 72.7% (*n* = 176) female participants, respectively. Participants had a median (interquartile range) of 10.0 (6.0–15.0) years (Q6W group) and 9.0 (5.0–15.0) years (Q4W) since MS symptom onset, with a median duration of 4 years exposure to natalizumab at baseline in both treatment groups. EDSS scores at baseline were a mean (SD) of 2.32 (1.3) and 2.31 (1.3) in the Q6W and Q4W groups, respectively.

3.2. Exploratory clinical efficacy outcomes

Based on the Kaplan-Meier estimates, estimated proportions of patients with EDSS improvement at week 72 were similar for Q6W (11.7%; 19/163) and Q4W (10.8%; 17/158) groups (HR 1.02 [95% CI, 0.53–1.98]; *P* = 0.95) (Fig. 1). At week 72, change from baseline in the LS mean (standard error [SE]) T25FW time was small for the Q6W group

Table 1
Demographic and disease characteristics at baseline (mITT population).

Demographic characteristic	Q6W (*n* = 247)	Q4W (*n* = 242)	Total (*N* = 489)
Age, years, mean (SD)	40.9 (9.66)	40.3 (9.94)	40.6 (9.80)
Sex, female, n (%)	174 (70.4)	176 (72.7)	350 (71.6)
Weight, kg, mean (SD)	79.70 (19.59)	78.62 (20.28)	79.16 (19.92)
≤80 kg, n (%)	146 (59.1)	138 (57.0)	284 (58.1)
Disease characteristic, median (IQR)			
Time since onset of MS symptoms, years[a]	10.0 (6.0–15.0)[b]	9.0 (5.0–15.0)	10.0 (6.0–15.0)[c]
Time since RRMS diagnosis, years[d]	8.0 (4.0–13.0)[e]	8.0 (4.0–12.0)[f]	8.0 (4.0–13.0)[g]
Number of relapses in the 12 months prior to initiation of natalizumab treatment	1.0 (0.0–2.0)[h]	1.0 (0.0–1.0)[i]	1.0 (0.0–1.0)[j]
Duration of natalizumab exposure at baseline, years	4.0 (2.1–6.6)	4.0 (2.2–6.1)	4.0 (2.1–6.5)
EDSS score at baseline, mean (SD)	2.32 (1.30)	2.31 (1.31)	2.31 (1.30)

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; mITT, modified intent to treat; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; Q4W, every 4 weeks; Q6W, every 6 weeks.

[a] Calculated as date of randomization minus date of MS onset.
[b] *n* = 246.
[c] *n* = 488.
[d] Calculated as date of randomization minus date of diagnosis.
[e] *n* = 245.
[f] *n* = 241.
[g] *n* = 486.
[h] *n* = 241.
[i] *n* = 236.
[j] *n* = 477.

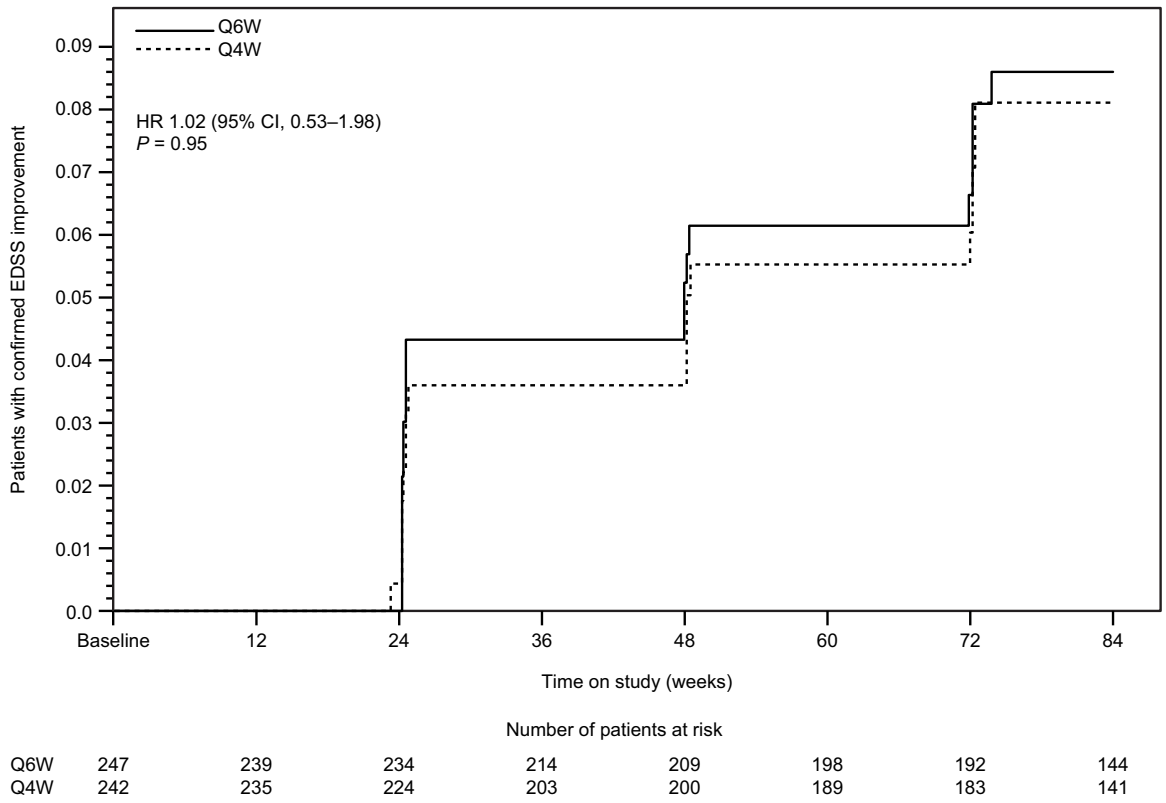

Fig. 1. Estimated proportions of patients with confirmed EDSS improvement (mITT population).
The mITT population was defined as all randomized participants who received ≥1 dose of study treatment and had ≥1 postbaseline efficacy assessment (Q6W = 247; Q4W = 242). Tentative EDSS improvement at week 72 was confirmed at week 84. HRs are based on a Cox regression model, with treatment as the classification variable and BL body weight (≤80 kg vs >80 kg), duration of natalizumab exposure at BL (≤3 years vs >3 years), and region (North America, United Kingdom, Europe and Israel, or Australia) as covariates.
Abbreviations: BL, baseline; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; mITT, modified intent-to-treat; Q4W, every 4 weeks; Q6W, every 6 weeks.

and for the Q4W group and without significant difference between the groups (0.10 [0.099] seconds and 0.11 [0.102] seconds, respectively; Fig. 2A). No significant differences were seen in the change from baseline in the LS mean (SE) 9HPT-D times for the Q6W group and the Q4W group (−0.49 [0.255] seconds and −0.70 [0.262] seconds, respectively; Fig. 2A). Similarly, no significant differences were observed in change from baseline in LS mean (SE) 9HPT-ND times (−0.41 [0.348] seconds and −0.49 [0.357] seconds; Fig. 2A). The proportion of participants with clinically meaningful worsening at week 72 in the T25FW was not significantly different between the Q6W and the Q4W group (20.3% vs 15.1%, respectively; OR 1.4 [95% CI, 0.9–2.3]; $P = 0.17$; Fig. 2B). A similar proportion of participants in the Q6W and Q4W groups had clinically meaningful worsening of 9HPT-D timings (7.5% and 7.1%, respectively; OR 1.0 [95% CI, 0.5–2.0]; $P = 0.99$) and 9HPT-ND timings (7.0% and 7.9%, respectively; OR 0.8 [95% CI, 0.4–1.7]; $P = 0.61$; Fig. 2B).

SDMT improved from baseline scores in both the Q6W and Q4W groups at weeks 24, 48, and 72, and there were no statistically significant differences between the 2 treatment groups at any timepoint (Fig. 3A). At week 72, no significant difference was observed in the LS mean (SE) for change from baseline in SDMT score (1.73 [0.550] for the Q6W group and 2.75 [0.564] for the Q4W group; difference of −1.03 [95% CI, −2.57 to 0.52]; $P = 0.194$; Fig. 3A). No significant difference was seen in the percentage of participants with clinically meaningful worsening in SDMT in the Q6W group as compared with the Q4W group (20.7% vs 15.8%; OR 1.4 [95% CI, 0.9–2.3]; $P = 0.19$).

At week 72, the LS mean (SE) change from baseline in composite overall response scores based on 4 components (EDSS, T25FW, 9HPT-D, and 9HPT-ND) was comparable between the groups (0.05 [0.156] for the Q6W group and 0.31 [0.161] for the Q4W group) with a nonsignificant difference of −0.26 (95% CI, −0.70 to 0.18; $P = 0.24$; Fig. 3B). At week 72, the LS mean (SE) change from baseline in composite overall response scores based on 5 components (EDSS, T25FW, 9HPT-D, 9HPT-ND, and SDMT) was also comparable for both groups (0.19 [0.172] for the Q6W group and 0.52 [0.178] for the Q4W group) with a nonsignificant difference of −0.33 (95% CI, −0.82 to 0.16; $P = 0.18$).

3.3. PROs

NOVA patients randomized to natalizumab Q6W or Q4W demonstrated small LS mean changes in all PROs assayed from baseline to week 72 (Fig. 4). No significant differences (Q6W−Q4W) in LS mean change were detected at 72 weeks for any PRO (Fig. 4). Likewise, no significant differences in LS mean change were seen at weeks 12 or 24 of treatment for any PRO (Table 2).

TSQM scores remained stable for both Q6W and Q4W groups during the study. At week 72, the LS mean (SE) change from baseline in the TSQM global satisfaction score was small and comparable for both groups (−0.55 [0.843] for the Q6W group and 0.45 [0.870] for the Q4W group), with a clinically and statistically nonsignificant difference of −1.0 (95% CI, −3.38 to 1.38; $P = 0.41$). At week 72, the LS mean (SE) decrease from baseline in the Neuro-QoL fatigue questionnaire score was comparable for both groups (−0.76 [0.344] for the Q6W group and −1.28 [0.354] for the Q4W group), with a clinically and statistically nonsignificant difference of 0.52 (95% CI, −0.45–1.49; $P = 0.29$).

The MSIS-29 psychological component scores demonstrated comparable improvement for both treatment groups at week 72 (LS mean [SE] change from baseline, −1.34 [0.818] for the Q6W group and −2.01

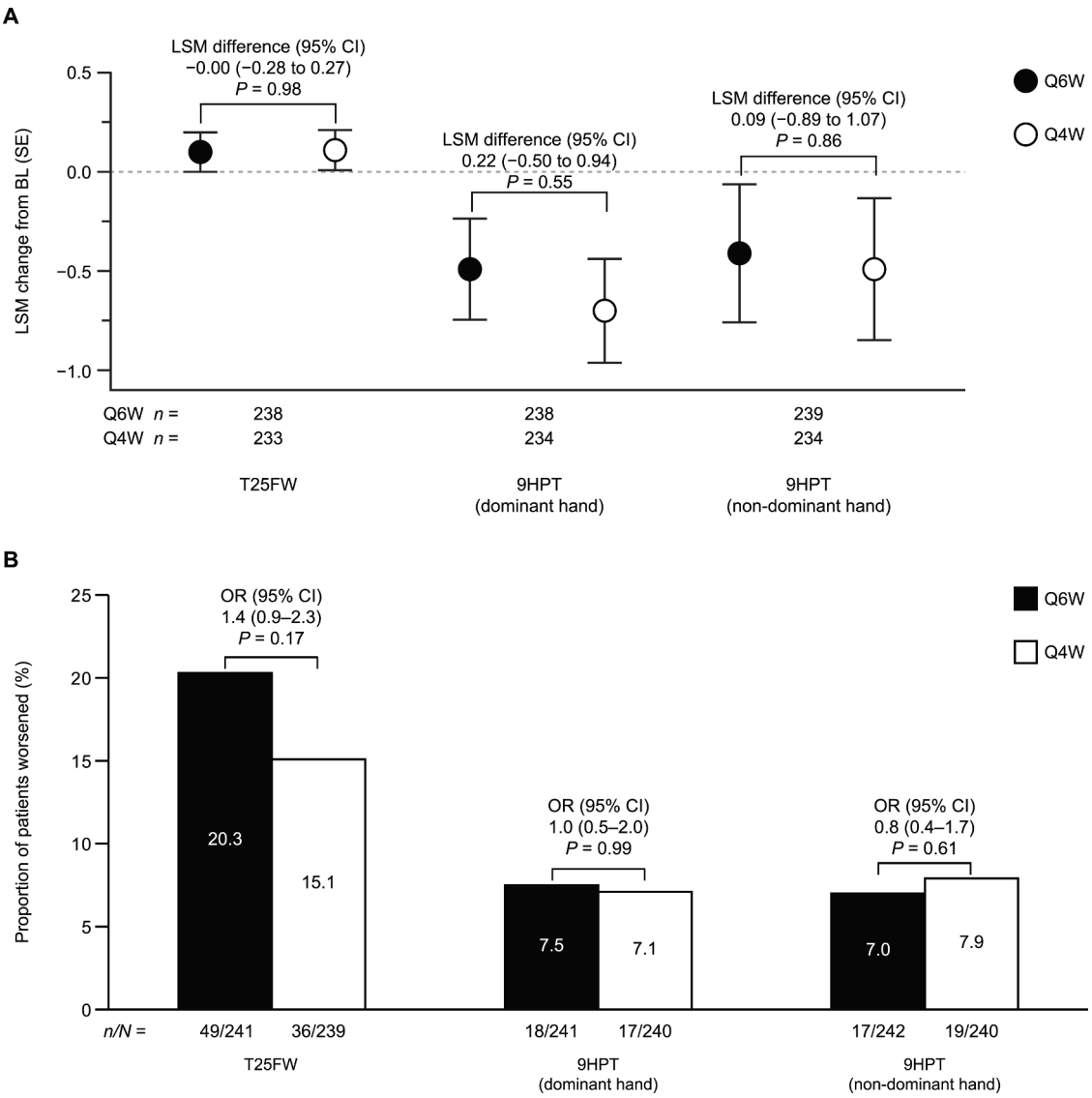

Fig. 2. (A) LSM change from baseline to week 72 in T25FW and 9HPT times. (B) Proportion of patients with clinically meaningful worsening in T25FW and 9HPT times.

In (A), estimated difference (95% CI) in LSM change from baseline for Q6W–Q4W was assessed using a mixed model of repeated measures. In (B), ORs (Q6W vs Q4W) for clinically meaningful worsening were assessed using a logistic regression model with treatment as the classification variable for the respective baseline scores of these endpoints in the model, and baseline body weight (≤80 kg vs >80 kg), duration of natalizumab exposure at baseline (≤3 years vs >3 years), and region (North America, United Kingdom, Europe and Israel, or Australia) as covariates.

Abbreviations: 9HPT, 9-Hole Peg Test; BL, baseline; CI, confidence interval; LSM, least squares mean; OR, odds ratio; Q4W, every 4 weeks; Q6W, every 6 weeks; SE, standard error; T25FW, Timed 25-Foot Walk.

[0.851] for the Q4W group), with a clinically and statistically nonsignificant difference of 0.67 (95% CI, −1.65 to 2.99; $P = 0.57$). At week 72, the MSIS-29 physical component increased for the Q6W group and slightly decreased for the Q4W group; the LS mean (SE) change from baseline was comparable for both groups (0.43 [0.647] for the Q6W group and −0.31 [0.673] for the Q4W group), with a clinically and statistically nonsignificant difference of 0.74 (95% CI, −1.10 to 2.57; $P = 0.43$). The EQ-5D-5 L index scores remained stable for the 2 treatment groups, with the LS mean (SE) change from baseline to week 72 the same for both groups (0.01 [0.008] for the Q6W group and 0.01 [0.009] for the Q4W group; difference: −0.00 [95% CI, −0.02 to 0.02; $P = 0.98$). There were no significant differences in proportions of Q6W and Q4W patients with a minimal clinically important improvement of Neuro-QoL fatigue, MSIS physical, MSIS psychological, and EQ-5D-5 L scores (Table 3). There were no significant differences in proportions of Q6W and Q4W patients with minimal clinically important worsening in PROs, with the exception of EQ-5D-5 L, for which a higher proportion of Q6W patients (19.0%) than Q4W patients (12.4%) reported worsening ($P = 0.048$).

At week 72, mean (SD) changes from baseline in CGI-Improvement reported by patients were similar between groups (Q6W, 3.6 [1.09], vs Q4W, 3.6 [0.95]; OR 1.2 [95% CI, 0.80–1.73]) (Fig. 5). The distribution of CGI-Improvement scores collected from participants was comparable between the Q6W and Q4W groups. At week 72, approximately 50% of the participants in the 2 treatment groups demonstrated no change in CGI-Improvement levels (51.0% in the Q6W group and 55.8% in the Q4W group). Varying levels of improvement were demonstrated by a similar proportion of participants in the Q6W and Q4W groups (24.3% and 21.9%, respectively). At week 72, 10.1% of the participants in the Q6W group and 5.8% of the participants in the Q4W group reported “minimally worse” CGI scores, and 2.0% of the participants in the Q6W group and 0 participants in the Q4W group reported

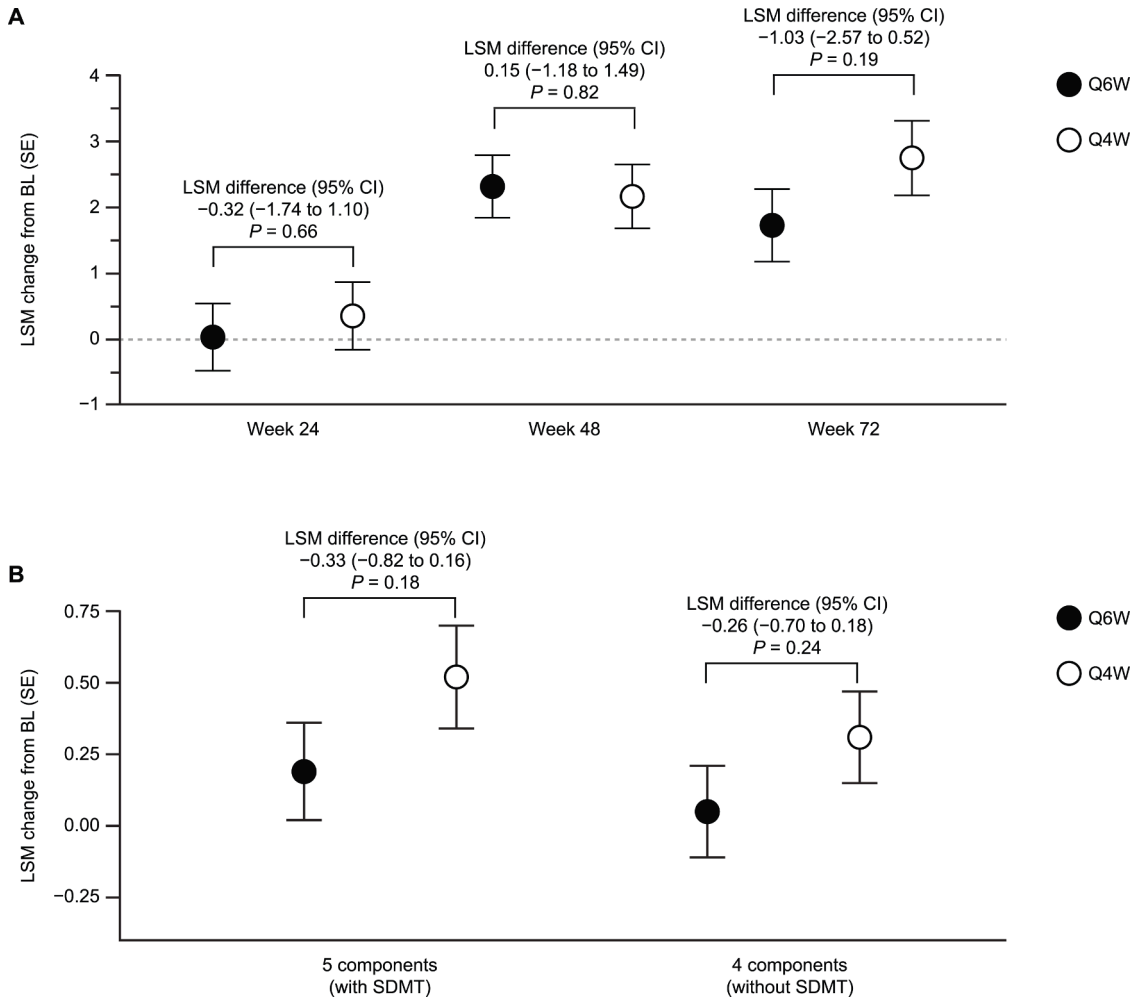

Fig. 3. LSM change from baseline in (A) SDMT scores and (B) clinical endpoint overall response scores.
In (A), LSM change from baseline SDMT score was assessed in 238 Q6W patients and 234 Q4W patients. Values above the data points are estimated difference (95% CI) in LSM change from baseline for Q6W–Q4W, assessed using a mixed model of repeated measures.
In (B), estimated mean treatment difference in LSM change from baseline to week 72 for Q6W−Q4W in overall response scores based on 5 components (EDSS, T25FW, 9HPT-D, 9HPT-ND, and SDMT) or 4 components (EDSS, T25FW, 9HPT-D, and 9HPT-ND) was assessed in 247 Q6W patients and 242 Q4W patients using a mixed model of repeated measures.
Abbreviations: 9HPT, 9-Hole Peg Test; BL, baseline; CI, confidence interval; D, dominant hand; EDSS, Expanded Disability Status Scale; LSM, least squares mean; ND, nondominant hand; Q4W, every 4 weeks; Q6W, every 6 weeks; SDMT, Symbol Digit Modalities Test; SE, standard error; T25FW, Timed 25-Foot Walk.

"much worse" CGI scores. No participant in either group reported "very much worse" CGI scores (OR 1.2 [95% CI, 0.80–1.73]). As reported by physicians, the mean change from baseline of CGI-Improvement score was similar for both the Q6W and Q4W groups (3.8 [0.81] vs 3.8 [0.79]; OR 0.8 [95% CI, 0.47–1.36]) at week 72. The distribution of CGI-Improvement scores collected from physicians was comparable between the Q6W and Q4W groups. At week 72, the majority of participants demonstrated no change in CGI-Improvement levels (72.1% in the Q6W group and 70.1% in the Q4W group; OR 0.8 [95% CI, 0.47–1.36]). At the same timepoint, mean (SD) change in physician-reported CGI-Severity was not different between the Q6W and Q4W groups (−0.1 [1.04] vs −1.0 [0.96]; OR 1.0 [95% CI, 0.71–1.54]). The distribution of CGI-Severity scores was comparable between the Q6W and Q4W groups: ≤−2 (8.1% and 7.0%, respectively), −1 (15.0% and 11.6%, respectively), 0 (45.3% and 47.1%, respectively), 1 (11.7% and 7.4%, respectively), and 2 (4.9% and 4.1%, respectively). From baseline to week 72, most Q6W and Q4W patients displayed stable scores for patient-reported CGI-Improvement (51.0% vs 55.8%) and physician-reported CGI-Improvement (72.1% vs 70.1%). A high percentage of patients also maintained stability as assessed by physician-reported CGI-Severity scores (45.3% vs 47.1%) (Fig. 6).

4. Discussion

After 72 weeks of treatment, there were no significant differences between the natalizumab Q6W and Q4W dosing groups in NOVA for exploratory clinical outcomes, including the proportion of patients with confirmed EDSS score improvement, or in change from baseline in T25FW, 9HPT-D, 9HPT-ND, and SDMT scores. Composite exploratory outcome scores (with and without SDMT) were also similar between groups. Additionally, there were no significant differences between natalizumab Q6W and Q4W dosing groups for all PROs measured in NOVA, including TSQM, Neuro-QoL fatigue, MSIS-29 physical and psychological scores, and the EQ-5D-5 L index.

The lack of difference between Q6W and Q4W groups in proportion of patients with confirmed EDSS score improvement is consistent with the previously reported observation of no significant difference in proportion of patients free from confirmed disability worsening (Foley et al., 2022). For both dosing groups, the observed LS mean changes in PROs from baseline to week 72 were small and comparable. The lack of difference in well-being as reported by patients in NOVA suggests that Q6W dosing of natalizumab is perceived as similarly efficacious to Q4W dosing for most patients. Likewise, physicians reported similar

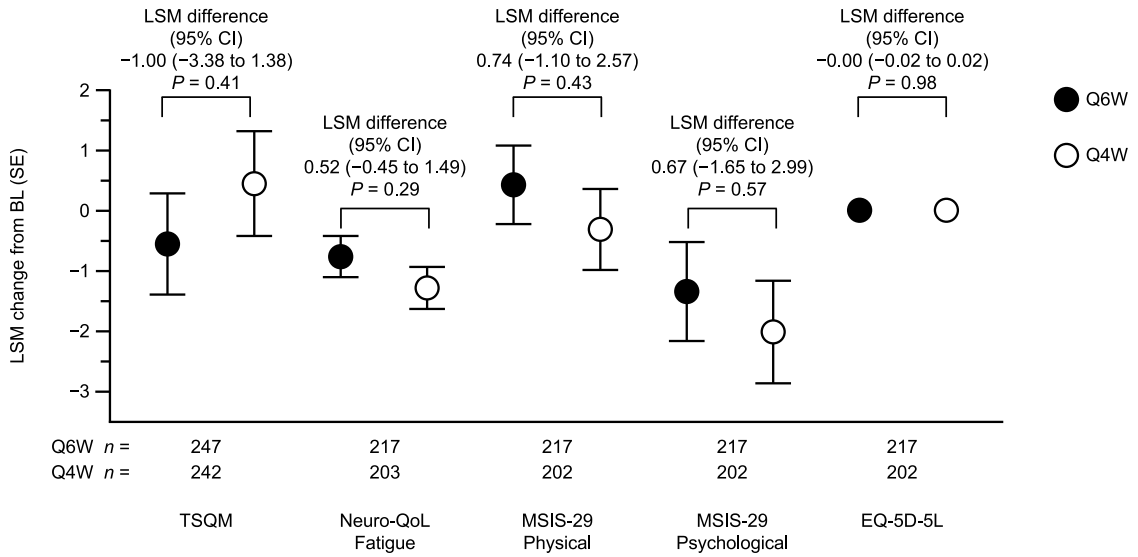

Fig. 4. LSM change from baseline in PROs at 72 weeks.
LSM changes in TSQM, Neuro-QoL fatigue questionnaire, MSIS-29 Physical, MSIS-29 Psychological, and EQ-5D-5 L Index from baseline to week 72 were analyzed using a mixed model of repeated measures adjusted for covariates.
Abbreviations: BL, baseline; CI, confidence interval; EQ-5D-5 L, 5-Level EuroQol 5 Dimensions; LSM, least squares mean; MSIS, Multiple Sclerosis Impact Scale; PRO, patient-reported outcome; Q4W, every 4 weeks; Q6W, every 6 weeks; SE, standard error; TSQM, Treatment Satisfaction Questionnaire for Medication.

Table 2
Change in PROs from baseline to weeks 12 and 24 in natalizumab Q6W and Q4W patients.

PRO, LSM (SE)	Week 12 Q6W ($n = 247$)	Q4W ($n = 242$)	LSM difference (95% CI) Q6W vs Q4W	Week 24 Q6W ($n = 247$)	Q4W ($n = 242$)	LSM difference (95% CI) Q6W vs Q4W
TSQM	0.64 (0.692)	−0.35 (0.696)	0.99 (−0.94 to 2.92) $P = 0.31$	−0.10 (0.738)	−0.32 (0.759)	0.22 (−1.86 to 2.30) $P = 0.83$
Neuro-QoL Fatigue	0.13 (0.294)	−0.16 (0.296)	0.28 (−0.54 to 1.10) $P = 0.50$	−0.24 (0.310)	−0.66 (0.319)	0.42 (−0.46 to 1.29) $P = 0.35$
MSIS-29 Physical	0.06 (0.534)	0.17 (0.545)	−0.11 (−1.61 to 1.39) $P = 0.89$	0.03 (0.547)	−0.26 (0.570)	0.30 (−1.25 to 1.85) $P = 0.71$
MSIS-29 Psychological	−2.06 (0.734)	−0.80 (0.745)	−1.26 (−3.32 to 0.80) $P = 0.23$	−0.98 (0.752)	−2.11 (0.780)	1.13 (−1.00 to 3.26) $P = 0.30$
EQ-5D-5 L Index Score	0.00 (0.007)	−0.00 (0.007)	0.00 (−0.02 to 0.02) $P = 0.80$	−0.00 (0.008)	0.00 (0.009)	−0.00 (−0.03 to 0.02) $P = 0.82$

LSM changes in the TSQM, Neuro-QoL fatigue questionnaire, MSIS-29 Physical, MSIS-29 Psychological, and EQ-5D-5 L Index from baseline were analyzed using a mixed model of repeated measures adjusted for covariates.
Abbreviations: CI, confidence interval; EQ-5D-5 L, 5-Level EuroQol 5 Dimensions; LSM, least squares mean; MSIS-29, Multiple Sclerosis Impact Scale; PRO, patient-reported outcome; Q4W, every 4 weeks; Q6W, every 6 weeks; SE, standard error; TSQM, Treatment Satisfaction Questionnaire for Medication.

Table 3
Proportion of patients reporting improvement or worsening in PROs.

PRO, n (%)	With MCID improvement Q6W ($N = 247$)	Q4W ($N = 242$)	P value[a]	With MCID worsening Q6W ($N = 247$)	Q4W ($N = 242$)	P value[a]
Neuro-QoL[b] fatigue	39 (15.79)	29 (11.98)	0.2413	24 (9.72)	16 (6.61)	0.2489
MSIS-29 Physical[c]	32 (12.96)	31 (12.81)	1.000	34 (13.77)	24 (9.92)	0.2094
MSIS-29 Psychological[c]	50 (20.24)	47 (19.42)	0.8218	35 (14.17)	30 (12.40)	0.5959
EQ-5D-5L Index Score[c]	46 (18.62)	38 (15.70)	0.4039	47 (19.03)	30 (12.40)	0.0475

MCID defined as a ± 5-point change for Neuro-QoL fatigue, as a ± 7.5-point change for MSIS-29 Physical, as a ± 10-point change for MSIS-29 Psychological, and as a ± 0.5 SD change for EQ-5D-5 L Index Score.
Abbreviations: EQ-5D-5 L, 5-Level EuroQol 5 Dimensions; MCID, Minimal Clinically Important Difference; MSIS-29, Multiple Sclerosis Impact Scale; PRO, patient-reported outcome; Q4W, every 4 weeks; Q6W, every 6 weeks; SD, standard deviation.
[a] P values based on Fisher exact test. [b]Neuro-QoL fatigue patients with 72-week measurements: Q4W, $n = 203$; Q6W, $n = 217$. [c]MSIS-29 physical, MSIS-29 psychological, and EQ-5D-5 L participants with 72-week measurements: Q4W, $n = 202$; Q6W, $n = 217$.

proportions of patients in the Q6W and Q4W treatment groups with stable CGI-Improvement scores at week 72 of treatment.

The Q6W dosing results are consistent with reports of Q4W natalizumab's effect on clinical outcomes and PROs. Treatment with natalizumab Q4W has been shown to elicit clinically meaningful improvement in ambulation as measured by the T25FW (Belachew et al., 2011; Cadavid et al., 2013; Voloshyna et al., 2015). Patients with early RRMS who were treated over 4 years with natalizumab Q4W have exhibited clinically meaningful improvement in cognitive processing speed as measured by the SDMT, and in physical and psychological function as assessed by the MSIS-29 (Perumal et al., 2022). Similar results were observed in these patients after 2 years of treatment, a duration more comparable to the NOVA trial (Perumal et al., 2019). Treatment with natalizumab Q4W has also been reported to improve fatigue, cognitive functioning (Iaffaldano et al., 2012; Stephenson et al., 2012), and quality of life (Kamat et al., 2009; Foley et al., 2017).

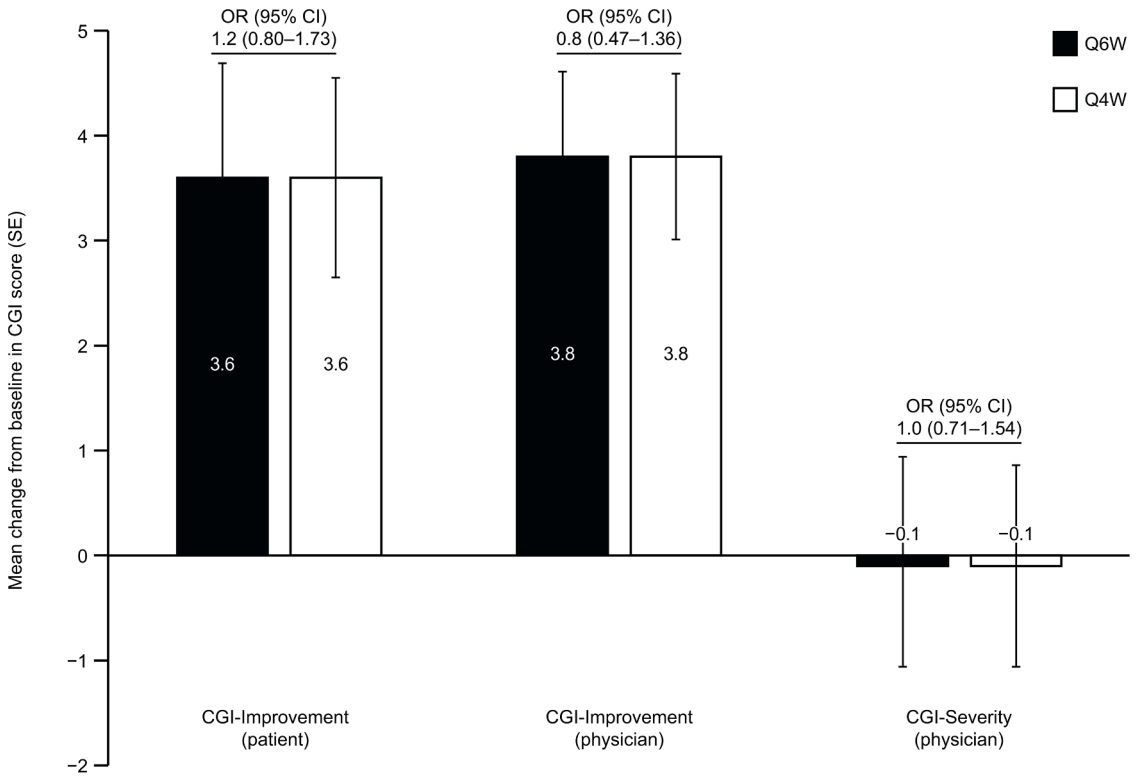

Fig. 5. Mean change in CGI scores at 72 weeks in natalizumab Q6W and Q4W patients.
CGI-Improvement (patient and physician) scores are tabulated as 0=not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. CGI-Severity scores are tabulated as ≤−2, −1, 0, 1, and ≥2, with 0 indicating no change, negative values indicating improvement, and positive values indicating worsening. ORs are estimated using an ordinal logistic regression model adjusted for baseline body weight (≤80 kg vs >80 kg), duration of natalizumab exposure at baseline (≤3 years vs >3 years), and region (North America, United Kingdom, Europe and Israel, or Australia).
Abbreviations: CGI, Clinical Global Impression; CI, confidence interval; OR, odds ratio; Q4W, every 4 weeks; Q6W, every 6 weeks; SE, standard error.

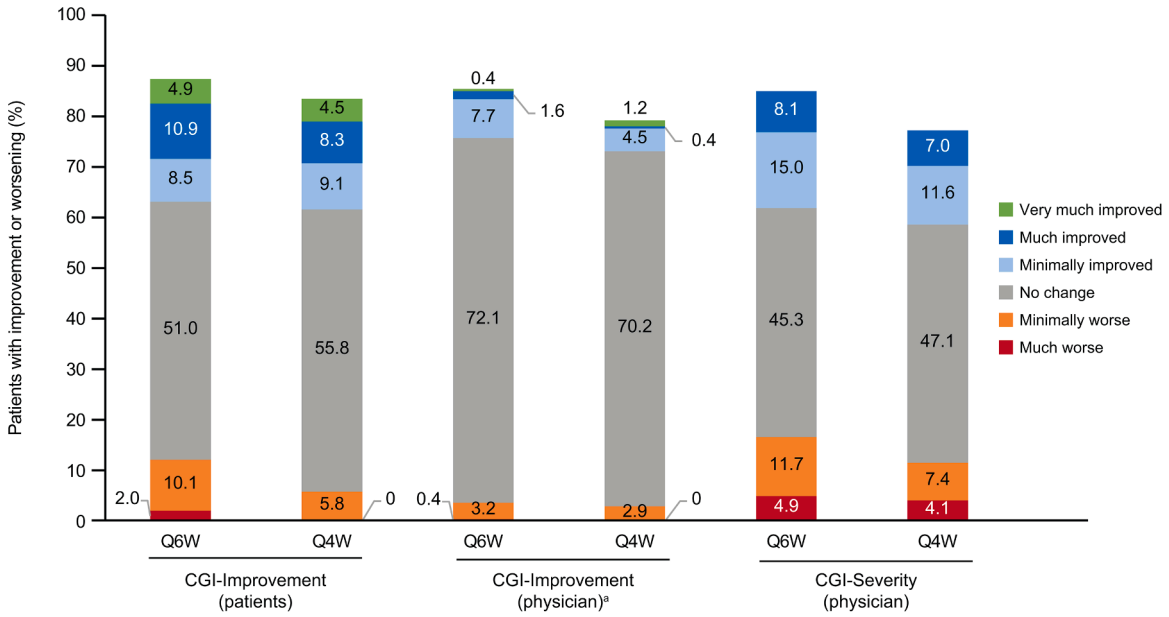

Fig. 6. Proportions of Q6W and Q4W patients with improvement or worsening in CGI scale scores at 72 weeks.
Proportions based on mITT populations (Q6W, $n = 247$; Q4W, $n = 242$). CGI-Improvement (patient and physician) scores are tabulated as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse (no patients were reported as "very much worse"). CGI-Severity scores are tabulated as much improved, minimally improved, no change, minimally worse, or much worse.
Abbreviations: CGI, Clinical Global Impression; mITT, modified intent-to-treat; Q4W, every 4 weeks; Q6W, every 6 weeks.
[a]Six Q6W (2.4%) and 5 Q4W (2.1%) patients were missing a CGI-Improvement (physician) assessment.

Although there were no statistically significant differences in exploratory clinical outcomes and PROs, there were subtle differences between Q6W and Q4W groups. A slightly higher proportion of patients in the Q6W group had worsening in T25FW and SDMT scores. A higher proportion of patients in the Q6W group reported minimal clinically important worsening on the EQ-5D-5 L. There have been reports of a "wearing-off" effect, often manifesting in increased fatigue, during the last week of the infusion cycle by subsets of patients receiving natalizumab (Ratchford et al., 2014; van Kempen et al., 2019; Bringeland et al., 2020, 2021). Reports exploring the relationship between the "wearing-off" effect and extended interval dosing are inconsistent (van Kempen et al., 2019; Bringeland et al., 2021). The "wearing-off" effect was not directly addressed in the NOVA trial, and further research is needed on this topic.

This study has limitations that should be considered. Interpretation of these results may be limited by the relatively short study duration; longer studies of Q6W dosing may provide a more detailed understanding of the outcomes reported here. At 6 months after natalizumab discontinuation, patients who switched from natalizumab to moderate-efficacy disease-modifying therapies have been reported to be at increased risk of disability progression as assessed by T25FW and 9HPT (Hersh et al., 2020), suggesting that a change in therapeutic efficacy with Q6W dosing might be apparent at the 72-week endpoint in NOVA. It should be noted that the proportion of patients with minimal clinically important differences in improvement or worsening observed in NOVA were low in both dosing groups (<20%) and this study did not have sufficient power to assess small differences in outcomes. Also, because the results reported here reflect changes at single timepoints, and not confirmed improvement or worsening, measurement errors may have confounded detection of differences between groups. Lastly, NOVA was not designed to assess noninferiority between 6-week and 4-week dosing, potentially limiting the interpretation of these results.

Our results support the findings of the primary and secondary magnetic resonance imaging and clinical outcomes of NOVA (Foley et al., 2022), and they support the conclusion that the majority of patients who are stable on natalizumab Q4W dosing can switch to Q6W without a clinically meaningful loss of efficacy. These data add to our overall understanding of patient-centric outcomes in patients with RRMS treated with natalizumab Q6W or Q4W. Follow-up of patients in the NOVA open-label extension study will provide information on clinical outcomes and PROs with longer-term Q6W dosing of natalizumab. These results are of value to patients and clinicians as they weigh the benefits and risks of natalizumab treatment for individuals with RRMS.

5. Disclosures

LZR: personal compensation for advisory board activities from Biogen, Genentech, Novartis; research support from Biogen, Celgene, Genentech.

JFF: personal compensation for consulting activities from Biogen, Octave; compensation (paid to institution) for data safety monitoring or advisory boards from Biogen, Genentech, Novartis.

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GC: has served on data and safety monitoring boards for AI Therapeutics, AMO Pharma, Applied Therapeutics, Astra-Zeneca, AveXis Pharmaceuticals, BioLineRx, Brainstorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green Valley Pharma, Horizon Pharmaceuticals, Immunic, Karuna Therapeutics, Mapi Pharmaceuticals, Merck, Mitsubishi Tanabe Pharma Holdings, Opko Biologics, Prothena Biosciences, Novartis, Regeneron, Sanofi-Aventis, Reata Pharmaceuticals, National Heart, Lung, and Blood Institute (Protocol Review Committee), Teva Pharmaceuticals, University of Texas Southwestern, University of Pennsylvania, Visioneering Technologies; consulting or advisory boards for Alexion, Antisense Therapeutics, Biogen, Clinical Trial Solutions, Entelexo Biotherapeutics, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Immunosis Pty Ltd, Klein-Buendel, Merck/Serono, Novartis, Perception Neurosciences, Protalix Biotherapeutics, Regeneron, Roche, SAB Biotherapeutics; is employed by the University of Alabama at Birmingham; is president of Pythagoras, Inc., a private consulting company located in Birmingham, AL, USA.

GG: consulting and/or speaker fees from AbbVie, Aslan, Atara Bio, Biogen, BMS-Celgene, GlaxoSmithKline, GW Pharma, Janssen/Actelion, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck & Co, Merck KGaA/EMD Serono, Novartis, Sanofi Genzyme, Roche/Genentech, Teva Pharmaceuticals.

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SS, RK, KB, TL: employees of and may hold stock and/or stock options in Biogen.

CRediT authorship contribution statement

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Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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