DX04. Natalizumab in anti-JC virus seronegative patients with early relapsing-remitting multiple sclerosis: interim results from the STRIVE study

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Disclosures and Acknowledgments

Disclosures

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Introduction

- In patients with RRMS, natalizumab significantly reduces disease activity on MRI, clinical relapse rates, and confirmed disability worsening relative to placebo[1]

  - Treatment with natalizumab earlier in the RRMS disease course may be associated with better clinical outcomes[2]

- Natalizumab treatment is associated with a risk of PML.[3] This study includes only anti-JCV antibody negative patients, whose risk of PML is estimated to be 0.1/1000[4]

- The benefit/risk profile of natalizumab is enhanced when natalizumab is used to treat patients who test negative for anti-JCV antibodies
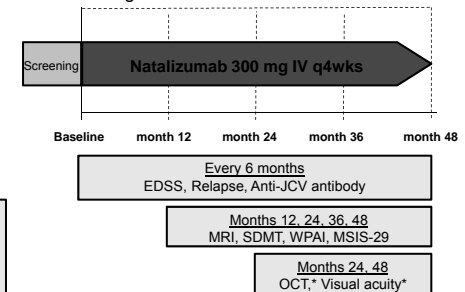
Learning objective: Gain an understanding of the STRIVE study design and its interim evaluation of the natalizumab treatment in anti-JCV negative patients with early RRMS

JCV=John Cunningham virus; PML=progressive multifocal leukoencephalopathy
1. Polman CH et al. *N Engl J Med*. 2006;354:899-910. 2. Butzkueven H et al. *J Neurol Neurosurg Psychiatry*. 2014;85:1190-1197.
3. Bloomgren G et al. *N Engl J Med*. 2012;366:1870-1880. 4. Biogen, data on file.
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Study Design

- **S**tudy of **T**ysabri in Early **R**elapsing-Rem**I**tting MS in anti-JCV Antibody Negati**VE** Patients (STRIVE) is a prospective, open-label, multicenter, single-country, observational, phase 4 study of anti-JCV antibody negative patients with early (<3 years) RRMS who are initiating treatment with natalizumab

Screening | **Natalizumab 300 mg IV q4wks**

Baseline | month 12 | month 24 | month 36 | month 48

Every 6 months
EDSS, Relapse, Anti-JCV antibody

OCT Substudy:
Assess the structure and function of the visual pathway to evaluate MS pathophysiology over time in 87 patients being treated with natalizumab

Months 12, 24, 36, 48
MRI, SDMT, WPAI, MSIS-29

Months 24, 48
OCT,* Visual acuity*

*Includes only patients in the OCT substudy.
EDSS=Expanded Disability Status Scale; IV=intravenous; MSIS-29=Multiple Sclerosis Impact Scale; OCT=optical coherence tomography; q4wk=every 4 weeks; SDMT=Symbol Digit Modalities Test; WPAI=Work Productivity and Activity Impairment Questionnaire.
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Objective and Endpoints

Objective

- To determine the proportion of patients with RRMS initiating natalizumab in the first 3 years of their disease course who demonstrate no evidence of disease activity (NEDA) at months 12 and 24

NEDA
• No 24-week confirmed EDSS worsening
• No relapses
• No gadolinium-enhancing (Gd+) lesions
• No new/enlarging T2 lesions

Clinical NEDA
• No 24-week confirmed EDSS worsening
• No relapses

Endpoints

- Primary: the proportion of patients who achieve NEDA at months 12 and 24, and the proportion of patients with clinical NEDA at months 36 and 48
- Key Secondary:
  - Identification of baseline characteristics that predict NEDA at month 12
  - Clinical NEDA at months 12, 24, 36, and 48
  - Annualized relapse rate at months 12, 24, 36, and 48
  - 24-week confirmed EDSS worsening and improvement at months 12, 24, 36, and 48

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Patient Population

Key inclusion criteria:

- Age 18–65 years, with an RRMS diagnosis of <3 years' duration
- EDSS score ≤4.0
- Negative test results for anti-JCV antibodies ≤6 months of screening*
- Treatment naive or prior treatment with disease-modifying therapy (DMT) for ≤36 months

Key exclusion criteria:

- Any prior treatment with natalizumab
- Anti-JCV antibody positive status at any time point prior to screening
- Current treatment with immunomodulatory or immunosuppressive therapy or a prior history of immunosuppressant use

*Patients who converted to anti-JCV antibody positive status during the course of the study may continue on natalizumab at the discretion of the treating neurologist.

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Patient Characteristics and Disposition

Baseline characteristic	Natalizumab (n=209)
Age, mean (SD), years	33.9 (8.9)
Female, n (%)	148 (70.8)
Time from diagnosis of MS, mean (SD), years	1.7 (0.8)
Number of relapses in the past 12 months, mean (SD)	1.4 (1.1)
EDSS score	
Mean (SD)	2.0 (1.1)
Median (range)	2.0 (0, 4.0)
T1 lesion volume, median (range), cc	0.7 (0, 29.5)*
T2 lesion volume, median (range), cc	4.5 (0, 73.1)*
Patients with no Gd+ lesions, n (%)	116 (57.7)*
Prior DMT treatment, n (%)	104 (49.8)

Patient disposition at month 12

Enrolled (N=231) → Received ≥1 dose of natalizumab (n=211)† → Discontinued (n=41)‡ / Ongoing in study (n=170)

*n=201. †Two patients did not meet inclusion /exclusion criteria and were excluded from the analyses.
‡Reasons given for discontinuation included withdrawal of consent, investigator decision, pregnancy/desire to become pregnant, safety concerns, lack of compliance with study protocol, and lack of efficacy.
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SD=standard deviation

Primary Endpoint: Overall NEDA Status

- In this prespecified interim analysis, 54.9% of STRIVE patients had NEDA at month 12 (95% CI: 47.5%–62.2%).

Proportion of patients with disease activity at month 12

	Natalizumab 300 mg	
Outcome	n	%
No relapses	185/209	88.5
No 24-week confirmed EDSS worsening	187/209	89.5
No new/enlarging T2 lesions	118/168	70.2
No Gd+ lesions	168/172	97.7
NEDA	**96/175**	**54.9**

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Baseline Characteristics Predicting NEDA

Proportion of patients with NEDA at month 12*
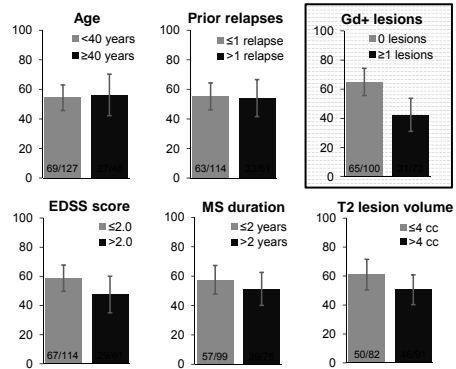
- A higher proportion of patients with no Gd+ lesions at baseline achieved NEDA at month 12 than those with Gd+ lesions (65.0% vs 42.5%; OR [95% CI]: 2.85 [1.39–5.83]; *p*=0.0041)

- There were no significant differences in NEDA at month 12 for the other baseline characteristics assessed

All analyses are based on logistic regression models adjusting for other baseline characteristics shown.
*Error bars show 95% CI.
9   CI=confidence interval; OR=odds ratio.

Clinical NEDA Status

- At month 12, 80.9% of STRIVE patients had clinical NEDA (95% CI: 75.5%–86.2%).

Proportion of patients with clinical disease activity at month 12

	Natalizumab 300 mg	
Outcome	**n**	**%**
No relapses	185/209	88.5
No 24-week confirmed EDSS worsening	187/209	89.5
Clinical NEDA	**169/209**	**80.9**

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Baseline Characteristics Predicting Clinical NEDA

Proportion of patients with clinical NEDA at month 12*

- A higher proportion of patients with baseline EDSS scores ≤2.0 achieved clinical NEDA at month 12 than those with EDSS scores >2.0 (86.6% vs 70.7%; OR [95% CI]: 2.49 [1.21–5.12]; *p*=0.0135)

- There were no significant differences in NEDA at month 12 for the other baseline characteristics assessed†


All analyses are based on logistic regression models adjusting for other baseline characteristics shown.
11   *Error bars show 95% CI.
†The effects of T2 lesion volume and Gd+ lesion numbers on clinical NEDA were not assessed.

Relapses

- The annualized relapse rate was significantly lower in the 12 months on natalizumab than in the 12 months prior to starting treatment

- During 12 months of natalizumab treatment, 24 of 209 patients experienced a relapse

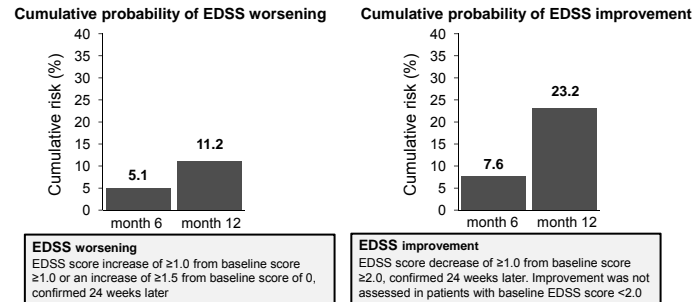**Annualized Relapse Rate***

Cumulative probability of relapse†
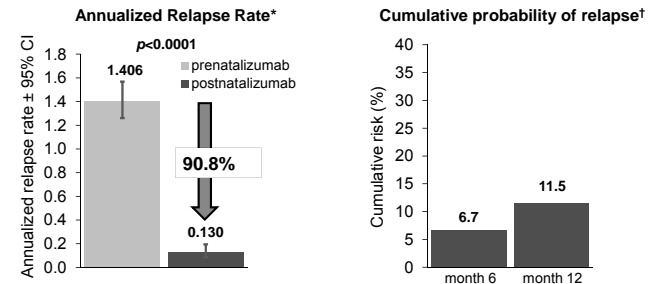
*Relapses in the 12 months prior to starting natalizumab were reported by the patient. On-treatment relapses were reported by the physician. P-value is based on a repeated negative binominal model.
12   †P-value is based on Kaplan-Meier analysis/Cox proportional hazard model.

Confirmed EDSS Worsening or Improvement

- At month 12, 22 out of 209 patients had 24-week confirmed EDSS worsening
- Of the 125 patients with baseline EDSS scores ≥2.0, 27 had 24-week confirmed EDSS improvement

Cumulative probability of EDSS worsening

Cumulative probability of EDSS improvement

EDSS worsening
EDSS score increase of ≥1.0 from baseline score ≥1.0 or an increase of ≥1.5 from baseline score of 0, confirmed 24 weeks later

EDSS improvement
EDSS score decrease of ≥1.0 from baseline score ≥2.0, confirmed 24 weeks later. Improvement was not assessed in patients with baseline EDSS score <2.0

13 Cumulative probabilities are based on Kaplan-Meier analysis/Cox proportional hazard model.
Time point listed is for onset of EDSS increase or decrease, which was then confirmed 24 weeks later.

Key Safety Data Through Month 12

Serious adverse events

Event, n (%)	n=209
Patients with ≥1 serious adverse event	6 (2.9)
Patients with ≥1 treatment-related serious adverse event	6 (2.9)
Death	2 (1.0)

Serious adverse events by preferred term, n (%)	n=209
MS relapse	2 (1.0)
Anaphylactic reaction	1 (0.5)
Conversion disorder	1 (0.5)
Ileus	1 (0.5)
Melanoma recurrent	1 (0.5)
Suicide attempt	1 (0.5)

Patients with negative anti-JCV antibody test

Time point	n	%
Screening	185/185	100
Month 12	156/169	92.3

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Summary and Conclusions

- In this prespecified 1-year analysis of STRIVE, a majority (54.9%) of patients initiating natalizumab early in the disease course attained NEDA
- Significantly more patients without Gd+ lesions on MRI at baseline had NEDA compared with patients with Gd+ lesions
- Having minimal or no disability when initiating treatment was associated with achieving clinical NEDA
- The likelihood of EDSS improvement (23.2%) was higher than the likelihood of EDSS worsening (11.2%)
- The adverse event profile is consistent with the well-established safety profile of natalizumab[1,2]
- These results support the effectiveness and safety of natalizumab in treating patients with early RRMS

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1. Polman CH et al. *N Engl J Med.* 2006;354:899-910.
2. Butzkueven H et al. *J Neurol Neurosurg Psychiatry.* 2014;85:1190-1197.

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