Evaluating the Efficacy and Safety of 6-Week Extended Interval Dosing of Natalizumab via a Prospective, Controlled, Randomized, Open-label, Rater-blinded Phase 3b Study (NOVA)

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Discussion

- **The Natalizumab, phase 3b, prospective, randomized, Open-label study comparing extended interval dosing Versus Approved dose (NOVA) study will provide the first randomized, controlled efficacy data for patients treated with extended interval dosing (EID) of natalizumab.**
- **In conjunction with prior safety data, the results from this study will provide information on the potential of EID as a future progressive multifocal leukoencephalopathy (PML) risk mitigation strategy.**
- **These study results will also help define a benefit/risk profile for natalizumab EID.**

Introduction

- Natalizumab, a highly efficacious therapy for relapsing-remitting multiple sclerosis (RRMS), is also associated with risk of PML.[1-5]
- Natalizumab EID has been suggested as a strategy to reduce PML risk.
- To date, there have been no randomized studies to compare the efficacy of natalizumab EID and standard interval dosing (SID).
  - In the absence of prospective, randomized efficacy data, no benefit-risk profile has been established for EID.
- This prospective study will examine if EID and SID have differential efficacy and will thereby provide information on the benefit-risk profile of natalizumab EID.

Objective

- To describe the design of a phase 3b study to evaluate the efficacy of natalizumab EID in patients who switch to EID after a stable period of SID compared with the efficacy of continuing SID.

Methods

- NOVA will be a prospective, randomized, interventional, controlled, rater-blinded, multinational study (clinicaltrials.gov no. NCT03689972).
- Patient inclusion criteria include age 18–60 years, an Expanded Disability Status Scale score ≤5.5, a diagnosis of RRMS, stability on natalizumab SID (having received ≥11 doses and having had no relapses in the prior 12 months), no prior immunosuppressant use, and no gadolinium-enhancing (Gd+) lesions at screening.
- Approximately 480 patients will be enrolled in NOVA.
  - Patients will be randomized 1:1 to natalizumab SID (300 mg intravenous [IV] every 4 weeks [26–33 days]) or EID (300 mg IV every 6 weeks [40–47 days]).
- Study duration will be 88 weeks (4 weeks screening, 72 weeks randomized treatment, and 12 weeks follow-up) (Figure 1).
- The primary endpoint is the number of new/newly enlarging T2 lesions at 48 weeks.
  - Key secondary endpoints include time to relapse, relapse rate, the number of new magnetic resonance imagine (MRI) lesions, and the incidence of serious adverse events. Exploratory endpoints include Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), and Symbol Digit Modality Test (SDMT) scores and confirmed disability worsening or improvement.
  - Data on natalizumab serum concentration, alpha-4 integrin saturation, lymphocyte counts, and body weight will be collected to explore relationships between pharmacokinetics (PK)/pharmacodynamics (PD) and efficacy.

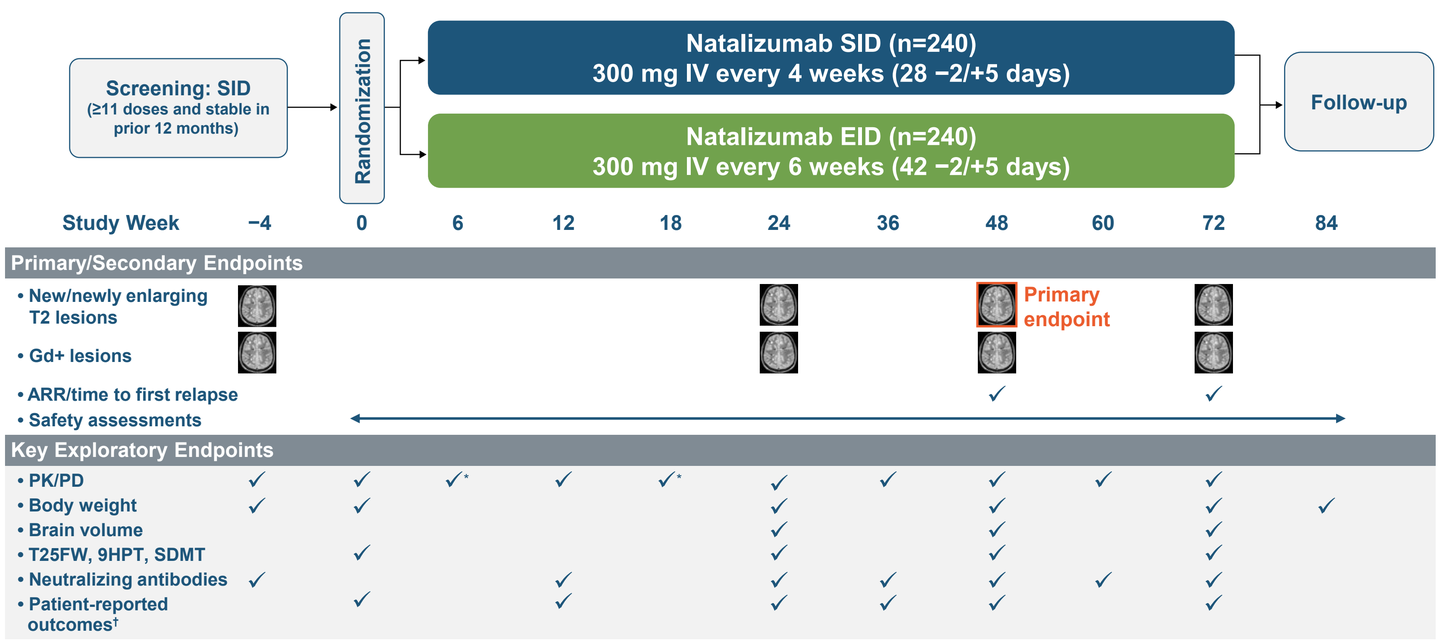
Results

- The EID intervals in NOVA were chosen to encompass the real-world dosing intervals associated with the lower risk of PML observed in the TOUCH analysis (Figure 2).[6]
- The rationale for the requirement of ≥12 months of disease stability on SID prior to random allocation and switching to EID is as follows:
  - Independent studies suggest comparable efficacy between SID and EID in patients switching to EID after 1–2 years of SID.[7-9]
  - Modeling shows that initiating patients on EID may result in inadequate protection from clinical and MRI disease activity.[10]
  - Analysis of patients in AFFIRM demonstrates that the efficacy of natalizumab improves after the first year of treatment (Figure 3A).[11]
  - Analysis of a pooled cohort of patients from four open-label studies of natalizumab indicates that the risk of PML in the first year of treatment is low regardless of index or prior use of immunosuppressants (Figure 3B).[12] Thus, incentive for EID as a PML risk mitigation strategy is low during the first year of treatment.
- The number of new or newly enlarging T2 hyperintense lesions at 48 weeks for the primary endpoint selection is an objective and sensitive measure of natalizumab efficacy.
  - In open-label trials, rater-blinded MRI endpoints remain fully objective, while relapse-based endpoints are more prone to bias in these contexts.
  - T2 hyperintense lesions represent a persistent footprint of demyelination and provide high-sensitivity detection of disease activity.[13]
- The sample size (N=480) provides >80% power to detect a difference between 0.3 (the predicted value for SID group in this population) and 0.5 in mean new or newly enlarging T2 lesions.

Literature

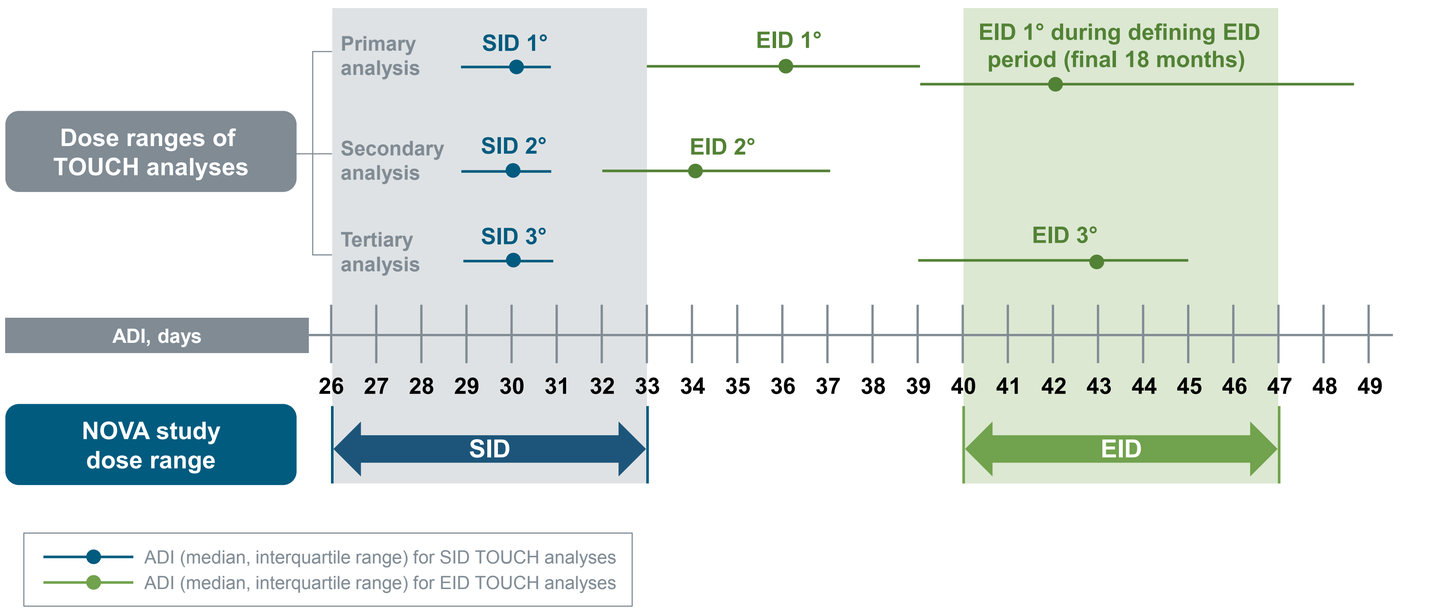
- A recent analysis of the TOUCH® Prescribing Program database demonstrated that natalizumab EID is associated with significantly lower PML risk than SID in anti–JC virus antibody positive patients.[6]
- Several retrospective studies have indicated that natalizumab efficacy is maintained with EID dosing schedules >4 weeks.[7,8] In addition, partial reversal of natalizumab's pharmacodynamic effects, resulting in restoration of immune surveillance, has been reported to occur 4–8 weeks after the last dose.[14]
- This study will provide the first randomized, controlled efficacy data for patients treated with natalizumab EID and will yield a more comprehensive understanding of both the effectiveness and the safety of natalizumab EID.

Figure 1. NOVA study endpoints and assessments



*EID group only. †Including TSQM (Treatment Satisfaction Questionnaire for Medication), Neuro-QoL (Quality of Life in Neurological Disorders) Fatigue, MSIS-29 (Multiple Sclerosis Impact Scale), and EQ-5D-5L (EuroQol 5-dimensional questionnaire).
ARR=annualized relapse rate.

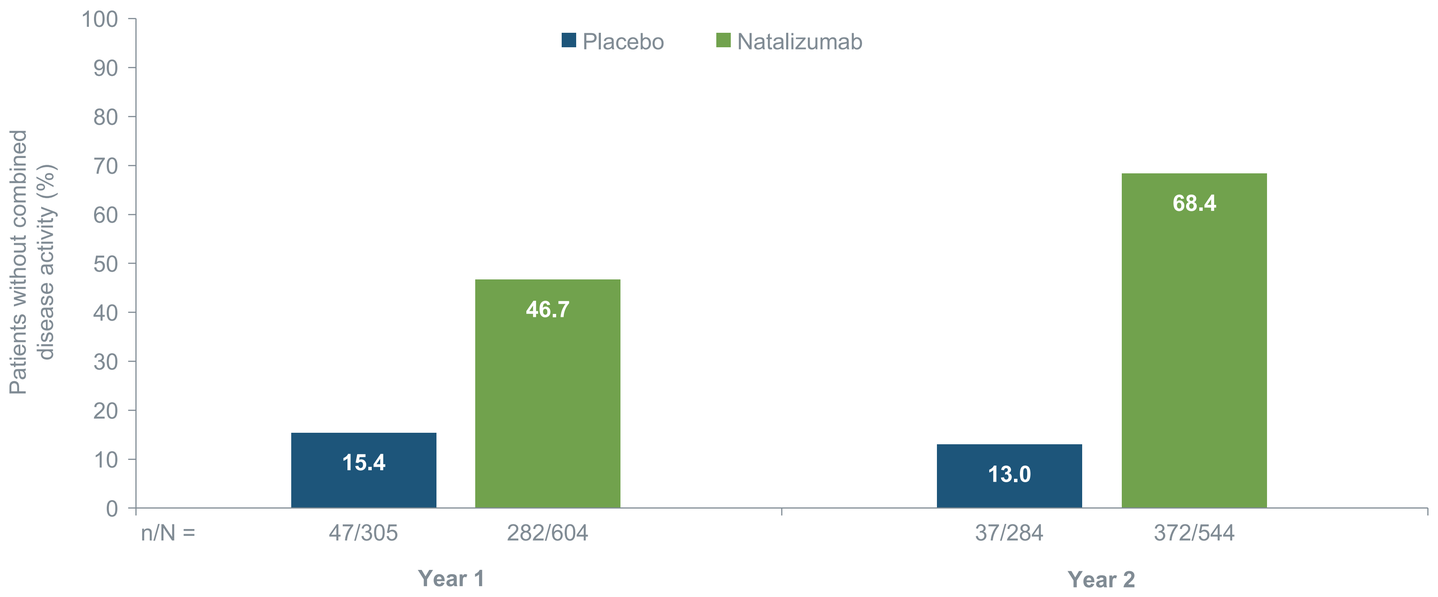
Figure 2. Rationale for study dosing intervals



Light-grey– and light-green–shaded areas indicate ranges of SID and EID dosing intervals for the NOVA study. SID 1° and EID 1°, SID 2° and EID 2°, and SID 3° and EID 3° refer to the definitions of SID and EID in the primary, secondary, and tertiary analyses, respectively, on PML risk in the TOUCH analysis.[6]
ADI=average dosing interval.

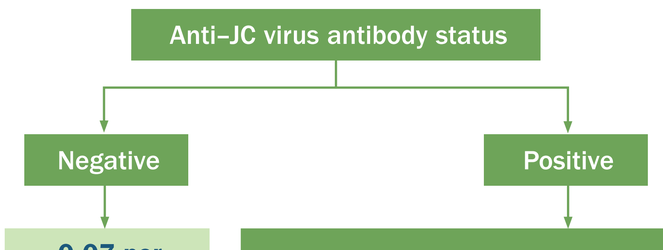
Figure 3. Rationale for including a patient population switching from SID to EID

A. Treatment effects of natalizumab are greater after year 1



Patients without clinical and radiologic disease activity after 1 and 2 years of natalizumab treatment in AFFIRM.[11] Absence of combined clinical and radiological measures was defined as no relapse, no progression of disability (sustained for 12 weeks), no Gd+ lesions, and no new or enlarging T2-hyperintense lesions.

B. PML risk is low in the first year of treatment



Natalizumab exposure (months)	Patients without previous immunosuppressant use, per 1000 patients (95% CI)			Patients with previous immunosuppressant use, per 1000 patients (95% CI)
	Index ≤0.9	Index >0.9 to ≤1.5	Index >1.5	
1–12	0.01 (0.00–0.03)	0.1 (0.0–0.2)	0.2 (0.0–0.5)	0.3 (0.0–1.9)
13–24	0.05 (0.00–0.14)	0.3 (0.0–0.6)	0.9 (0.3–1.6)	0.4 (0.0–2.3)
25–36	0.2 (0.0–0.4)	0.8 (0.1–1.5)	2.6 (1.4–3.9)	3.6 (1.4–7.4)
37–48	0.4 (0.0–1.0)	2.0 (0.2–3.8)	6.8 (4.4–9.1)	8.3 (4.3–14.5)
49–60	0.5 (0.0–1.2)	2.4 (0.2–4.5)	7.9 (4.9–10.9)	8.4 (3.7–16.6)
61–72	0.6 (0.0–1.5)	3.0 (0.2–5.8)	10.0 (5.6–14.4)	5.5 (1.1–16.0)§

Conditional probability of developing PML using the life-table method in each year of treatment with multiple imputation to account for missing data in a pooled cohort (n=21,696)[12] of natalizumab-treated patients from 4 large, observational, open-label studies: STRATIFY-2,[15] STRATA,[16] TOP,[4] and TYGRIS.[17] The orange box highlights the risk of PML during the first year of treatment.

References 1. Miller DH, *et al. N Engl J Med*. 2003;348:15-23; 2. Polman CH, *et al. N Engl J Med*. 2006;354:899-910; 3. Prosperini L, *et al. J Neurol*. 2017;264:284-294; 4. Butzkueven H, *et al. J Neurol Neurosurg Psychiatry*. 2014;85:1190-1197; 5. TYSABRI® (natalizumab) [prescribing information]. Cambridge, MA: Biogen; 2018; 6. Zhovtis Ryerson L, *et al*. Presented at ACTRIMS; February 1–3, 2018; San Diego, CA. LB250; 7. Zhovtis Ryerson L, *et al. J Neurol Neurosurg Psychiatry*. 2016;87:885-889; 8. Bomprezzi R, Pawate S, *Ther Adv Neurol Disord*. 2014;7:227-231; 9. Muralidharan KK, *et al*. Presented at ECTRIMS; September 14–17, 2016; London, UK. P1672; 10. Muralidharan KK, *et al. J Pharmacokinet Pharmacodyn*. 2017;44:263-275; 11. Havrdová E, *et al. Lancet Neurol*. 2009;8:254-260; 12. Ho PR, *et al. Lancet Neurol*. 2017;16:925-933; 13. Rovira A, *et al. Ther Adv Neurol Disord*. 2013;6:298-310; 14. O'Connor P, *et al. Neurology*. 2014;83:78-86; 15. Foley J, *et al. Mult Scler*. 2016;22(Suppl 3):646-647. P1229; 16. Plavina T *et al. Neurology*. 2017; 89:1584-1593; 17. Campagnolo D, *et al. Neurology*. 2016;87(2):e25.
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