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

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Introduction: Natalizumab, a highly efficacious therapy for relapsing-remitting multiple sclerosis (RRMS), is also associated with progressive multifocal leukoencephalopathy (PML) risk. A recent analysis of the TOUCH dataset demonstrated that extended interval dosing (EID) is associated with significantly lower PML risk in anti–JC virus antibody positive patients. There have been no randomized studies to assess EID efficacy.

Objective: To describe the design of a phase 3b study to evaluate the efficacy of EID natalizumab initiated after a stable period of standard interval dosing (SID) compared with continuing SID.

Methods: A prospective, interventional, controlled, randomized, open-label, rater-blinded, global study will be conducted. Eligibility requirements include age 18-60, Expanded Disability Status Scale ≤5.5, RRMS, stable on SID natalizumab for ≥1 year with no relapses in the prior year, no prior immunosuppressant use, and no gadolinium-enhancing (Gd+) lesions at screening. Patients will be randomized 1:1 to natalizumab SID (every 4 weeks) or EID (every 6 weeks). Study duration will be 88 weeks (4-week screening, 72 weeks randomized treatment, 12 weeks follow-up). The primary endpoint is number of new/newly enlarging T2 lesions at 48 weeks. Key secondary endpoints include time to relapse, relapse rate, number of new radiologic lesions, and incidence of serious adverse events. Exploratory endpoints include Timed 25-Foot Walk, Nine-Hole Peg Test, Symbol Digit Modality Test, 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/pharmacodynamics and efficacy.

Results: Approximately 480 patients will be enrolled. The rationale for study sample size, inclusion criteria, dosing intervals, and endpoints will be presented.

Conclusions: This study will provide the first randomized, controlled efficacy data for patients treated with EID natalizumab and will inform on the potential of EID as a future PML risk mitigation strategy.

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