**INTRODUCTION**

Multiple sclerosis (MS) is the most common cause of chronic neurologic disability beginning in early to middle adulthood. In most patients, MS begins as a relapsing–remitting disorder (relapsing–remitting MS, or RRMS), usually changing to a chronic, neurodegenerative condition characterized by progressive neurologic disability.1

- Approximately 10% to 15% of patients begin with a purely progressive course, termed primary progressive MS (PPMS), characterized by no periods of relapse or remission, usually occurring in adults in their late 30s and 40s.
- The unique clinical characteristics of PPMS pose difficulties in excluding other causes of progressive syndromes and in confirming the diagnosis of MS, which is not adequately addressed by current diagnostic criteria.
- Definitive presence of oligoclonal bands (OB) and IgG synthesis along with MRI criteria are immunologic evidence for the disease.
- With optimized, standard methods, >85% of patients with MS have OB or IgG class not clearly attributable to other causes.
- In addition, >95% of patients with PPMS have OB or IgG class not clearly attributable to other causes.
- Currently, there are no approved therapies for PPMS and no treatments effective for the prevention of long-term disability.
- Substantial evidence exists for a pathogenic role of B cells and B-cell lymphocytes in the pathogenesis of MS. Specifically, autoreactive B cells and humoral immune mechanisms play a large role in mediating tissue damage.2
- Rituximab (Riataximab) is a genetically engineered chimeric monoclonal antibody that binds to CD20 on B cells (both mature cells or plasma cells), efficiently depleting them from the peripheral circulation.
- By binding CD20, rituximab depletes CD20-positive B cells through a combination of cell-mediated and complement-dependent cytolysis and the promotion of apoptosis.3
- Cell depletion affects antibody production, cytokines, as well as B-cell–mediated antigen presentation and activation of T cells and macrophages.
- To evaluate the safety and efficacy of rituximab in adults with PPMS, we initiated a 96-week placebo-controlled clinical trial.

**METHODS**

**Design**

- Figure 1 illustrates the Phase IIb study design.
- The trial is a Phase IIb, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the safety and efficacy of rituximab in adults with PPMS. The study is intended to enroll approximately 439 patients at all sites in the United States and Canada.
- The study consists of four periods: screening (Week -4 to Week 0 [Days -28 to -15]), a pretreatment period (Week -2 to Week 0 [Days -14 to -1]), a treatment period (Week 0 to Week 96), and a follow-up period (Weeks 97 to 120).
- A total of 5,852 MRI scans are evaluated over 120 weeks.
- Week -2 to 0
- Weeks 6, 48, 96, 122
- The course of study drug treatment is administered on Days 1 and 15.
- Patients are dosed every 28 weeks, with the last course of treatment administered on Weeks 72 and 74.
- When patients completed the 96-week treatment period, they enter the follow-up period.
- Patients who withdraw or discontinue from the study early are collected for follow-up of safety data for 48 weeks from the time of their last dose of study drug.

**Exclusion Criteria**

- Patients with a history of progression or a relapse prior to Week 56 may discontinue from the treatment period and receive alternative treatment during the safety follow-up period, if judged appropriate by the Principal Investigator. Patients with an exacerbation are allowed to continue in the treatment period, if judged clinically appropriate by the Principal Investigator.
- An external, independent data monitoring committee (DMC) reviews the safety data throughout the treatment period, including MRI and laboratory data. Safety reviews are performed every 3 months. The timelines for DMC meetings will concur with the final study drug inhalation to the first enrolled patient.

**Objectives**

**Primary:**

- To assess the efficacy of rituximab relative to placebo, as measured by the time to confirmed progression of disease in a 96-week treatment period.
- Time to PPMS progression is defined as an increase of ≥0.5 points from baseline Expanded Disability Status Scale (EDSS), if the baseline EDSS was between 2.0 and 5.5 points inclusive, or an increase of ≥1.0 points if the baseline EDSS was ≥5.5 points (inclusive) for which change is not attributable to another etiology (e.g., concurrent fatigue, MS relapse or exacerbation, or concomitant medication).
- Confirmation of disease progression should have occurred at a regularly scheduled visit at least 3 days (96 weeks) after the initial rituximab administration.
- Evaluate the safety and tolerability of rituximab in patients with PPMS.

**Secondary:**

- Evaluate the effect of rituximab compared with placebo in:
  - The change in total volume of brain T2 lesions on MRI scan from baseline to Week 96
  - The change in brain volume (i.e., brain atrophy) on MRI scan from baseline to Week 96

**RESULTS**

- Table 1 shows the pooled demographics from the ongoing blinded trial.
- Approximately half of 439 patients were female with a mean age of 50.4 years. Of the 439 patients randomized, 60.9% had not used any prior MS therapies, 34.1% had stopped therapy ≥90 days before randomization, and 5% were treated with 90 days of disease-modifying therapy.
- Patients entering this trial had advanced PPMS disease as evidenced by EDSS and MRI evaluations.
- A total of 56% had baseline EDSS ≥4.0 with a mean of 4.0 (±0.4) scores since PPMS diagnosis and 3.2 (±0.6) years since MS symptom onset.
- At randomization, patients had a median (SD) gadolinium (Gd)-enhancing lesion count of 12 (±12) per scan, the majority (75%) with Gd-enhancing lesions, but 24.6% with Gd-enhancing lesions.
- Mean Gd-enhancing lesion volume was 42.1 (±18.6) mm^3, mean T2 lesion volume was 1256 (±227) mm^3.

**CONCLUSION**

- This trial required that all patients demonstrated either a positive intrathecal oligoclonal bands (or IgG) index. This might explain why the cohort in this trial had relatively active inflammatory disease on imaging (approximately 25% had enhancing lesions).
- A previous trial (PROMISE study) failed to demonstrate a treatment effect of glatiramer acetate on PPMS; however, PROMISE did not require an inclusion criterion of oligoclonal bands or oligoclonal bands at baseline, and their cohort had less lesion activity at baseline, which may have contributed to the unanticipated low rate of disability progression observed in that study.
- In conclusion, the MRI findings of baseline Gd-enhancement in 25% of patients, with the inclusion criteria of active CSF in all patients, suggest an enrichment for active disease in this trial. The presence of a cohort with greater CNS inflammatory activity may increase the possibility of detecting a therapeutic effect.

**REFERENCES**


