Discussion

• The Natalizumab phase 3B, prospective, randomized, open-label study comparing extended dosing intervals Versus Approval dose (NOVA) study will provide the first randomized, controlled efficacy data for patients treated with extended dosing interval (EDI) of natalizumab.

• In conjunction with prior safety data, the results from this study will provide information on the potential of EDI as a future progressive multifocal leukoencephalopathy (PML) risk mitigation strategy.

• These study results will also help define a benefit-risk profile for natalizumab EDI.

Introduction

• Natalizumab, a highly efficacious therapy for relapse-modifying multiple sclerosis (MSRM), is also associated with risk of PML.

• Natalizumab EDI has been suggested as a strategy to reduce PML risk.

• To date, there have been no randomized studies to compare the efficacy of natalizumab EDI and standard interval dosing (SID).

• In the absence of prospective, randomized efficacy data, no benefit-risk profile has been established for EDI.

• This prospective study will examine if EDI and SID have differential efficacy and will thereby provide information on the benefit-risk profile of natalizumab EDI.

Objective

• To describe the design of a phase 3B study to evaluate the efficacy of natalizumab EDI in patients with relapsing-remitting multiple sclerosis (RRMS) after a stable period of SID compared with the efficacy of continuing SID.

Methods

• NOVA will be a prospective, randomized, interventional, controlled, open-label, multinational study.

• The rationale for the requirement of ≥12 months of disease saturation, lymphocyte counts, and body weight will be confirmed disability worsening or improvement.

• In conjunction with prior safety data, the results from this study will provide information on the potential of EDI as a future progressive multifocal leukoencephalopathy (PML) risk mitigation strategy.

Results

• The EDI intervals in NOVA were chosen to encompass the real-world use associated with the risk of PML observed in the TOUCH analysis (Figure 2).

• The rationale for the requirement of ≥12 months of disease stability on SID before random allocation and switching to EDI is as follows:

• Independent studies suggest comparable efficacy between SID and EDI in switching to EDI (≥12 months).

• Natalizumab: patients initiating EDI may result in inadequate protection from clinical and MRI disease activity.

• Analysis of patients in ARTROMO demonstrates that the efficacy of natalizumab improves after the first year of treatment (Figure 3A).

• 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).

• Thus, inferences for EDI on PML risk mitigation strategy is low during the first year of treatment.

• The number of new or newly enlarging T2 lesions at 48 weeks for the primary endpoint is an objective, while relapse-based endpoints are more prone to objective, while relapse-based endpoints are more prone to

• The sample size (N=480) provides >90% power to detect a difference of 25% in defined outcomes (PML risk in first year in this population) and 0.5% is mean or newly enlarging T2 lesions.

• A recent analysis of the TOUCH Prescribing Program database demonstrated that natalizumab EDI is associated with significantly lower PML risk than in INNOVATE, anti-virus antibody positivity risks.

• Several retrospective studies have indicated that natalizumab efficacy is maintained with EDI dosing schedules ≥14 weeks.

• In addition, partial reversal of natalizumab pharmacodynamic effects, resulting in reactivation of immune responses has been reported to occur 4-6 weeks after the last dose.

• This study evaluated the first randomized, controlled efficacy data for patients treated with natalizumab EDI and will yield a more comprehensive understanding of both the effectiveness and the safety of natalizumab EDI.

Figure 1. NOVA study endpoints and assessments

Figure 2. Rationale for study dosing intervals

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

• A treatment effect of natalizumab are greater after year 1.

• Anti-JCV virus antibody status

• Negative

• Positive

• 0.07 per 1000 patients (95% CI)

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients without previous immunosuppressant use</th>
<th>Patients with previous immunosuppressant use</th>
<th>NSCD (1000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>0.01 (0.00-0.03)</td>
<td>0.01 (0.00-0.03)</td>
<td>0.01 (0.00-0.03)</td>
</tr>
<tr>
<td>13-24</td>
<td>0.09 (0.00-0.24)</td>
<td>0.09 (0.00-0.24)</td>
<td>0.09 (0.00-0.24)</td>
</tr>
<tr>
<td>25-36</td>
<td>0.2 (0.04-0.4)</td>
<td>0.2 (0.04-0.4)</td>
<td>0.2 (0.04-0.4)</td>
</tr>
<tr>
<td>37-48</td>
<td>0.4 (0.10-1.0)</td>
<td>0.4 (0.10-1.0)</td>
<td>0.4 (0.10-1.0)</td>
</tr>
<tr>
<td>49-60</td>
<td>0.5 (0.12-2.4)</td>
<td>0.5 (0.12-2.4)</td>
<td>0.5 (0.12-2.4)</td>
</tr>
</tbody>
</table>

Extended interdosing intervals (≥14 weeks) reduce PML risk compared with standard (≤6 weeks) dosing intervals. A herpetic re-activation is the most likely cause of PML. PML risk is low in the first year of treatment.

P71