These Clinical Study Results are provided for informational purposes only.

The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2. PROTOCOL SYNOPSIS

Protocol number:	BEL-TYS-14-10675
Protocol title:	A Multicenter, Open-Label Safety Study of Natalizumab administered to Subjects with Relapsing Forms of Multiple Sclerosis who participated in STRATA
Version date:	11 August 2014 Version 1 – Final
Study design:	Prospective, non-interventional, multicenter, open label long-term safety study
Study duration:	Up to 24 months
Recruitment period:	From December 2014 to January 2015
Study objectives:	**Primary objective:** The primary objective for this study was long-term safety in patients receiving natalizumab. **Secondary objectives:** Secondary objectives included the long-term efficacy of natalizumab in delaying the progression of disability, reducing the frequency of relapses, decreasing the disease activity observed by magnetic resonance imaging (MRI), and the evaluation of the quality of life and cognitive function in patients on treatment with natalizumab for more than 8 years.
Endpoints:	**Primary endpoint:** The primary endpoint of the open label study was the incidence of adverse events (AEs) and serious adverse events (SAEs). **Secondary endpoints:** The secondary endpoints of this study were: • Disability progression as determined by Expanded Disability Status Scale (EDSS) (based on neurological examination, "physical EDSS") every 6 months, • Multiple sclerosis (MS) disease activity as determined by the occurrence of clinical relapses (distribution of the total number of relapses over 2 years), • JC virus (JCV) status (anti-JCV antibody positive or negative according to the STRATIFY JCV® Test, Unilabs, Denmark), • Frequent MRI monitoring according to the Belgian Study Group for MS (BSGMS) guidelines, • Health-related quality of life (HRQoL) measurement by EuroQol-5 Dimensions (EQ-5D) every 6 months, • Cognitive evaluation by Symbol Digit Modalities Test (SDMT) every 6 months.

Study population:	Patients with relapsing-remitting MS who participated in STRATA, had stable disease for at least 7 years during STRATA, and did not meet reimbursement criteria for Tysabri® in Belgium, upon termination of the STRATA study. **Inclusion Criteria** 1. Had the ability to understand the purpose and risks of the study and provided signed and dated informed consent and any authorizations required by local law in accordance with national and local subject privacy regulations. 2. Had participated in the STRATA study, had stable disease and did not meet reimbursement criteria for natalizumab (Tysabri®) in Belgium, upon termination of the STRATA study. 3. Were ≥18 years old. 4. Patients of child bearing potential had to practice effective contraception during the study and be able to continue contraception for 3 months after their last infusion. **Exclusion Criteria** 1. Patients participating in STRATA who were in line with current Belgian reimbursement criteria when they started in one of the feeder studies (Affirm or Sentinel). 2. Patients with any significant change in clinical status that, in the opinion of the Investigator, would have made them unsuitable to participate in this study. The Investigator had to review the patient's medical fitness for participation and consider any diseases that would have precluded treatment. 3. Patients that were unwilling or unable to comply with study requirements, or were deemed unsuitable for study participation as determined by the Investigator. 4. Female patients who were considering becoming pregnant while in the study. 5. Female patients of childbearing potential who were not using the appropriate contraception as determined by the Investigator. 6. Female patients who were currently pregnant or breastfeeding. 7. Any prescheduled elective procedure during the study period that, in the opinion of the Investigator, would have interfered with study parameters. 8. Any other condition, clinical finding, or reason that, in the opinion of the Investigator, was determined to be unsuitable for enrollment into this study.
Number of patients:	10 patients in 4 sites in Belgium were planned for enrollment.
Visit schedule:	Eligible patients were planned to receive natalizumab under this protocol for up to 24 months. After the Baseline/Enrollment Visit, clinic visits occurred at month 6 (week 24), month 12 (week 48), month 18 (week 72) and month 24 (week 96). The End of Treatment Visit was the month 24 visit. Patients who discontinued natalizumab early completed the same assessments specified for the End of Treatment Visit.

Assessments:	**Clinical safety assessments:** The following clinical assessments were performed to assess the safety profile of natalizumab: • Natalizumab pre-infusion checklist, • Physical and neurological examinations, • Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure and respiratory rate, • Monitoring of AEs and SAEs (except for hospitalizations due to MS relapses that are non-fatal), • Monitoring of concomitant medications, • MRI. **Laboratory safety assessments:** The following laboratory test was performed to assess the safety profile of natalizumab: • Anti-JCV antibodies (STRATIFY JVC® Test, Unilabs Denmark). **Clinical efficacy assessments:** The following clinical tests/assessments were performed to assess the efficacy of natalizumab: • Clinical relapses, • EDSS, • EQ-5D, • SDMT.
Statistical Analysis:	All statistical analyses were descriptive.
Interim Analyses:	There was no interim analysis performed for this study.

3. SUMMARY OF RESULTS AND CONCLUSIONS

Number of patients (planned and analyzed):

The study projection was for 10 patients to participate in the study; 7 patients were enrolled and were included in the analysis (full analysis set).

Criteria for Evaluation:

Primary endpoint:

The primary endpoint of the open label study is the incidence of AEs and SAEs.

Secondary endpoints:

The secondary endpoints of this study were:

- Disability progression as determined by EDSS (based on neurological examination, "physical EDSS") every 6 months,
- MS disease activity as determined by the occurrence of clinical relapses (distribution of the total number of relapses over 2 years),
- JCV status (anti-JCV antibody positive or negative according to the STRATIFY JCV® Test, Unilabs, Denmark),
- Frequency of MRI monitoring according to the BSGMS guidelines,
- HRQoL measurement every 6 months, using the EQ-5D questionnaire,
- Cognitive evaluation by SDMT every 6 months.

Results:

Primary endpoint

- Overall, 10 AEs were reported in 5 patients over the 2 year-study period. None of the AEs was assessed by the Investigator to be related to the study treatment. Each AE was only reported once (except for urinary infection, which was reported twice).
- One SAE was reported for 1 patient. This SAE was a right malleolar fracture. Although the causality was not reported, this AE seems very unlikely to be related to the study treatment.
- There was no fatal AE reported during the study.

Secondary endpoints

- EDSS score: For each patient, the EDSS score remained stable throughout the study period, with differences between the first and the last assessments limited to maximum 0.5. The median EDSS score in the study population remained stable throughout the study period (range: 2.0 to 2.5).
- MS disease activity: MS disease activity was assessed by the occurrence of clinical relapses over the study period. The MS relapses were to be reported as AEs or SAEs and no MS relapse was reported throughout the study.
- Anti-JCV status: Overall, the available information decreased with time, from 7/7 patients at week 0 to 0/7 patients at week 96. Therefore, a robust comparison of the proportion of positive patients at each timepoint was not possible. However, from an individual point of view, the anti-JCV status remained generally stable. One patient moved from a negative status to a positive status between

week 48 and week 72, while other patients were positive at study start and remained positive throughout the study period.

- MRI monitoring: The proportion of MRI assessments performed in line with the BSGMS guidelines was low on weeks 24 and 48. Most of these assessments were performed 6 months after the previous assessment while, for JCV-positive patients with MS for 3 years or more, the guidelines recommend an MRI every 4 months. On weeks 72 and 96, 2 patients (40% and 50% of the patients still in the study, respectively) had a documented MRI performed within 4 months, which was in line with the BSGMS guidelines.
- HRQoL: Overall, the self-estimated quality of life was good, with a median EQ-5D score ranging from 7.00 to 7.50 across timepoints (mean: 6.73 to 7.75). No trend in the evolution of the EQ-5D score could be observed, either from an individual or an overall point of view.
- Cognitive evaluation: Overall, the test was performed on most timepoints for the patients still in the study. However, the scores of the SDMT were rarely reported (only 2 times for 1 patient), which did not allow for a proper evaluation of this assessment.