The French Health Products Safety Agency is now in the final stage of the establishment of a prospective cohort of MS patients in collaboration with national network of neurologists and pharmacovigilance regional centres. A synopsis of the study is provided below. This study is planned to start in November 2007.

Name of Product: TYSABRI®

Protocol Title: Cohort of multiple sclerosis patients treated with natalizumab using the French European Database for Multiple sclerosis -TYSEDMUS

Study Duration: The study is anticipated to last for 5 years	**Phase of development:** 4 Post-authorisation

Objectives:

Primary:

- To characterize the safety profile of natalizumab (short, mid and long term) and determine the incidence of adverse events of special interest; specifically infusion related events, hypersensitivity reactions, antibodies against natalizumab and persistent antibodies, serious infection and particularly opportunistic infections, cardiovascular events, pregnancies and their issues, malignancies and other signal detected in post marketing in patients treated with natalizumab in a real life setting.

Secondary:

- To describe the clinical evolution of patients treated with natalizumab.
- To determine the utilisation patterns of the product in a real life setting and to follow the proper use of natalizumab.
- Comparison of incidence of serious infections and particularly opportunistic infections and malignancies in the natalizumab exposed population versus a non exposed one.

Primary Study Endpoints:

- Occurrence of adverse events of special interest

Secondary Study Endpoints:

- EDSS score, number and frequency of relapses
- Characteristics of treated patients (MS diagnosis, number of relapses in past 12 months, date of MS diagnosis)
- Utilisation data with regards to the EU SPC (treatment duration, frequency of infusions, concomitant treatment, discontinuation rate and reasons, respect to contra-indications,)

Confounding factors and others variables

- History of immunosuppressive and antineoplastic therapies

Study Design:

This is a multicentric cohort study of multiple sclerosis patients treated and non treated with TYSABRI®. The cohort consists of patients who are registered in the French European Database for Multiple sclerosis.

Study Population:

The European database for multiple sclerosis (EDMUS) project was created in January 1990 with the objectives of :

- developing and diffusing a software allowing to capture data about patients affected with multiple sclerosis (MS)
- increasing the use of such a software in order to improve **treatments and care** of the patients with MS in the clinics of neurology
- using the software's **standardised language** to perform clinical and scientific studies on multiple sclerosis, in order to enlarge our knowledge of the disease and the treatment possibilities. These activities may either be monocenter- or metacentre-oriented and carried out at the local, national or

international level

- creating **a network** of the centres who use the EDMUS system, through sharing of the essential data on their patients with MS and creating a central database about MS

In France, 42 centres including the major neurological centres of French Hospitals with best experience in MS used the EDMUS software and are involved in the EDMUS network. Data on Approximately 20 000 MS patients had been entered in the database corresponding to 1/3 of the estimated French MS population.

Patients will be recruited from all prescribes of TYSABRI in France who have accepted to participate to the current study. In all cases, the decision to treat the patient will be made prior to the decision to enter the subject into the study.

Inclusion and non inclusion criteria:

Patients are included in the study if they meet the following inclusion criteria:

- Patients with a confirmed diagnosis of multiple sclerosis

Patients are excluded if they do not have a confirmed diagnosis of MS.

Exposed and non exposed patients

Exposed subjects:

- Treated at least once with TYSABRI®.

Non exposed subjects :

- Registered in the French European Database for Multiple sclerosis.
- Never treated with natalizumab but treated or not with chronic therapy.

Estimated Number of Patients: The estimate of TYSABRI® exposure in France is about 4500 patients from 2007 to 2012.

Study power:

The study is designed to estimate an incidence of AE of 0.5% with a relative precision of 40%.

Statistical Analysis:

Descriptive statistics will be used for patient demographics, prescribers characteristics.

Data from any subject in whom natalizumab has been used outside of the authorized use i.e. off label will be described. Data summaries will also be provided by region.

Incidence rates of adverse events of special interest together with 95% two-sided confidence intervals will be provided. Kaplan-Meier procedures will be used to characterize time to onset of adverse events of special interest.

A stratified analysis on gender, age, date of diagnosis and region will be conducted.

To estimate the tysabri® treatment effect on the AEs occurrence, analytical statistics using Log rank tests and Cox proportional hazards models or Poisson regression will be performed.