Title of Trial: Post-authorisation safety study (PASS) to assess the potential association between the safety profile of interferon beta-1a and the body mass index and other pharmacodynamic markers during the titration dose phase in patients with remitting-relapsing multiple sclerosis.

Investigational Product: Interferon β-1a (IFN-beta-1a, Rebif®)

Trial No.: 26756

Study Centers: This study was conducted in 12 centers.

Trial Initiation Date: 31 July 2008

Trial Completion Date: 15 November 2010

Development Phase: Phase 4

Publication (reference): Not published at the time of issuing this report.

Study Objective:

The study endpoints included the levels of the three biomarkers throughout the titration period and the relationship between these biomarkers and the body mass index and the safety profile.

Methodology:

Postmarketing surveillance multicentre single group study to evaluate the association between body mass index (BMI) and frequency of adverse reactions or change of biological surrogate markers in subjects during the titration phase receiving interferon beta-1a. This was a safety post-authorization multicentre single group study. Blood samples had to be taken at four different times. Treatment was administered according to the SmPC of the product (Rebif®) and subjects were controlled as per usual clinical practice in every participant centre. Any adverse event that could have taken place along the study was monitored and recorded properly.

Number of Subjects (Planned and Analyzed):

Up to 100 subjects of both sexes with relapsing multiple sclerosis were intended to be recruited, from 19 planned centres contributing with 4-6 subjects each.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Subjects were selected if aged between 18 and 60 years, were diagnosed with relapsing-remitting MS, had had one or more relapses within the prior 12 months, and had not been previously treated with IFN-β or other immunomodulators. Their EDSS score had to range between 0 and 5.5, with no coexistent severe clinical disease or relevant analytical abnormalities. They all signed an informed consent.

Study Treatment:

IFN-β1a (Rebif®, Merck Serono) was administered subcutaneously starting on day 1 at a dose of 8.8 µg 3 times per week and during the following 2 weeks. At day 14th, the dosage was increased to 22 µg 3 times per week and maintained during the following 2 weeks, till day 28th when the final dosage of 44 µg was reached. Subjects finished the study on day 56 and were treated thereafter according to their physician's criteria (maintain Rebif or not). The duration of treatment 4 weeks. From the 5th week on, subjects continued on the tailored dose as per physician's criteria (maintain Rebif or not).

Duration of Treatment: 4 weeks. From the 5th week on, patients continued on the tailored dose as per physician's criteria.

Criteria for Evaluation:

Primary: Potential relevant positive or negative association (r >0.5 or <-0.5), between BMI on one hand, and any of the pharmacodynamic surrogate markers or the reported adverse events, on the other hand.

Secondary: Potential relevant positive or negative association (r >0.5 or <-0.5), between any of the pharmacodynamic surrogate markers and the reported adverse events.

Statistical Methods:

The population to be analysed was formed by all the subjects included (intent to treat analysis – ITT). The possible association between the magnitude of the more frequent adverse events (namely, hypertransaminasemia, leukocytopenia and plaquetopenia) and the level of biological markers **(**β2-microglobuline, neopterin and 2'- 5'OAS) was explored. The presence or nor of qualitative adverse events (i.e., flu-like syndrome) defined two discrete populations, whose changes in biological markers were compared by means of the t- or U- tests, depending on the case.

Results:

Subject Disposition: Overall, 84 subjects were finally enrolled in the study, of which one was lost to follow up after the first visit, so there were 83 patients fully studied in the end.

Demographics and Baseline Characteristics: Mean weight (kg) was 70.7 (SD: 17.0), Height (cm) was 166.3 (9.7), age (years) was 36.6 (9.2), time from diagnosis to therapy (days) 16.4 (3.95), EDSS at recruitment 1.68 (0.97), BMI (kg/m^2) was 25.5 (5.5). There were 33.7% males, and BMI was normal in 60.2%, overweight in 25.3% and obese in 14.5%.

Safety Results: A statistically significant decrease of the mean value of the next variables was observed in the enrolled subjects along the study period between the last and the basal visit: leukocytes (-31.3%), granulocytes (-39.5%), lymphocytes (-24.1%) and platelets (- 23.3%). Conversely, there was an increase of the mean for the following variables: GOT (94.9%), GPT (129.5%) and GGT (89.5%) regarding the baseline. Biomarkers had also a significant increase

when comparing their means on the 56th day and baseline: β2-microglobulin (45.3%), 2-5OAS (262.8%) and neopterin (92.8%).

Overall, headache was reported by 15 subjects (18.1%), influenza-like syndrome by (33.7%), and local reactions to the administration of IFN-β took place in 11 subjects (13.3%). No differences were found between BMI categories.

Conclusions:

The primary hypothesis that BMI index could predict a higher risk of adverse events or changes of biochemical or hematologic values was not met. Moreover, biomarkers were not useful neither in terms of discriminating the likelihoodness of qualitative adverse events nor of any clinically significant variations of analytical values.