Title of Trial: Multicenter, open-label, 12 weeks Phase IV study to assess adherence to treatment in relapsing remitting multiple sclerosis (RRMS) subjects switching from other injectable DMDs using ReBiSmart™ to self-inject Rebif® New Formulation (RNF) in a multi-dose cartriDGE

Investigational Product: Rebif® New Formulation (RNF)

Trial No.: EMR 701048-525

Study Center: This study was conducted in total of 20 centers in Italy

Trial Dates:

Trial Initiation Date: 10 October 2009

Trial Completion Date: 31 August 2010

Development Phase: Phase IV

Publication (reference): NA

Study Objectives:

Primary Objective:

- To assess adherence over 12 weeks of treatment in patients with RRMS switching from other injectable DMDs using ReBiSmart™ to self-inject RNF in a multi-dose cartridge

Secondary Objective:

- To assess overall patient satisfaction in administering RNF by ReBiSmart™ using Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) items 13-23, 35 and 36-38
- To assess longitudinal changes in anxiety symptoms as measured by the Hospital Anxiety and Depression Scale (HADS)
- To evaluate the correlation between the assessment of adherence at the end of treatment and assessment of cognitive function by Paced Auditory Serial Addition Task (PASAT) at Baseline
- To determine overall patient evaluation of ReBiSmart™ use by a Convenience Questionnaire at the end of treatment

Safety Objective:

- To monitor the incidence of Treatment-Emergent Adverse Events (TEAEs), including serious adverse events (SAEs), and laboratory parameters, physical examination, concomitant medications and procedures

Methodology:

The dose of RNF will be titrated up from 8.8 µg during the initial four weeks. Thereafter, the patients will receive a final dose of RNF 44 µg sc tiw by ReBiSmart™. Adherence to treatment over the 12-week period is calculated as 100 x the number of completed

injections the patient administered divided by the scheduled number of injections over 12 weeks. The patients will be assessed at Screening, Baseline, Weeks 4, 8 and 12. Adherence to treatment will be measured at Weeks 4, 8, and 12. The patients will fill in the MSTCQ items 13- 23 (Side Effects) for subscales flu-like symptoms (FLSs), injection site reaction (ISRs), and Global Side-Effects (GSEs), item 35 (Benefits), items 36-38 [Short- Form McGill Pain Questionnaire, Visual Analogy Scale (VAS), and Rating of Pain] regarding injection pain at Weeks 4, 8, and 12. Cognitive function will be assessed by PASAT at Baseline. The patients will fill in HADS to capture their specific anxiety at Baseline, Weeks 4, 8, and 12 of treatment. Neurological examinations including Expanded Disability Status Scale (EDSS) will be performed at Baseline and Week 12. Physical examination including recording of vital signs will be performed at Screening, Baseline and at Weeks 4, 8, and 12 while routine laboratory tests at Screening and at Week 12. The patients will fill in the Convenience Questionnaire on the overall evaluation of ReBiSmart™ use at Week 12. Assessment of Safety will be based on incidence, severity, and relationship to treatment of TEAEs, SAEs, clinically significant changes in routine haematology, chemistry and urinalysis laboratory tests, physical examination including recording of vital signs including SAP/DAP, HR and BT, neurological examination including EDSS

Number of Subjects (Planned and Analyzed):

Number of planned Patients: 120

Number of analysed Patients: 119

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria

- Males and females between 18 and 65 years of age
- Female patients must be neither pregnant nor breast-feeding and must lack child-bearing potential
- Have RRMS according to the revised McDonald Criteria (2005)
- Eligible for treatment with RNF (44 µg)
- Patients switching from another injectable DMD
- Able to self-inject treatment using ReBiSmart™
- Willing and able to comply with the protocol for the duration of the study
- Have given written informed consent

Exclusion criteria:

- Have any disease other than MS that could better explain his/her signs and symptoms
- Have received any immunosuppressive agents within 3 months prior to Baseline
- Have a relapse within 30 days prior to Baseline
- Have inadequate liver function, defined by alanine aminotransferase (ALT)
- 3 x upper limit of normal (ULN), or alkaline phosphatase > 2 x ULN, or total bilirubin > 2 x ULN if associated with any elevation of ALT or alkaline phosphatase
- Have inadequate bone marrow reserve, defined as a white blood cell count less than 0.5 x lower limit of normal (LLN)

- Have moderate to severe renal impairment
- Any visual or physical impairment that precludes the patients from self- injecting the treatment using ReBiSmartTM
- Have any contra-indications to treatment with IFNβ-1a according to Summary of Product Characteristics
- Have any contra-indications to treatment with ibuprofen according to Summary of Product Characteristics
- Have participated in any other investigational trial within 30 days from Baseline
- Have any other significant disease that in the Investigator's opinion would exclude the patient from the trial

Study Treatment:

Test Product: Dose and Mode of Administration:

RNF has been supplied as a sterile solution in a pre-filled multi-dose cartridge. Each cartridge pre-filled with 1.5 ml of solution contains 132 µg of IFNβ-1a. The cartridge is designed to deliver 3 individual doses of 0.5 ml solution for injection containing 44 µg of IFNβ-1a. The cartridge is ready to use for administration of RNF sc by ReBiSmart™. The excipients are: Mannitol, Poloxamer 188, L-Methionine, Benzyl alcohol, Sodium acetate buffer, Acetic acid for pH adjustment, Sodium hydroxide for pH adjustment, Water for injection, pH 3.7 to 4.1.

Duration of Treatment: The treatment period is 12 weeks

Reference Therapies, Dose and Mode of Administration:

Not applicable

Criteria for Evaluation:

Primary endpoint:

Proportion of patients with at least 80% of completed injections at Week 12 of treatment. ReBiSmart™ records an injection as completed (light to go off) when the 0.50 ml solution containing 44 µg of IFNβ-1a, or different volume and dose during titration period, has been injected [ReBiSmart™ data connected to e-Case Report Form (CRF)]. Adherence is calculated as 100 x the number of injections the patient administered divided by the expected number of injections over 12 weeks.

Secondary endpoints:

- Changes in MSTCQ scores of items 13-23 (Side Effects) for subscales flu-like symptoms (FLS), injection site reaction (ISR), and GSEs; item 35 (Benefits); items 36-38 (Short-Form McGill Pain Questionnaire, Visual Analogue Scale [VAS], and Rating of Pain) regarding injection pain at Weeks 4, 8, and 12 of treatment
- Changes in HADS scores at Weeks 4, 8, and 12 of treatment from Baseline
- Overall evaluation of ReBiSmart™ use based on Convenience Questionnarie at Week 12 of treatment
- Reasons of missed injections
- Proportion of patients prematurely terminated and reasons for premature termination

from treatment

- Correlation of adherence assessed at end of treatment with PASAT score at Baseline

Safety endpoint:

Safety monitoring: Occurrence of TEAEs, including SAEs, and laboratory parameters, physical examination, concomitant medications and procedures. All Patients who received at least one dose of Rebif were assessed for clinical safety and tolerability and were included in the safety analyses. All AEs and SAEs reported while patients are on-study or within 30 days after discontinuing treatment will be tabulated. Patients who prematurely withdraw from the study will be displayed in a by- Patient listing, and summarised by primary withdrawal reason.

The appearance of AEs will be assessed at each visit. Withdrawal from the study is warranted upon any of the following:

- Patient request
- Investigator request
- Evidence of severe systemic disease

Evidence of severe treatment-related (IFNβ-1a) AEs or laboratory results

Statistical Methods:

Primary endpoint:

The proportion of compliant patients and its 95% CI will be computed. The primary analysis will be conducted on the Intention-To-Treat (ITT) population. The Per Protocol (PP) population will be analysed as well.

Percent compliance at a time point will be calculated as 100 x the number of injections the patient administered divided by the expected number of injections at that time point. A patient will be classified as "compliant" with an adherence at 12 weeks of ≥80%. Repeated measures analysis of variance (RMANOVA) will be conducted on adherence with time as "within" factor.

Secondary endpoints:

The evolution of ordinal scores (MSTCQ subscales, HADS, ratings) over time will be analysed by means of a Friedman nonparametric test. Some MSTCQ items will be reported descriptively. VAS will be assessed with a RMANOVA while change of EDSS scores between Baseline and Week 12 by Wilcoxon test. Convenience Questionnaire, reasons of missed injections and for withdrawal from the study will be analysed descriptively. The predictive value of PASAT to assess non-compliance will be assessed by Student *t*-test. Adherence and PASAT scores will be correlated non-parametrically using Spearman's ρ correlation Iin case of non-normality.

Sample size is based on the estimate that 80% of patients treated for 12 weeks will be 80% adherent to treatment. In this case, a sample size of 120 patients produces a 95% CI equal to the sample proportion plus or minus 7%.

Safety endpoint:

Clinically significant changes of laboratory tests and vital signs will be summarised in shift-tables. Other TEAEs will be summarised descriptively.

The number of MS relapses during the 12 weeks of the study will be recorded. Other safety endpoints will include SAEs, changes in laboratory parameters and vital signs, neurological examination, need for concomitant medications and procedures.

Results:

Efficacy:

A total of 125 patients were screened and 119 were included. 109 patients completed the study while 10 discontinued treatment. The mean (± SD) age was 37 (9.7) years, 76% of patients were women, with mean duration of MS of 5.8 (5.31) years; mean PASAT score of 42.7 (11.14) and mean Expanded Disability Status Scale (EDSS) score of 2.1 (1.2).

Primary endpoint:

In the ITT population, 88.2% (105/119) of patients administered ≥80% of scheduled injections at Week 12, with 95% CI from 82.4% to 94.0%. Therefore, the primary endpoint anticipated by the BRIDGE Study was met (Table 11-8 and Figure 11-2). Same results were obtained in the PP population, i.e. 99 patients: 93% (92/99) of patients in the ITT population self-administered ≥80% of injections at Week 12. As expected, treatment adherence declined significantly ($p<0.001$) from Week 4 (99.2%) to Week 12 (81.5%) but, at Week 12, it was always >80%. Adherence was similarly high for patients with EDSS score ≤3.5 (88%; 85/97) and those with EDSS score >3.5 (89%; 17/19). Adherence was not influenced by DMDs, PASAT, EDSS, gender, age and other baseline variables. Patients who administered 100% of scheduled injections at Week 12 (part of the ITT population) shows that 67.2% of patients (80/119) administered all (100%) of scheduled injections at Week 12.

Overall, the reasons for non-compliance (missed injections) were: medical (36%); forgotten injections (21%); and other reasons (28%).

In addition, pain at the injection site and problems using the self-injection device accounted for 3.4% and 5.7% of missed injections, respectively.

At Weeks 4 and 8, the majority of missed injections were due to medical reasons (46.4% and 44.1%, respectively).

At Week 12, the majority of missed injections were due to forgetfulness (41.7%) while medical reasons accounted for 12.5% of missed injections.

Secondary endpoints:

Statistical analysis showed that all items of MSTCQ related to FLS improve significantly over time ($p= 0.002$) while those relevant to GSEs significantly worsen over time ($p= 0.002$) and ISR score shows no significant changes ($p= 0.902$).

Item 37 related to VAS ($p<0.001$) as well as that to MSTCQ item 38 worsen significantly over time ($p<0.001$ for both). Also HADS items do not vary significantly ($p= 0.156$ and $p= 0.482$ for anxiety and depression, respectively) but show a tendency to improve

over time.

Overall convenience was consistently reported by patients in MSTCQ (item 35) as the most important benefit of the electronic self-injection device at Weeks 4 (38%), 8 (42%) and 12 (45%). At Week 4, the next most important benefits reported by patients were less injection pain (24%), and fewer FLSs at Weeks 8 and 12 (20% and 24%, respectively). The overall mean (±SD) evaluation score was 1.6 (±0.59) on a scale of 0–5 where lower scores indicate greater convenience. Overall patient evaluation of the electronic self-injection device at the end of treatment are summarised as follows: in general, the device was rated as highly convenient to use by the majority of patients. Most patients thought the device was very easy to hold (56%), it was very easy to inject (62%), change the cartridge (74%), and needle attachment (56%), it was very easy to detach the needle (56%), and transport (58%), compact/portable (50%); a minority of patients (44%) thought the device was attractively designed, quiet (44%), had comfort setting (47%), and it was easy to change the batteries (36%).

Safety endpoint:

Four hundred twenty-three AEs were reported, 98.8% were mild or moderate in severity and 62% possibly/probably treatment-related. Only one SAEs occurred (bone fracture after accidental fall) and it required hospitalisation. As expected, the most common TEAEs were FLSs (136 occurrences in 50% of patients), nervous system disorders (87 occurrences in 35% of patients) and ISRs (36 occurrences in 23.5% of patients).

The laboratory results showed expected changes that are associated with IFNβ- 1a treatment, like abnormal liver function test, slight change in renal function and thrombocytopenia. The Student's t-test shows that there are significant differences for platelet count, transaminases, T4 and proteins in urine but all the values remained within the normal ranges. These findings were observational and the study was too short to see definitive changes in liver function tests or other parameters. The analysis of vital signs shows that, at Baseline, there were some clinical significant values which actually were not present at Week 12

Conclusion:

The BRIDGE Study met the primary endpoint anticipated by the protocol: over 80% of patients self-administered at least 80% of scheduled injections over the 12-week course of the study. Convenience and ease of use were the main benefits of the device, consistent with previous studies. No safety issues have been raised.