ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 06/18/2015

ClinicalTrials.gov ID: NCT00110396

Study Identification

Unique Protocol ID:	25632
Brief Title:	Rebif New Formulation (RNF) in Relapsing Forms of Multiple Sclerosis
Official Title:	A Multicentre, Single Arm, Open-Label, Phase IIIB Study to Evaluate the Safety and Antigenicity of Rebif® (Interferon-beta-1a) in Subjects With Relapsing Forms of Multiple Sclerosis
Secondary IDs:	

Study Status

Record Verification:	June 2015
Overall Status:	Completed
Study Start:	January 2005
Primary Completion:	April 2007 [Actual]
Study Completion:	April 2007 [Actual]

Sponsor/Collaborators

Sponsor:	EMD Serono
Responsible Party:	
Collaborators:	Pfizer

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes

	Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: BB-IND-5371 Serial Number: 276 Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 12/09/2004 Board Name: Coast IRB, LLC Board Affiliation: Department of Health and Human Services Phone: 949-218-9969 Email: info@coastirb.com
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary:	The primary objective of the study is to compare the immunogenicity of the new fetal bovine serum (FBS)-free/human serum albumin (HSA)-free Rebif® formulation (RNF) to historical data.
Detailed Description:	As has been seen with other recombinant protein molecules, the use of injectable recombinant proteins may result in the development of neutralising antibodies (NAbs). Antibodies are considered neutralising by their ability to inhibit the biological effect of interferon in a bioassay system. EMD Serono has actively pursued improvements in the formulation of interferon (IFN) beta-1a to reduce aggregate levels and to develop a formulation that is HSA-free. Reducing aggregates should reduce antigenicity of the product while removal of HSA may have an unpredictable effect on antigenicity. EMD Serono will conduct a study to assess the immunogenicity and safety of the new HSA-free formulation, manufactured using IFN-ß-1a drug substance produced by a new clone from the FBS-free process.

Conditions

Conditions:	Multiple Sclerosis
Keywords:	Multiple Sclerosis Relapsing forms of multiple sclerosis

Study Design

Study Type:	Interventional

Primary Purpose:	Treatment
Study Phase:	Phase 3
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	260 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Rebif New Formulation Cohort	Biological/Vaccine: Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week. Total study period is 96 weeks.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	60 Years
Gender:	Both
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- Participant has a relapsing form of Multiple Sclerosis (MS); diagnosis of MS is in accordance with the McDonald criteria
- Participant is eligible for interferon therapy
- Participant is between 18 and 60 years old
- Participant has an Expanded Disability Status Scale (EDSS) < 6.0.
- Participant is willing to follow study procedures
- Participant has given written informed consent
- Female participants must be neither pregnant nor breast-feeding, and must lack childbearing potential, as defined by either:
- Being post-menopausal or surgically sterile, or

- Using a hormonal contraceptive, intra-uterine device, diaphragm with spermicide or condom with spermicide for the duration of the study.
- Confirmation that the participant is not pregnant must be established by a negative serum or urinary hCG test within 7 days prior to start of study treatment. A pregnancy test is not required if the participant is post-menopausal or surgically sterile.

Exclusion Criteria:

- Participant has a Clinically Isolated Syndrome (CIS), Primary Progressive MS, or Secondary Progressive MS without superimposed relapses.
- Participant had any prior interferon beta therapy (either beta-1b or beta-1a)
- Participant has an ongoing MS relapse.
- Participant received any other approved disease modifying therapy for MS (e.g. glatiramer acetate) or any cytokine or anti-cytokine therapy within the 3 months prior to Study Day 1(SD1).
- Participant had prior use of cladribine or has previously received total lymphoid irradiation.
- Participant received oral or systemic corticosteroids or adrenocorticotropic hormone (ACTH) within 30 days of SD1.
- Participant received intravenous immunoglobulins or underwent plasmapheresis within the 6 months prior to SD1.
- Participant received immunomodulatory or immunosuppressive therapy (including but not limited to cyclophosphamide, cyclosporin, methotrexate, azathioprine, linomide, mitoxantrone, teriflunomide, natalizumab, laquinimod, Campath) within the 12 months prior to SD1.
- Participant requires chronic or monthly pulse corticosteroids during the study.
- Participant received any investigational drug or experimental procedure within 12 weeks of SD1.
- Participant has inadequate liver function, defined by a total bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or alkaline phosphatase > 2.5 times the upper limit of the normal values.
- Participant has inadequate bone marrow reserve, defined as a white blood cell count less than 0.5 x lower limit of normal.
- Participant suffers from current autoimmune disease.
- Participant suffers from major medical or psychiatric illness that in the opinion of the investigator creates undue risk to the subject or could affect compliance with the study protocol.
- Participant has a known allergy to IFN or the excipients.

Contacts/Locations

Study Officials: Bettina Stubinski, MD
Study Director
Merck Serono SA - Geneva

Locations: United States, Massachusetts
Local US Medical Information
Rockland, Massachusetts, United States, 02370

References

Citations: [Study Results] Giovannoni G, Barbarash O, Casset-Semanaz F, Jaber A, King J, Metz L, Pardo G, Simsarian J, Sørensen PS, Stubinski B; RNF Study Group. Immunogenicity and tolerability of an investigational formulation of interferon-beta1a: 24- and 48-week interim analyses of a 2-year, single-arm, historically controlled, phase IIIb study in adults with multiple sclerosis. Clin Ther. 2007 Jun;29(6):1128-45. PubMed 17692727

[Study Results] Giovannoni G, Barbarash O, Casset-Semanaz F, King J, Metz L, Pardo G, Simsarian J, Sørensen PS, Stubinski B; Rebif New Formulation Study Group. Safety and immunogenicity of a new formulation of interferon beta-1a (Rebif New Formulation) in a Phase IIIb study in patients with relapsing multiple sclerosis: 96-week results. Mult Scler. 2009 Feb;15(2):219-28. doi: 10.1177/1352458508097299. Epub 2008 Aug 28. PubMed 18755819

Links: URL: http://www.mslifelines.com
Description Full FDA approved prescribing information can be found here

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	Participants were enrolled from 25 Jan 2005 and attended the last visit on 16 April 2007. Two hundred and eighty two participants were screened for enrollment and 260 were enrolled.
Pre-Assignment Details	Screening phase of up to 28 days before the start of interferon-beta-1a treatment. There were 47 centres in: Argentina (5), Australia (4),Canada (1), Denmark (1),Ireland (2), Israel (2), Lithuania(2), Russia (10), Spain (4), Sweden (1), UK (5) and US (10). 1 additional centre in Australia screened 1 participant who was not enrolled into the trial.

Reporting Groups

	Description
Rebif New Formulation (RNF) Cohort	Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week

Overall Study

	Rebif New Formulation (RNF) Cohort
Started	260
Completed	224 [1]
Not Completed	36

	Rebif New Formulation (RNF) Cohort
Adverse Event	15
Lost to Follow-up	1
Administration of plasmapheresis	1
Initiated mitoxantrone therapy	1
Lack of Efficacy	1
Decided not to continue treatment	1
Patient non-compliance	1
Patient refused to continue	1
Patient refused to participate	1
Patient will	1
Patient's decision	1
Participation in MS vaccine study	1
Pregnancy	1
Pregnancy (Protocol violation)	2
Protocol Violation	2
Patient refused to come back	1
The patient has refused	2
The patient has refused to visit site	1
Patient is to be administered copaxone	1

[1] 260 participants included in the Safety Population.207 completed treatment. 224 completed the trial

Baseline Characteristics

Reporting Groups

	Description
Rebif New Formulation (RNF) Cohort	Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week

Baseline Measures

	Rebif New Formulation (RNF) Cohort
Number of Participants	260
Age, Categorical [units: participants]	
<=18 years	0
Between 18 and 65 years	260
>=65 years	0
Age, Continuous [units: years] Mean (Standard Deviation)	34.9 (9.5)
Gender, Male/Female [units: participants]	
Female	186
Male	74
Region of Enrollment [units: participants]	
Argentina	14
Australia	10
Canada	4
Denmark	4
Ireland	4
Israel	4
Lithuania	20
Russian Federation	134
Spain	13
Sweden	5
United Kingdom	23
United States	25

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants Who Were Neutralising Antibody (NAb) Positive at the Week 96 Visit.
Measure Description	The NAb positive value was defined as NAb value greater or equal to 20 NU/mL. NAbs were detected using a viral cytopathic assay.
Time Frame	96 weeks
Safety Issue?	No

Analysis Population Description

ITT (One participant did not have any post-baseline NAb assessments). LOCF imputation

Reporting Groups

	Description
Rebif New Formulation (RNF) Cohort	Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week

Measured Values

	Rebif New Formulation (RNF) Cohort
Number of Participants Analyzed	259
Number of Participants Who Were Neutralising Antibody (NAb) Positive at the Week 96 Visit. [units: participants]	45

2. Secondary Outcome Measure:

Measure Title	Number of Participants Who Were Neutralising Antibody (NAb) Positive at Anytime During the Study
Measure Description	The NAb positive value was defined as NAb value greater or equal to 20 NU/mL. NAbs were detected using a viral cytopathic assay.
Time Frame	96 weeks
Safety Issue?	No

Analysis Population Description

ITT (One participant did not have any post-baseline NAb assessments). LOCF imputation

Reporting Groups

	Description
Rebif New Formulation (RNF) Cohort	Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week

Measured Values

	Rebif New Formulation (RNF) Cohort
Number of Participants Analyzed	259
Number of Participants Who Were Neutralising Antibody (NAb) Positive at Anytime During the Study [units: participants]	49

3. Secondary Outcome Measure:

Measure Title	Number of Participants With Binding Antibodies (BAb) at Week 96
Measure Description	Presence of BAbs. BAbs were measured by ELISA (Enzyme-linked immunosorbent assay).
Time Frame	96 weeks
Safety Issue?	No

Analysis Population Description

ITT (One participant did not have any post-baseline NAb assessments) LOCF imputation

Reporting Groups

	Description
Rebif New Formulation (RNF) Cohort	Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week

Measured Values

	Rebif New Formulation (RNF) Cohort
Number of Participants Analyzed	259
Number of Participants With Binding Antibodies (BAb) at Week 96 [units: Participants]	74

Reported Adverse Events

Time Frame	Adverse event reporting began at signature of informed consent and continued until 4 weeks after the last administration of trial medication.
Additional Description	Investigator recorded AE's at every visit.

Reporting Groups

	Description
Rebif New Formulation (RNF) Cohort	Interferon-beta-1a FBS-free/HSA-free Pre-filled syringes 44mcg/injected subcutaneous 3x per week

Serious Adverse Events

	Rebif New Formulation (RNF) Cohort	
	Affected/At Risk (%)	# Events
Total	15/260 (5.77%)	
Cardiac disorders		
Angina unstable [A] †	1/260 (0.38%)	1
Gastrointestinal disorders		
Coeliac disease [A] †	1/260 (0.38%)	1
Periproctitis [A] †	1/260 (0.38%)	1
Infections and infestations		
Pneumonia [A] †	1/260 (0.38%)	1
Injury, poisoning and procedural complications		
Drug toxicity [A] †	1/260 (0.38%)	1
Humerus fracture [A] †	1/260 (0.38%)	1
Joint dislocation [A] †	1/260 (0.38%)	1
Limb injury [A] †	1/260 (0.38%)	1
Near drowning [A] †	1/260 (0.38%)	1
Investigations		

	Rebif New Formulation (RNF) Cohort	
	Affected/At Risk (%)	# Events
Alanine aminotransferase increased [A] †	1/260 (0.38%)	1
Aspartate aminotransferase increased [A] †	1/260 (0.38%)	1
Metabolism and nutrition disorders		
Diabetes mellitus non-insulin-dependent [A] †	1/260 (0.38%)	1
Psychiatric disorders		
Depression [A] †	3/260 (1.15%)	3
Hypomania [A] †	1/260 (0.38%)	1
Renal and urinary disorders		
Renal colic [A] †	1/260 (0.38%)	1
Reproductive system and breast disorders		
Endometriosis [A] †	1/260 (0.38%)	1
Menstrual disorder [A] †	1/260 (0.38%)	1
Ovarian cyst ruptured [A] †	1/260 (0.38%)	1

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (8.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Rebif New Formulation (RNF) Cohort	
	Affected/At Risk (%)	# Events
Total	247/260 (95%)	
Blood and lymphatic system disorders		
Neutropenia [A] †	18/260 (6.92%)	23
Gastrointestinal disorders		
Diarrhoea [A] †	17/260 (6.54%)	21

	Rebif New Formulation (RNF) Cohort	
	Affected/At Risk (%)	# Events
Nausea [A] †	26/260 (10%)	34
Vomiting [A] †	13/260 (5%)	16
General disorders		
Asthenia [A] †	16/260 (6.15%)	25
Chills [A] †	18/260 (6.92%)	24
Fatigue [A] †	24/260 (9.23%)	26
Influenza like illness [A] †	176/260 (67.69%)	329
Injection site erythema [A] †	63/260 (24.23%)	76
Injection site haemorrhage [A] †	25/260 (9.62%)	30
Injection site pain [A] †	17/260 (6.54%)	21
Pyrexia [A] †	18/260 (6.92%)	32
Infections and infestations		
Nasopharyngitis [A] †	17/260 (6.54%)	22
Upper respiratory tract infection [A] †	23/260 (8.85%)	36
Urinary tract infection [A] †	14/260 (5.38%)	27
Viral upper respiratory tract infection [A] †	15/260 (5.77%)	25
Investigations		
Alanine aminotransferase increased [A] †	19/260 (7.31%)	22
Aspartate aminotransferase increased [A] †	15/260 (5.77%)	19
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	21/260 (8.08%)	32
Back pain [A] †	26/260 (10%)	31
Pain in extremity [A] †	20/260 (7.69%)	26

	Rebif New Formulation (RNF) Cohort	
	Affected/At Risk (%)	# Events
Nervous system disorders		
Dizziness [A] †	19/260 (7.31%)	22
Headache [A] †	98/260 (37.69%)	229
Psychiatric disorders		
Insomnia [A] †	13/260 (5%)	14

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (8.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

SPONSOR shall have the right to publish or present any results or information, including the Study Results, arising in connection with the STUDY for any purposes. The INSTITUTION, its officers, agents, employees and affiliated entities shall not publish or use any results or information arising in connection with the STUDY, including the Study Results, for professional, research, training or other purposes without SPONSOR’s prior written consent.

Results Point of Contact:

Name/Official Title: Bettina Stubinski/Medical Responsible
Organization: Merck Serono SA
Phone: +41224143396
Email: