ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/26/2014

ClinicalTrials.gov ID: NCT00367484

Study Identification

Unique Protocol ID:	24810
Brief Title:	Study To Evaluate The Immunogenicity And Safety Of r-hIFN Beta-1a (Rebif®) Using Clone 484-39 In Multiple Sclerosis
Official Title:	Multicentre, Single Arm, Open, Phase IV Study To Evaluate Immunogenicity And Safety Of Subcutaneous r-hIFN Beta-1a (Rebif®) Using Clone 484-39 In The Treatment Of Relapsing Remitting Multiple Sclerosis
Secondary IDs:	

Study Status

Record Verification:	January 2014
Overall Status:	Completed
Study Start:	May 2004
Primary Completion:	January 2006 [Actual]
Study Completion:	January 2006 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No

Review Board:	Approval Status: Approved Approval Number: CCPP RB 2004-047B Board Name: C.C.P.P.R.B. Lyon B, Board Affiliation: Independent Phone: +372 6 59 39 24 Email:
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	France: Institutional Ethical Committee

Study Description

Brief Summary:	The objectives of the study are: - comparison of the incidence and time course of the development of neutralizing antibodies (NAbs) to Rebif after 48 weeks of therapy, to historical data from Serono clinical trial databases to assess the safety and tolerability of Rebif®
Detailed Description:	

Conditions

Conditions:	Relapsing Remitting Multiple Sclerosis
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 4
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	Non-Randomized
Endpoint Classification:	Safety Study
Enrollment:	460 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Rebif® (clone 484-39) Rebif® 44 mcg, three times per week (tiw), subcutaneously (s.c.) During the first 4 weeks of the study, subjects underwent a dose titration regimen of 40% of Rebif® 22 mcg or 20% of Rebif® 44 mcg tiw (8.8 mcg per injection) in the first and second week followed by 100% of Rebif® 22 mcg or 50% of Rebif® 44 mcg (22 mcg per injection) in the third and fourth week. After 4 weeks, subjects received 44 mcg injected s.c. tiw.	Biological/Vaccine: Rebif® (clone 484-39) s.c. administered Rebif® Other Names: • Recombinant-human interferon beta-1a • r-hIFN Beta-1a

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 60 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Have multiple sclerosis (MS) with two or more relapses in the past two years and is eligible for interferon therapy.
- Be between 18 and 60 years of age, inclusive.
- Have given written informed consent, prior to any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.
- Be willing and able to follow all study procedures for the duration of the study.
- Have an Expanded Disability Scale Score (EDSS) less than 6.0
- If female, she must either

    a. be post menopausal or surgically sterilised; or
    b. use a hormonal contraceptive, intra uterine device, diaphragm with spermicide, or condom with spermicide, for the duration of the study; and
    c. be neither pregnant nor breast feeding. Confirmation that the subject is not pregnant must be established by a negative SERUM human Chorionic Gonadotrophin (hCG) pregnancy test between 28 to 7 days before Study Day 0.Urine pregnancy test must be done if serum hCG pregnancy test was performed more than 7 days before Study Day 0. A pregnancy test is not required if the subject is post menopausal or surgically sterilised.

Exclusion Criteria:

- Prior Interferon beta therapy (either beta-1b or beta-1a).

- 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.
- Significant immunosuppressive therapy within the 6 months prior to enrolment.
- Known history of hypersensitivity to natural or recombinant interferon beta, human serum albumin, or any other component of the formulation.
- Epilepsy with a history of seizures not adequately controlled by treatment.
- Have greater than Grade 1 toxicity for liver function tests (Aspartate Transaminase (AST), Alanine Transaminase (ALT), Gamma-Glutamyl Transferase (GGT) or total bilirubin) at the Screening visit
- Have significant leukopenia (greater than Grade 1 toxicity for total white blood cell count or lymphopenia) at the Screening visit
- Have had treatment with oral or systemic corticosteroids or Adrenocorticotrophic hormone (ACTH) within 1 month of the Screening visit or between the screening visit and study day 0.
- Cytokine or anti-cytokine therapy within the 3 months prior to the Screening visit or between the screening visit and study day 0.
- Use of immunomodulatory or immunosuppressive therapy (including but not limited to cyclophosphamide, cyclosporin, methotrexate, azathioprine, linomide) within the 6 months prior to the Screening visit or between the screening visit and study day 0.
- Have taken intravenous immunoglobulin or glatiramer acetate or mitoxantrone or any investigational drug or experimental procedure within the 3 months prior to the Screening visit or between the screening visit and study day 0.
- Prior use of cladribine or have received total lymphoid irradiation.
- Presence of systemic disease that might interfere with patient safety, compliance or evaluation of the condition under study (e.g. poorly controlled insulin-dependent diabetes, Lyme disease, clinically significant cardiac disease, human immunodeficiency virus (HIV), human T-lymphotrophic virus 1 (HTLV-1)).

Other concurrent systemic disorders incompatible with the study (at the Investigator's discretion).

Contacts/Locations

Study Officials: Bettina Stubinski, M.D.
Study Director
Merck Serono SA - Geneva

Locations:

References

Citations:

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	Subjects were screened for enrollment from 27 May 2004 and attended the last visit on 30 January 2006. Four hundred and eighty four subjects were screened for enrollment and 460 were enrolled. Two subjects (0.4%) were excluded from the ITT Population since they had no post-Baseline NAb assessment due to withdrawing from the study prematurely.
Pre-Assignment Details	At Week –4 (to Week –1), subjects provided written informed consent and underwent screening procedures. Twenty four subjects were not included in the study: the reasons were “Not met all eligibility criteria” (18 subjects) and “Other” (6 subjects)

Reporting Groups

	Description
Rebif® (Clone 484-39)	subcutaneously administered Rebif® 44mcg three times per week

Overall Study

	Rebif® (Clone 484-39)
Started	460
Completed	443 [1]
Not Completed	17
Adverse Event	7
Withdrew informed consent	5
Travel to USA	1
Lost to Follow-up	1
Protocol Violation	1
The choice of the patient	1
Lack of Efficacy	1

[1] Safety population = 460 Intent To Treat (ITT) population = 458

Baseline Characteristics

Reporting Groups

	Description
Rebif® (Clone 484-39)	subcutaneously administered Rebif® 44mcg three times per week

Baseline Measures

	Rebif® (Clone 484-39)
Number of Participants	458
Age, Categorical [1] [units: participants]	
<=18 years	0
Between 18 and 65 years	458
>=65 years	0
Age, Continuous [1] [units: years] Mean (Standard Deviation)	36.0 (8.9)
Gender, Male/Female [1] [units: participants]	
Female	336
Male	122
Region of Enrollment [1] [units: participants]	
Estonia	36
France	2
United Kingdom	13
Hungary	23
Lithuania	69
Morocco	5
Poland	69
Romania	87

	Rebif® (Clone 484-39)
Russian Federation	43
Serbia	80
Tunisia	31
Neutralising Antibody (NAb) Status [2] [units: Participants not testing NAb positive]	458

[1] ITT population

[2] Participants who did not test positive for NAb at baseline. The NAb+ value was defined as NAb ≥ 20 NU/ml.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants Testing Positive for Neutralising Antibody (NAb)
Measure Description	Participants who were NAb+ at 48 weeks (or at the last available NAb assessment up to Week 48). The NAb+ value was defined as NAb ≥ 20 NU/ml.
Time Frame	48 Weeks
Safety Issue?	Yes

Analysis Population Description

Intent To Treat (ITT) population, Last Observation Carried Forward (LOCF)

Reporting Groups

	Description
Rebif® (Clone 484-39)	subcutaneously administered Rebif® 44mcg three times per week

Measured Values

	Rebif® (Clone 484-39)
Number of Participants Analyzed	458
Number of Participants Testing Positive for Neutralising Antibody (NAb) [units: NAb+ participants]	73

Reported Adverse Events

Time Frame	48 weeks
Additional Description	Comprehensive assessments of any apparent toxicity experienced by the subject were performed throughout the course of the study. Study site personnel reported any AE, whether observed by the Investigator or reported by the subject.

Reporting Groups

	Description
Rebif® (Clone 484-39)	subcutaneously administered Rebif® 44mcg three times per week

Serious Adverse Events

	Rebif® (Clone 484-39)	
	Affected/At Risk (%)	# Events
Total	11/460 (2.39%)	
Blood and lymphatic system disorders		
Anaemia [A] †	1/460 (0.22%)	1
Cardiac disorders		
Angina pectoris [A] †	1/460 (0.22%)	1
Endocrine disorders		
Hyperparathyroidism primary [A] †	1/460 (0.22%)	1
Immune system disorders		
Drug hypersensitivity [A] †	1/460 (0.22%)	1
Infections and infestations		
Herpes zoster [A] †	1/460 (0.22%)	1
Injection site abscess [A] †	1/460 (0.22%)	1
Injection site cellulitis [A] †	1/460 (0.22%)	1

	Rebif® (Clone 484-39)	
	Affected/At Risk (%)	# Events
Pneumonia [A] †	2/460 (0.43%)	2
Urinary tract infection [A] †	1/460 (0.22%)	1
Injury, poisoning and procedural complications		
Ankle fracture [A] †	1/460 (0.22%)	1
Fall [A] †	1/460 (0.22%)	1
Thermal burn [A] †	1/460 (0.22%)	1
Musculoskeletal and connective tissue disorders		
Back pain [A] †	1/460 (0.22%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Parathyroid tumour benign [A] †	1/460 (0.22%)	1
Renal cell carcinoma stage I [A] †	1/460 (0.22%)	1
Respiratory, thoracic and mediastinal disorders		
Pneumothorax [A] †	1/460 (0.22%)	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® (Clone 484-39)	
	Affected/At Risk (%)	# Events
Total	378/460 (82.17%)	
Blood and lymphatic system disorders		
Blood and lymphatic system disorders [A] †	36/460 (7.83%)	56
Gastrointestinal disorders		
Nausea [A] †	24/460 (5.22%)	26

	Rebif® (Clone 484-39)	
	Affected/At Risk (%)	# Events
General disorders		
Asthenia [A] †	29/460 (6.3%)	35
Chills [A] †	35/460 (7.61%)	39
Fatigue [A] †	37/460 (8.04%)	40
Influenza like illness [A] †	188/460 (40.87%)	284
Injection site erythema [A] †	67/460 (14.57%)	71
Pyrexia [A] †	50/460 (10.87%)	57
Infections and infestations		
Influenza [A] †	32/460 (6.96%)	58
Upper respiratory tract infection [A] †	37/460 (8.04%)	45
Urinary tract infection [A] †	27/460 (5.87%)	32
Investigations		
Alanine aminotransferase increased [A] †	25/460 (5.43%)	26
Musculoskeletal and connective tissue disorders		
Back pain [A] †	26/460 (5.65%)	36
Myalgia [A] †	43/460 (9.35%)	53
Nervous system disorders		
Headache [A] †	129/460 (28.04%)	208
Psychiatric disorders		
Insomnia [A] †	31/460 (6.74%)	34
Skin and subcutaneous tissue disorders		
Skin and subcutaneous tissue disorders [A] †	40/460 (8.7%)	53

† 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.

Results Point of Contact:

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