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

ClinicalTrials.gov ID: NCT00619307

Study Identification

Unique Protocol ID:	27571
Brief Title:	Transition to Rebif New Formulation (TRANSFER)
Official Title:	A Randomized, Multicenter, Two-arm, Open-label, Phase IIIb Study to Evaluate the Satisfaction in Relapsing Multiple Sclerosis Subjects Transitioning to Rebif® New Formulation From Rebif® (Interferon Beta-1a) With Ibuprofen When Necessary (PRN) or as Prophylaxis
Secondary IDs:	

Study Status

Record Verification:	January 2014
Overall Status:	Completed
Study Start:	July 2007
Primary Completion:	April 2008 [Actual]
Study Completion:	April 2008 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 20-Jun-07 Board Name: Germany: Landesärztekammer (Regional Medical Society) Board Affiliation: Germany : Ethics Commission Phone: 49 (06131) 28822-0 Email:
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) France: Institutional Ethical Committee Germany: Ethics Commission Germany: Federal Institute for Drugs and Medical Devices

Study Description

Brief Summary:	To assess patient satisfaction with respect to the incidence of flu-like symptoms (FLS) in patients with multiple sclerosis transitioned from current Rebif (subcutaneously injected interferon beta-1a, 44 mcg three-times-weekly) to the new formulation of Rebif (RNF) while receiving ibuprofen either prophylactically or only when necessary (PRN) after the occurence of flu-like symptoms.
Detailed Description:	

Conditions

Conditions:	Relapsing Multiple Sclerosis
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Supportive Care
Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	2

Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	
Enrollment:	117 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: Transition with prophylactic ibuprofen	Drug: Rebif New Formulation + prophylactic Ibuprofen Subjects, currently on Rebif® 44 mcg three times a week, using Rebiject II as an injection device and having received Rebif® full dose 44 mcg three times a week for at least 6 months, receives systematically 400 mg ibuprofen as prophylactic treatment against flu-like symptoms on days when Rebif New Formulation 44 mcg three times a week is injected
Active Comparator: Transition with PRN ibuprofen	Drug: Rebif New Formulation + ibuprofen PRN Subjects, currently on Rebif® 44 mcg three times a week, using Rebiject II as an injection device and having received Rebif® full dose 44 mcg three times a week for at least 6 months, should not administer Ibuprofen before the first Rebif New Formulation injection. If flu-like symptoms occur after the 44 mcg Rebif New Formulation injection then the subject can administer 400 mg ibuprofen. This should only be administered after the Rebif New Formulation injection and not before the Rebif New Formulation injection.

Outcome Measures

[See Results Section.]

Eligibility

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

- Subject with relapsing forms of Multiple Sclerosis (MS)
- Expanded disability status scale (EDSS) score < 5.5 at study entry
- Subjects who have been administering Rebif 44 mcg three times a week for at least 6 months prior to study enrolment

- Subject currently using Rebiject II and who will use their own Rebiject II for the Rebif New Formulation injections
- Subject is between 18 and 60 years old inclusive
- Female subjects must be neither pregnant nor breast-feeding and must lack childbearing potential, as defined by either: post-menopausal or surgically sterile, or use a highly effective method of contraception.
- Subject is willing to follow study procedures
- Subject is willing and must not present any contra-indication to taking ibuprofen during 4 weeks of the study
- Subject has given written informed consent

Exclusion Criteria:

- Secondary Progressive Multiple Sclerosis without superimposed attacks
- Use of any other injectible medications during the week prior to the screening period, during the screening or treatment periods
- Subject receiving MS therapy in addition (i.e. combination therapy) to Rebif within 3 months prior to study enrolment or at any time during study protocol
- History of any chronic pain syndrome
- Subjects that use any investigational drug or experimental procedure within 12 weeks of visit
- Subject received corticosteroids or adrenocorticotrophic hormone (ACTH) within 30 days of visit 1
- Subject with flu-like symptoms (FLS) associated with any cause (i.e. no current flu and no FLS related to Interferon in the week prior to baseline)
- Subject has abnormal liver function, defined by a total bilirubin > 1.5 times the upper limit of normal, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the upper limit of the normal values.
- Subject has inadequate bone marrow reserve, defined as a total white blood cell count < 3.0 x 109/L, platelet count < 75 x 109/L, haemoglobin < 100 g/L.
- Subject suffers from an active autoimmune disease other than MS
- Subject suffers from major medical or psychiatric illness
- Subject has seizures history or is currently experiencing seizures not adequately controlled by anti-epileptics
- Subject is pregnant or attempting to conceive
- Visual or physical impairment that precludes completion of diaries and questionnaires by himself/herself
- Contraindication to ibuprofen:known hypersensitivity to the active ingredient ibuprofen
- Known hypersensitivity to non-steroidal anti-inflammatory drugs which can lead to asthmatic attacks, gastric and/or intestinal ulcers, gastro-intestinal bleeding, cerebro-vascular bleeding or other active bleeding, severe hepatic dysfunction, severe kidney dysfunction, severe cardiac insufficiency, or systemic lupus erythematosus

Contacts/Locations

Study Officials: Sabine Latour, MD
Study Director
Merck Serono International S.A., an affiliate of Merck KGaA, Darmstadt, Germany

Locations: France
Local Medical Information
Paris, France

Germany
Local Medical Information
Munich, Germany

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	Subjects were enrolled from 16 July 2007 and attended the last visit on 11 April 2008. One hundred and twenty three subjects gave informed consent and 117 were enrolled. Of these, all were treated except one subject scheduled to receive prophylactic ibuprofen, who withdrew consent before treatment.
Pre-Assignment Details	There were 17 active centres, 6 centres in France and 11 centres in Germany. Screening visit took place within 2 weeks of randomisation. Six subjects were screening failures.

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Overall Study

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen
Started	60	57
Completed	56	53
Not Completed	4	4
Adverse Event	0	1
Lost to Follow-up	0	1
Protocol Violation	3	0
Withdrew consent	1	0
Severe migraine	0	1
MS attack plus steroids	0	1

Baseline Characteristics

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Baseline Measures

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen	Total
Number of Participants	60	57	117
Age, Categorical [units: participants]			
<=18 years	0	0	0

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen	Total
Between 18 and 65 years	60	57	117
>=65 years	0	0	0
Age, Continuous [units: years] Mean (Standard Deviation)	41.7 (8.4)	41.5 (8.9)	41.6 (8.6)
Gender, Male/Female [units: participants]			
Female	48	40	88
Male	12	17	29
Region of Enrollment [units: participants]			
France	14	14	28
Germany	46	43	89

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Flu-like Symptom Score
Measure Description	This is defined as the sum of the scores for the “side effects” section questions 1-4, with a minimum possible total score of 1 and a maximum possible total score of 20 in the MSTCQ. The lower the score, the better the outcome.
Time Frame	4 weeks
Safety Issue?	No

Analysis Population Description

ITT

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.

	Description
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Measured Values

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen
Number of Participants Analyzed	56	54
Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Flu-like Symptom Score [units: MSTCQ score (units on a scale)] Mean (95% Confidence Interval)	8.5 (7.4 to 9.6)	9.1 (8.1 to 10.2)

2. Secondary Outcome Measure:

Measure Title	Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Total Score
Measure Description	This is defined as the sum of the scores for the “injection systems” section questions 1-9 and the “side effects” section questions 1-11, with a minimum possible total score of 20 and a maximum possible total score of 100. The lower the score, the better the outcome.
Time Frame	4 weeks
Safety Issue?	No

Analysis Population Description

ITT

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.

	Description
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Measured Values

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen
Number of Participants Analyzed	57	54
Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Total Score [units: MSTCQ score (units on a scale)] Mean (95% Confidence Interval)	36.8 (34.5 to 39.1)	38.3 (35.4 to 41.1)

3. Secondary Outcome Measure:

Measure Title	Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Injection Satisfaction Score
Measure Description	This is defined as the sum of the scores for the “injection systems” section questions 1-9, with a minimum possible total score of 9 and a maximum possible total score of 45. The lower the score, the better the outcome.
Time Frame	4 weeks
Safety Issue?	No

Analysis Population Description

ITT

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.

	Description
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Measured Values

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen
Number of Participants Analyzed	57	55
Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Injection Satisfaction Score [units: MSTCQ score (units on a scale)] Mean (95% Confidence Interval)	14.3 (13.3 to 15.2)	15.0 (13.8 to 16.1)

4. Secondary Outcome Measure:

Measure Title	Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Injection Site Reaction Score
Measure Description	This is defined as the sum of the scores for the “side effects” section questions 5 to 8, with a minimum possible total score of 1 and a maximum possible total score of 20. The lower the score, the better the outcome.
Time Frame	4 weeks
Safety Issue?	Yes

Analysis Population Description

ITT

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.

	Description
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Measured Values

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen
Number of Participants Analyzed	57	54
Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Injection Site Reaction Score [units: MSTCQ score (units on a scale)] Mean (95% Confidence Interval)	9.4 (8.5 to 10.3)	9.2 (8.0 to 10.4)

5. Secondary Outcome Measure:

Measure Title	Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Global Side Effects Score
Measure Description	This is defined as the sum of the scores for “side effects” section questions 9 to 11, corresponding to minimum possible total score of 3 and a maximum possible total score of 15. The lower the score, the better the outcome.
Time Frame	4 weeks
Safety Issue?	Yes

Analysis Population Description

ITT

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.

	Description
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Measured Values

	Transition With Prophylactic Ibuprofen	Transition With PRN Ibuprofen
Number of Participants Analyzed	57	55
Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Global Side Effects Score [units: MSTCQ score (units on a scale)] Mean (95% Confidence Interval)	4.7 (4.2 to 5.1)	5.0 (4.4 to 5.6)

Reported Adverse Events

Time Frame	4 Weeks
Additional Description	Each subject was given a diary card for recording any adverse events. The table of Other Adverse Events shows all adverse events occurring at or above the reporting threshold.

Reporting Groups

	Description
Transition With Prophylactic Ibuprofen	subjects received ibuprofen as prophylactic treatment against FLS on days when RNF 44 mcg tiw was injected (3 times weekly). Mandatory 400 mg of ibuprofen was administered prophylactically 30 to 60 minutes before each RNF injection. Optionally the subject could take another 400 mg 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours.
Transition With PRN Ibuprofen	subjects were instructed not to administer ibuprofen before the first RNF injection. Ibuprofen was taken solely as needed, PRN, after RNF injections to alleviate the symptoms of FLS. If FLS occurred after a RNF injection, then the subject could administer the first dose of ibuprofen 400 mg. The second dose of ibuprofen 400 mg could be taken 6 hours after the first ibuprofen dose or upon waking if more than 6 hours later and if necessary a third dose of 400 mg 6 hours later, adding up to a maximum of 1200 mg within 24 hours of RNF injection.

Serious Adverse Events

	Transition With Prophylactic Ibuprofen		Transition With PRN Ibuprofen	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	1/59 (1.69%)		0/57 (0%)	
Gastrointestinal disorders				
Abdominal pain [A] †	1/59 (1.69%)	1	0/57 (0%)	0

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

Other Adverse Events

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

	Transition With Prophylactic Ibuprofen		Transition With PRN Ibuprofen	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	50/59 (84.75%)		47/57 (82.46%)	
Ear and labyrinth disorders				
Vertigo [A] †	0/59 (0%)	0	3/57 (5.26%)	3
General disorders				
Chills [A] †	4/59 (6.78%)	5	4/57 (7.02%)	5
Fatigue [A] †	15/59 (25.42%)	36	7/57 (12.28%)	10
Influenza-like illness [A] †	39/59 (66.1%)	182	38/57 (66.67%)	170
Infections and infestations				
Nasopharyngitis [A] †	2/59 (3.39%)	2	3/57 (5.26%)	3
Musculoskeletal and connective tissue disorders				
Arthralgia [A] †	2/59 (3.39%)	2	4/57 (7.02%)	10
Back pain [A] †	3/59 (5.08%)	3	2/57 (3.51%)	2
Myalgia [A] †	3/59 (5.08%)	3	5/57 (8.77%)	17
Nervous system disorders				
Headache [A] †	22/59 (37.29%)	41	16/57 (28.07%)	33

	Transition With Prophylactic Ibuprofen		Transition With PRN Ibuprofen	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Migraine [A] †	0/59 (0%)	0	4/57 (7.02%)	5

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

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:

Name/Official Title: Merck KGaA Communication Center
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