ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
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ClinicalTrials.gov ID: NCT01134627

Study Identification

Unique Protocol ID:	IMP 26588
Brief Title:	Minocycline as add-on to Interferon Beta-1a [IFN Beta-1a] (Rebif®) in Relapsing-Remitting Multiple Sclerosis [RRMS] (RECYCLINE)
Official Title:	A Multi-centre, Double Blind, Randomized, Placebo Controlled, Parallel Group Trial Investigating Minocycline Versus Placebo as Add-on Therapy in Patients Who Are on Treatment With Interferon-beta-1a 44 mcg Tiw (Rebif®) for the Treatment of Relapsing-Remitting Multiple Sclerosis
Secondary IDs:	2005-004289-18 [EudraCT Number]

Study Status

Record Verification:	December 2013
Overall Status:	Terminated
Study Start:	February 2006
Primary Completion:	April 2011 [Actual]
Study Completion:	April 2011 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?: Yes

Applicable Trial?: Section 801 Clinical Trial? No
Delayed Posting? No

IND/IDE Protocol?: No

Review Board: Approval Status: Approved
Approval Number: Dnro 16/13/03/01/10
Board Name: Helsingin ja Uudenmaan Sairaanhoitopiiri
Board Affiliation: Naistentautien ja synnytysten, korva-ja silmätautien, neurologian ja neurokirurgian eettinen toimikunta
Phone: +358 (0)9 471 71607
Email: monica.hippi@hus.fi

Data Monitoring?: Yes

Plan to Share Data?:

Oversight Authorities: Denmark: Ethics Committee
France: National Consultative Ethics Committee for Health and Life Sciences
Finland: Ethics Committee
Norway:National Committee for Medical and Health Research Ethics
Sweden: Regional Ethical Review Board
Switzerland: Ethikkommission

Study Description

Brief Summary: This is a multicentric, double-blind, placebo-controlled, randomized, parallel group study to estimate the effect of minocycline as add-on to interferon beta-1a (IFN beta-1a) in subjects with relapsing-remitting multiple sclerosis (RRMS).

Detailed Description: Interferon beta-1a is the approved standard therapy in RRMS. The beneficial effects of minocycline in the experimental autoimmune encephalomyelitis (EAE) model and its possible inhibitory effect on the degradation of IFN beta-1a suggest that minocycline treatment may have beneficial effects in MS as add-on therapy in subjects who are on treatment with IFN beta-1a. Adjuvant treatment with minocycline is easy to administer, well tolerated and relatively inexpensive. This is a multicentric, double blind, placebo controlled, randomized, parallel group study. Eligible subjects already started with IFN beta-1a (Rebif®) will be randomized 1:1 for treatment with either minocycline 2*100 mg daily as add-on therapy or placebo. The subjects will be examined clinically at baseline and after 12, 24, 48, 72 and 96 weeks. Laboratory tests (hematology and clinical chemistry) will be performed at baseline and after 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96 weeks (at 4, 8, 36, 60 and 84 weeks only an additional liver enzyme test will be scheduled). The MRI (T1-weighted and T2-weighted) before treatment and after 96 weeks and immunological studies before treatment and after 48 weeks will be performed in a limited number of subjects in selected centers.

OBJECTIVES

Primary Objective:

The effect of minocycline versus placebo in subjects receiving treatment with IFN beta-1a on the time to the first documented relapse

Secondary Objectives:

- To estimate the effect of minocycline versus placebo in subjects receiving treatment with IFN beta-1a on the mean number of documented relapses per subject up to year 2
- To estimate, in a limited number of 120 subjects at pre-selected sites, the effect of minocycline versus placebo in subjects receiving treatment with IFN beta-1a on the number of new or enlarging lesions on T2-weighted MRI, changes in brain volume measured on MRI

Tertiary Objectives:

- Time to onset of disability progression sustained over at least 6 months based on change from baseline in EDSS in subjects with RRMS who recently started treatment with IFN beta-1a. (Disability progression is defined as an increase of: 1.0 point on the EDSS if EDSS was >= 1.0 at baseline; and 1.5 point on the EDSS if EDSS was 0.0 at baseline)
- Time to sustained progression by 2 points in 1 Functional System or 1 point in 2 Functional Systems
- The total number of reported relapses (documented and undocumented). An undocumented relapse is defined as the appearance of new symptoms or worsening of an old symptom, in the absence of fever, over at least 24 hours that could be attributed to MS activity, preceded by stability or improvement for at least 30 days
- The requirement for treatment with glucocorticoids due to relapses
- The time to first relapse
- The number of relapse-free (documented and undocumented relapses) subjects without progression
- The disease activity measured on the integrated disability status scale (IDSS)
- The number of subjects with a permanent loss of disability of 1.0 score on the EDSS, confirmed at 2 consecutive visits with an interval of 6 months
- The total area of MS lesions on T1 and T2-weighted MRI
- Analyze the safety with respect to the combination of Rebif® and minocycline
- Rate of dose reduction of IFN beta-1a (Rebif®)
- Relapse severity based on the EDSS and IDSS
- Immunological analyses in a limited number of subjects (MRI subgroup)
- Frequency of increase of liver enzymes according to World Health Organization (WHO) II criteria

Conditions

Conditions: Multiple Sclerosis, Relapsing-Remitting

Keywords: Multiple Sclerosis, Relapsing-Remitting
Interferon-β
Rebif®
Minocycline

Study Design

Study Type: Interventional

Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Double Blind (Subject, Investigator)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	305 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Minocycline group	Drug: Minocycline Participants who are self-administering Rebif® (IFN beta-1a) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly will also receive minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Placebo Comparator: Placebo Group	Drug: Placebo Participants who are self-administering Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly will also receive placebo tablets twice daily for 96 weeks.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	55 Years
Gender:	Both
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- Subjects who have given written informed consent prior to any trial related activities. Trial related activities are any procedures that would not have been performed during normal management of the subject
- Subjects with stable disease without relapses in the last 30 days

- Subjects aged between 18 and 55 years (both included)
- Subjects who suffer from definite RRMS according to Poser criteria (clinical definite multiple sclerosis [CDMS] or laboratory supported definite multiple sclerosis [LSDMS]) or definite MS according to McDonald criteria
- Subjects who have started treatment with Rebif® 44 mcg 3 months ago (+/- 1 month) including the titration phase
- Subjects who have a disability equivalent to an EDSS of 5.5 or less
- Subjects who have shown clinical activity defined as at least 1 documented relapse within the last year (A documented relapse is defined as the development of new or the exacerbation of existing neurological symptoms or signs, in the absence of fever, persisting for more than 48 hours and with a previous period for more than 30 days with a stable or an improving condition. The exacerbation must be equivalent to an increase of at least 1 point in 2 functional systems or to an increase of 2 points in 1 system, either in the pyramidal, cerebellar, brain-stem, sensory, bowel and bladder, visual, cerebral or other functional system or an increase of at least half a point on the EDSS. Changes in bowel and bladder or cerebral functions should not solely be responsible for documentation of a relapse. The relapses must have been evaluated by a neurologist, retrospectively if necessary)
- Subjects must be prepared to and considered able to follow the protocol during the whole trial period and to attend the planned visits, even if the treatment has to be withdrawn
- Female subjects must either: be post-menopausal or surgically sterilized; or use a hormonal contraceptive or intra-uterine device (only following contraceptives are allowed: birth control pills, intra-uterine device, depot injection of gestagen, subdermal implant, hormonal vaginal ring and transdermal depot patches); or be sexually inactive for the duration of the study, and be neither pregnant nor breast-feeding (confirmation that the subject is not pregnant must be established by a negative serum human chorionic gonadotropin (hCG) pregnancy test within 28 days of Study Day 1 and a negative urine pregnancy test on Study Day 1. A pregnancy test is not required if the subject is post-menopausal or surgically sterilized)

Exclusion Criteria:

- Subjects with any condition that might give rise to similar symptoms as MS
- Subjects who have received any other immunomodulatory or immunosuppressive treatment 6 months prior to inclusion into the trial (the obligatory pre-study 3 months [+/- 1 month] period of Rebif® treatment not included)
- Subjects who have received mitoxantrone or total lymphoid radiation at any time
- Subjects who have received treatment with glucocorticoids or adrenocorticotropic hormone (ACTH) later than 1 month prior to inclusion into the trial
- Subjects who have experienced a relapse within 1 month prior to inclusion into the trial
- Subjects who have suffered from major depression
- Subjects with alcohol or drug dependency
- Subjects with cardiac insufficiency, cardiomyopathy, significant cardiac dysrhythmias, unstable or advanced ischemic heart disease (New York Heart Association [NYHA] grade III or IV), or significant hypertension (Blood Pressure > 180/110 millimeter of mercury [mmHg])
- Subjects with renal insufficiency defined as serum creatinine > 1.5 times the upper normal reference limit
- Subjects with alanine aminotransferase (ALAT) and asparagine aminotransferase (ASAT) (or either 1 if only 1 of the 2 is measured) levels more than 2 times the normal upper reference limit.
- Subjects with leucopoenia < 2500 per microliter (microL) or thrombopenia < 100000 per microL
- Subjects with any medical illness requiring treatment with systemic corticosteroids
- Subjects with any systemic disease that can influence the subject's safety and compliance, or the evaluation of the disability
- Female subjects who are pregnant or breastfeeding or who plan to become pregnant during the study
- Subjects with known or suspected allergy to minocycline or other tetracyclines

- Subjects who have participated in any other studies, involving other investigational products, within 30 days prior to participating in this trial

Contacts/Locations

Study Officials: Per Soelberg Sørensen, Professor
Study Principal Investigator
Rigshospitalet,Blegdamsvej 9, 2100 København Ø, Scleroseklinikken afsnit 2082

Locations: Denmark
Scleroseklinikken afsnit 2082
Copenhagen, Denmark, 2100

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	One out of 305 participants was randomized by mistake and did not receive study medication.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Overall Study

	Rebif®+ Minocycline	Rebif® + Placebo
Started	149 [1]	155 [1]
Completed	80	88
Not Completed	69	67
Adverse Event	47	31
Lost to Follow-up	1	2
Protocol Violation	3	5
Lack of Efficacy	2	12
Withdrawal by Subject	4	3
Planning to become pregnant/pregnancy	1	0
Unspecified	11	14

[1] Number of participants treated.

Baseline Characteristics

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Baseline Measures

	Rebif®+ Minocycline	Rebif® + Placebo	Total
Number of Participants	149	155	304
Age, Continuous [units: years] Mean (Standard Deviation)	36.2 (8.8)	37.7 (8.6)	37.0 (8.7)

	Rebif®+ Minocycline	Rebif® + Placebo	Total
Gender, Male/Female [units: participants]			
Female	96	102	198
Male	53	53	106

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants Who Experienced First Documented Relapse
Measure Description	Documented relapse: development of new/exacerbation of existing neurological symptoms, persisting for >48 hrs and with previous period for >30 days with stable/improving condition. Exacerbation = at least (>=)1 point increase in 2 functional systems/2 points increase in 1 system,either in pyramidal, cerebral, brain-stem, sensory, bowel and bladder, visual, cerebral or other functional system or >=0.5 point increase on expanded disability status scale (EDSS) which assesses disability in 8 functional systems with overall score ranging from 0 (normal) to 10 (death due to multiple sclerosis [MS]).
Time Frame	Baseline up to 96 weeks (+/- 1 week) or early termination (ET)
Safety Issue?	No

Analysis Population Description

The Intention to Treat (ITT) population included all the participants who were randomized and received study medication.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	149	155
Number of Participants Who Experienced First Documented Relapse [units: participants]	32	39

2. Secondary Outcome Measure:

Measure Title	Number of Participants With Documented Relapses
Measure Description	Documented relapse: development of new/exacerbation of existing neurological symptoms, persisting for >48 hrs and with previous period for >30 days with stable/improving condition. Exacerbation was >=1 point increase in 2 functional systems /2 points increase in 1 system, either in pyramidal, cerebral, brain-stem, sensory, bowel and bladder, visual, cerebral or other functional system or >=0.5 point increase on EDSS which assesses disability in 8 functional systems with overall score ranging from 0 (normal) to 10 (death due to MS).
Time Frame	Baseline up to 96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

ITT population included all the participants who were randomized and received study medication.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	149	155
Number of Participants With Documented Relapses [units: participants]		
0	117	116
1	27	29
2	2	9
3	2	0
4	1	1

3. Secondary Outcome Measure:

Measure Title	Number of New or Enlarging Lesions on Time Constant 2 (T2) Weighted Magnetic Resonance Imaging (MRI)
Measure Description	Inflammatory disease activity was assessed by MRI measurement of the number of new or enlarging T2 lesions.
Time Frame	Final visit (96 weeks [+/- 1 week]) or ET
Safety Issue?	No

Analysis Population Description

Sub-group of ITT population included limited number of participants at pre-selected sites selected on basis of availability of MRI scanning facilities and the willingness of the site to participate.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	23	27
Number of New or Enlarging Lesions on Time Constant 2 (T2) Weighted Magnetic Resonance Imaging (MRI) [units: lesions] Mean (Standard Deviation)	3.0 (3.3)	3.0 (4.6)

4. Secondary Outcome Measure:

Measure Title	Changes in Brain Volume Measured on Magnetic Resonance Imaging (MRI)
Measure Description	Changes in brain volume were measured as the brain parenchymal fraction using MRI scans.
Time Frame	Screening , final visit (96 weeks [+/- 1 week]) or ET
Safety Issue?	No

Analysis Population Description

Sub-group of ITT population included limited number of participants at pre-selected sites selected on basis of availability of MRI scanning facilities and the willingness of the site to participate.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	23	26
Changes in Brain Volume Measured on Magnetic Resonance Imaging (MRI) [units: cubic millimeter (mm^3)] Mean (Standard Deviation)	-2997.4 (25799.3)	5834.9 (20809.4)

5. Other Pre-specified Outcome Measure:

Measure Title	Number of Participants With Onset of Disability Progression
Measure Description	Disability progression was defined as an increase, compared to baseline evaluation of >= 1.0 points on EDSS if EDSS was >= 1.0 at baseline or >=1.5 point on EDSS if EDSS was 0.0 at baseline. EDSS assesses disability in 8 functional systems with overall score ranging from 0 (normal) to 10 (death due to MS).
Time Frame	Baseline up to 96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

ITT population included all the participants who were randomized and received study medication.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.

	Description
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	149	155
Number of Participants With Onset of Disability Progression [units: participants]	6	3

6. Other Pre-specified Outcome Measure:

Measure Title	Number of Time Constant 2 (T2) Active Lesions
Measure Description	Inflammatory disease activity was assessed by MRI measurement of the number of T2 active lesions.
Time Frame	Week 48 up to Week 96 (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

Data was not analyzed due to insufficient number of participants available for the analysis of this measure and the study was prematurely terminated.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

7. Other Pre-specified Outcome Measure:

Measure Title	Percentage of Time Constant 2 (T2) Active Scans Per Participant
Measure Description	Inflammatory disease activity was assessed by MRI measurement of the percentage of T2 active scans.
Time Frame	Baseline up to 96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

Data was not analyzed due to insufficient number of participants available for the analysis of this measure and the study was prematurely terminated.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

8. Other Pre-specified Outcome Measure:

Measure Title	Burden of Disease
Measure Description	The burden of disease (BOD) is the total area of MS lesions (abnormal plaques) in the brain measured on Time Constant 1 (T1) or T2 weighted MRI.
Time Frame	Baseline up to 96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

Sub-group of ITT population included limited number of participants at pre-selected sites selected on basis of availability of MRI scanning facilities and the willingness of the site to participate.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	23	27
Burden of Disease [units: square millimeter (mm^2)] Mean (Standard Deviation)		
Total area of lesions on T1 weighted MRI	1599.4 (3196.3)	1716.8 (2145.5)
Total area of lesions on T2 weighted MRI	4813.9 (8385.5)	5717.3 (6587.0)

9. Other Pre-specified Outcome Measure:

Measure Title	Relapse Count
Measure Description	A relapse was defined as the development of new or the exacerbation of existing neurological symptoms or signs, in the absence of fever, persisting for more than 48 hours and with a previous period for more than 30 days with a stable or an improving condition.
Time Frame	Week 48 (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

Data was not analyzed due to insufficient number of participants available for the analysis of the measure and the study was prematurely terminated.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.

	Description
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

10. Other Pre-specified Outcome Measure:

Measure Title	Number of Relapse Free Participants Without Progression
Measure Description	Analysis based on documented relapses (relapse: development of new/exacerbation of existing neurological symptoms, persisting for >48 hrs and with previous period for >30 days with stable/improving condition; relapse documented by exacerbation >=1 point increase in 2 functional systems/2 points increase in 1 functional system, or >=0.5 point increase on EDSS which assesses disability in 8 functional systems with overall score ranging from 0 [normal] to 10 [death due to MS]) and overall relapses (documented and undocumented relapses); undocumented relapses only fulfilled condition for relapse.
Time Frame	Baseline up to 96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

ITT population included all the participants who were randomized and received study medication. Number of participants analyzed "N" included those participants who were evaluated for this particular measure.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	141	147

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Relapse Free Participants Without Progression [units: participants]		
Relapse free participants (documented relapse)	105	108
Relapse free participants (overall relapse)	96	89

11. Other Pre-specified Outcome Measure:

Measure Title	Number of Participants With Total Number of Reported Relapses (Documented and Undocumented Relapses)
Measure Description	Documented relapses (relapse: development of new/exacerbation of existing neurological symptoms, persisting for >48 hrs and with previous period for >30 days with stable/improving condition; relapse documented by exacerbation >=1 point increase in 2 functional systems/2 points increase in 1 functional system, or >=0.5 point increase on EDSS which assesses disability in 8 functional systems with overall score ranging from 0 [normal] to 10 [death due to MS]) and undocumented relapses only fulfilled condition for relapse.
Time Frame	Baseline up to 96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

ITT population included all the participants who were randomized and received study medication.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	149	155
Number of Participants With Total Number of Reported Relapses (Documented and Undocumented Relapses) [units: participants]		

	Rebif®+ Minocycline	Rebif® + Placebo
0	107	96
1	30	38
2	6	17
3	4	3
4	1	0
5	1	1

12. Other Pre-specified Outcome Measure:

Measure Title	Relapse Severity Based on Expanded Disability Status Scale (EDSS)
Measure Description	EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. EDSS progression was defined as increase by at least 1 point if last value of EDSS was equal to 5.5 and by at least 0.5 points if last EDSS was more than 5.5.
Time Frame	96 weeks (+/- 1 week) or ET
Safety Issue?	No

Analysis Population Description

ITT population included all the participants who were randomized to study medication. Number of participants analyzed "N" included those participants who were evaluated for this particular measure.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Measured Values

	Rebif®+ Minocycline	Rebif® + Placebo
Number of Participants Analyzed	125	136
Relapse Severity Based on Expanded Disability Status Scale (EDSS)	1.90 (1.38)	2.02 (1.42)

	Rebif®+ Minocycline	Rebif® + Placebo
[units: Units on a scale] Mean (Standard Deviation)		

Reported Adverse Events

Time Frame	Baseline to Week 100 (+/- 1 week) or ET.
Additional Description	An adverse event (AE) was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered.

Reporting Groups

	Description
Rebif®+ Minocycline	Participants who self-administered Rebif® (interferon beta-1 alpha [IFN beta-1a]) 44 microgram (mcg) as subcutaneous (sc) injection thrice weekly also received minocycline 100 milligram (mg) tablet twice daily as an add-on therapy in accordance with clinical practice for 96 weeks.
Rebif® + Placebo	Participants who self-administered Rebif® (IFN beta-1a) 44 mcg as sc injection thrice weekly also received placebo tablets twice daily for 96 weeks.

Serious Adverse Events

	Rebif®+ Minocycline	Rebif® + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	11/149 (7.38%)	21/155 (13.55%)
Blood and lymphatic system disorders		
Lymphadenopathy [A] *	1/149 (0.67%)	0/155 (0%)
Neutropenia [A] *	1/149 (0.67%)	0/155 (0%)
Thrombocytopenia [A] *	0/149 (0%)	1/155 (0.65%)
Cardiac disorders		
Arrhythmia [A] *	1/149 (0.67%)	0/155 (0%)

	Rebif®+ Minocycline	Rebif® + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Ear and labyrinth disorders		
Deafness unilateral [A] *	0/149 (0%)	1/155 (0.65%)
Endocrine disorders		
Autoimmune thyroiditis [A] *	0/149 (0%)	1/155 (0.65%)
Eye disorders		
Retinopathy [A] *	0/149 (0%)	1/155 (0.65%)
Gastrointestinal disorders		
Abdominal pain [A] *	1/149 (0.67%)	1/155 (0.65%)
Constipation [A] *	0/149 (0%)	1/155 (0.65%)
General disorders		
Chest pain [A] *	0/149 (0%)	1/155 (0.65%)
Hernia [A] *	1/149 (0.67%)	0/155 (0%)
Hepatobiliary disorders		
Hepatic mass [A] *	1/149 (0.67%)	0/155 (0%)
Immune system disorders		
Food allergy [A] *	1/149 (0.67%)	0/155 (0%)
Hypersensitivity [A] *	0/149 (0%)	1/155 (0.65%)
Infections and infestations		
Erysipelas [A] *	0/149 (0%)	1/155 (0.65%)
Pneumonia [A] *	1/149 (0.67%)	0/155 (0%)
Injury, poisoning and procedural complications		
Joint dislocation [A] *	0/149 (0%)	1/155 (0.65%)
Musculoskeletal and connective tissue disorders		

	Rebif®+ Minocycline	Rebif® + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Intervertebral disc protrusion [A] *	1/149 (0.67%)	0/155 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Breast cancer [A] *	1/149 (0.67%)	2/155 (1.29%)
Lymphoma [A] *	0/149 (0%)	1/155 (0.65%)
Testis cancer [A] *	1/149 (0.67%)	0/155 (0%)
Nervous system disorders		
Hypoesthesia [A] *	0/149 (0%)	1/155 (0.65%)
Motor dysfunction [A] *	0/149 (0%)	1/155 (0.65%)
Paresthesia [A] *	0/149 (0%)	1/155 (0.65%)
Sciatica [A] *	0/149 (0%)	1/155 (0.65%)
Subarachnoid hemorrhage [A] *	0/149 (0%)	1/155 (0.65%)
Syncope [A] *	1/149 (0.67%)	1/155 (0.65%)
Tremor [A] *	0/149 (0%)	1/155 (0.65%)
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous [A] *	1/149 (0.67%)	0/155 (0%)
Psychiatric disorders		
Depressive delusion [A] *	0/149 (0%)	1/155 (0.65%)
Reproductive system and breast disorders		
Fallopian tube cyst [A] *	1/149 (0.67%)	0/155 (0%)
Respiratory, thoracic and mediastinal disorders		
Painful respiration [A] *	1/149 (0.67%)	0/155 (0%)
Pleurisy [A] *	1/149 (0.67%)	0/155 (0%)
Skin and subcutaneous tissue disorders		

	Rebif®+ Minocycline	Rebif® + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Urticaria [A] *	0/149 (0%)	1/155 (0.65%)
Surgical and medical procedures		
Abscess drainage [A] *	0/149 (0%)	1/155 (0.65%)
Hysterectomy [A] *	1/149 (0.67%)	0/155 (0%)
Plastic surgery [A] *	0/149 (0%)	1/155 (0.65%)
Thyroidectomy [A] *	0/149 (0%)	1/155 (0.65%)
Transplant [A] *	0/149 (0%)	1/155 (0.65%)
Vascular disorders		
Hypotension [A] *	0/149 (0%)	1/155 (0.65%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events

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

	Rebif®+ Minocycline	Rebif® + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	51/149 (34.23%)	35/155 (22.58%)
Gastrointestinal disorders		
Diarrhea [A] *	13/149 (8.72%)	7/155 (4.52%)
Nausea [A] *	22/149 (14.77%)	7/155 (4.52%)
General disorders		
Influenza like illness [A] *	9/149 (6.04%)	6/155 (3.87%)
Infections and infestations		
Nasopharyngitis [A] *	7/149 (4.7%)	11/155 (7.1%)
Investigations		

	Rebif®+ Minocycline	Rebif® + Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hepatic enzyme increased [A] *	6/149 (4.03%)	8/155 (5.16%)
Nervous system disorders		
Dizziness [A] *	9/149 (6.04%)	2/155 (1.29%)
Headache [A] *	13/149 (8.72%)	15/155 (9.68%)
Psychiatric disorders		
Depression [A] *	11/149 (7.38%)	8/155 (5.16%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

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
Organization: Merck Serono, a division of Merck KGaA
Phone: +49-6151-72-5200
Email: service@merckgroup.com