Clinical trial results:
Prospective Phase IV Clinical Trial on Effectiveness and adherence to Rebif Treatment of CIS and RMS Patients in Romania by using Electronic Device RebiSmart®

Summary

EudraCT number	2014-001290-14
Trial protocol	RO
Global end of trial date	02 January 2017

Results information

Result version number	v1 (current)
This version publication date	08 September 2017
First version publication date	08 September 2017

Trial information

Trial identification

Sponsor protocol code	EMR 200136_583

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02254304
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Merck KGaA, Communication Center Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Merck KGaA, Communication Center Merck KGaA, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 January 2017
Global end of trial reached?	Yes
Global end of trial date	02 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate effectiveness and adherence to treatment in patients with CIS and in patients with relapsing multiple sclerosis (RMS) using RebiSmart® to self-inject Rebif® in multi dose cartridge.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 106
Worldwide total number of subjects	106
EEA total number of subjects	106

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	106
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 7 sites in Romania.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rebif In RMS Subjects

Arm description:

Rebif was administered in subjects with Relapsing Multiple Sclerosis (RMS) at a dose of 44 microgram (mcg) subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Rebif
Investigational medicinal product code	
Other name	Interferon beta-1a
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Rebif was administered in RMS subjects at a dose of 44 mcg subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months

Arm title	Rebif in CIS Subjects

Arm description:

Rebif was administered in subjects with Clinically Isolated Syndromes (CIS) at a dose of 44 microgram (mcg) subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Rebif
Investigational medicinal product code	
Other name	Interferon beta-1a
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Rebif was administered in CIS subjects at a dose of 44 mcg subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.

Number of subjects in period 1	Rebif In RMS Subjects	Rebif in CIS Subjects
Started	89	17
Completed	75	13
Not completed	14	4
personal decision	1	-
Consent withdrawn by subject	3	-
Adverse event, non-fatal	2	1
personal causes	4	1
Lost to follow-up	2	2
Protocol deviation	1	-
Injection site pain and Injection fear	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rebif In RMS Subjects
Reporting group description:	
Rebif was administered in subjects with Relapsing Multiple Sclerosis (RMS) at a dose of 44 microgram (mcg) subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.	
Reporting group title	Rebif in CIS Subjects
Reporting group description:	
Rebif was administered in subjects with Clinically Isolated Syndromes (CIS) at a dose of 44 microgram (mcg) subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.	

Reporting group values	Rebif In RMS Subjects	Rebif in CIS Subjects	Total
Number of subjects	89	17	106
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	36.1	31.6	
standard deviation	± 10.71	± 9.63	-
Gender, Male/Female			
Units: Subjects			
Female	58	7	65
Male	31	10	41
Number of Subjects Living in City or Rural Area			
Number of subjects living in city or rural area were presented.			
Units: Subjects			
City	71	13	84
Rural	18	4	22
Geographical Allocation			
Number of subjects depending upon the geographical location were presented.			
Units: Subjects			
North eastern	18	3	21
North western	23	3	26
South eastern	45	10	55
South western	3	1	4
Nicotine Used Status			
Number of subjects with Nicotine used status was categorized under never used, regular user, occasional user and former user.			
Units: Subjects			
Never used	63	10	73
Regular user	19	3	22
Occasional user	0	0	0
Former user	7	4	11
Alcohol Consumption			
Units: Subjects			

Subjects consumed alcohol	3	1	4
Subjects did not consume alcohol	86	16	102

End points

End points reporting groups

Reporting group title	Rebif In RMS Subjects

Reporting group description:

Rebif was administered in subjects with Relapsing Multiple Sclerosis (RMS) at a dose of 44 microgram (mcg) subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.

Reporting group title	Rebif in CIS Subjects

Reporting group description:

Rebif was administered in subjects with Clinically Isolated Syndromes (CIS) at a dose of 44 microgram (mcg) subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.

Subject analysis set title	Rebif in RMS and CIS Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

Rebif was administered in RMS and CIS subjects at a dose of 44 mcg subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.

Primary: Percentage of Relapse-free RMS Subjects

End point title	Percentage of Relapse-free RMS Subjects[1][2]

End point description:

A relapse was defined as the appearance of a new symptom or worsening of an old symptom, attributable to multiple sclerosis (MS), accompanied by an appropriate new neurological abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days. Relapse-free RMS subjects were those who did not had relapse during 12 month treatment period. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Data was planned to be reported for "Rebif in RMS Subjects" arm.

End point type	Primary

End point timeframe:

Month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Rebif In RMS Subjects			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage of subjects				
number (not applicable)	66.3			

Statistical analyses

No statistical analyses for this end point

Primary: Time to the First Relapse for CIS Subjects

End point title	Time to the First Relapse for CIS Subjects[3][4]

End point description:

A relapse was defined as the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by an appropriate new neurological abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days. Time to the First Relapse was defined as the duration from start of the treatment until first relapse. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Data was planned to be reported for "Rebif in CIS Subjects" arm. 99999 = Median Kaplan Meier time to first relapse and inter-quartile range was not reached in the study because relapse was reported in only 1 subject.

End point type	Primary

End point timeframe:

Baseline up to 12 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Rebif in CIS Subjects			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Adherence

End point title	Percentage of Subjects With Treatment Adherence

End point description:

According to the World Health Organisation (WHO), treatment adherence is defined as both compliance (taking the medication in the correct dose and according to the schedule prescribed) and persistency (maintenance of the drug regimen over the long-term). Percentage of subjects with treatment adherence under different categories (<=50%, >50-75%, >75-90%, >90%) were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	17		
Units: percentage of subjects				
number (not applicable)				
Adherence <=50%	2.2	11.8		
Adherence >50-75%	2.2	0		
Adherence >75-90%	13.5	0		
Adherence >90%	80.9	88.2		
Missing	1.1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Relapse by Adherence Category

End point title	Percentage of Subjects With Relapse by Adherence Category

End point description:

A relapse was defined as the appearance of a new symptom or worsening of an old symptom, attributable to multiple sclerosis (MS), accompanied by an appropriate new neurological abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days. According to the World Health Organisation (WHO), treatment adherence is defined as both compliance (taking the medication in the correct dose and according to the schedule prescribed) and persistency (maintenance of the drug regimen over the long-term). Percentage of subjects with relapses by adherence categories (<=50%, >50-75%, >75-90%, >90%) were presented. Adherence missing are the subjects who withdrew before 12 months and who did not have any relapses before withdrawal. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	17		
Units: percentage of subjects				
number (not applicable)				
Relapse Status Yes, Adherence <= 50% (n=2, 2)	0	0		
Relapse Status Yes, Adherence >50-75% (n=2, 0)	0	0		
Relapse Status Yes, Adherence >75-90% (12, 0)	16.7	0		
Relapse Status Yes, Adherence >90% (n=72, 15)	19.4	6.7		
Relapse Status Yes, Adherence Missing (n=1, 0)	0	0		
Relapse Status No, Adherence <= 50% (n=2, 2)	0	50		

Relapse Status No, Adherence >50-75% (n=2, 0)	50	0		
Relapse Status No, Adherence >75-90% (n=12, 0|)	50	0		
Relapse Status No, Adherence >90% (n=72, 15)	72.2	73.3		
Relapse Status No, Adherence Missing (n=1, 0)	0	0		
Relapse Status Missing, Adherence <=50% (n=2, 2)	100	50		
Relapse Status Missing, Adherence >50-75% (n=2, 0)	50	0		
Relapse Status Missing,Adherence >75-90%(n=12, 2)	33.3	0		
Relapse Status Missing, Adherence >90% (n=72, 15)	8.3	20		
Relapse Status Missing, Adherence Missing (n=1, 0)	100	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who Prematurely Terminated Treatment and Reasons

End point title	Percentage of subjects who Prematurely Terminated Treatment and Reasons

End point description:

Percentage of subjects who prematurely terminated treatment and reasons were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	17		
Units: percentage of subjects				
number (not applicable)				
Adverse Event	2.2	5.9		
Lost to follow-up	2.2	11.8		
Protocol Non-compliance	1.1	0		
Withdrew Consent	3.4	0		
Pain at Injection site and fear of Injection	1.1	0		
personal causes	4.5	5.9		
personal decision	1.1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Free From Clinical Disease Activity

End point title	Percentage of Subjects Free From Clinical Disease Activity

End point description:

Data could not be analyzed for this outcome because this is a composite outcome dependent on subjects free from relapses and Expanded Disability Status Scale (EDSS) progression, where EDSS progression requires to be collected every 3/6 months and confirmed 3/6 months later. Since EDSS progression was only done at Month 12, therefore this derived outcome could not be estimated.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[5] - EDSS progression was only done at Month 12, therefore this derived outcome could not be estimated

[6] - EDSS progression was only done at Month 12, therefore this derived outcome could not be estimated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Free from Disability Progression

End point title	Percentage of Subjects Free from Disability Progression

End point description:

Data could not be analyzed for this outcome because this Expanded Disability Status Scale (EDSS) progression requires EDSS to be collected every 3/6 months and confirmed 3/6 months later. Since EDSS progression was only done at Month 12, therefore this derived outcome could not be estimated.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[7] - EDSS progression was only done at Month 12, therefore this derived outcome could not be estimated.
[8] - EDSS progression was only done at Month 12, therefore this derived outcome could not be estimated.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Relapses in RMS Subjects

End point title	Mean Number of Relapses in RMS Subjects[9]

End point description:

A relapse was defined as the appearance of a new symptom or worsening of an old symptom, attributable to multiple sclerosis (MS), accompanied by an appropriate new neurological abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

End point values	Rebif In RMS Subjects			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: relapses				
arithmetic mean (standard deviation)	0.2 (± 0.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Reasons of Missed Injections

End point title	Number of Subjects With Reasons of Missed Injections

End point description:

Number of subjects with the reasons of missed injections were presented. Aspartate transaminase and alanine transaminase are abbreviated as ALT and AST respectively. Glutamic oxaloacetic transaminase and glutamic pyruvic transaminase are abbreviated as GOT and GPT respectively. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects who missed the injections are evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Rebif in RMS and CIS Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	62			
Units: subjects				
Forgot to Injection	48			
Tired	23			
Fear of Injection	11			
Did not want to have Injection	5			
Pain at Injection site	5			
Flu-like symptoms	4			
Adverse event	2			
Device broken	1			
Device malfunctions	1			
Device not functioning	1			
Difficulty using the device	1			
Elevated ALT and AST	1			
Elevated liver enzymes	2			
Increased GOT and GPT levels	2			
Local erythema and induration	1			
Missed study medication	1			
Forgot the device at home	1			
No access to medication	1			
could not came at the scheduled visit	1			
Patient redrawn intracutaneous	1			
Stop the treatment	1			
Technical problems with Rebismart	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Evaluation of RebiSmart use as Assessed by Investigator

End point title	Overall Evaluation of RebiSmart use as Assessed by Investigator

End point description:

Evaluation of RebiSmart was categorized under very easy, quite easy, Neither easy nor difficult, very difficult and missing. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	17		
Units: subjects				
Very easy	46	13		
Quite easy	32	1		
Neither easy nor difficult	9	1		
Quite difficult	0	0		
Very difficult	1	2		
Missing	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Visits to Clinic by Subjects due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Visits to Clinic by Subjects due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of visits to clinic by subjects due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects who visited clinic for MS.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: visits				
arithmetic mean (standard deviation)	0.2 (± 0.49)	0.1 (± 0.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Subjects Visiting Different Types of Doctors During Their Clinical Visit

End point title	Healthcare Resource Utilization Questionnaire - Number of Subjects Visiting Different Types of Doctors During Their Clinical Visit

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Subjects who took consultations with specialists, general practitioners for MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects who visited to doctors for MS.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	1		
Units: subjects				
General practitioner	1	1		
Specialist	15	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Visits by Healthcare Professional to Subject's Home

End point title	Healthcare Resource Utilization Questionnaire - Number of Visits by Healthcare Professional to Subject's Home

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of visits by healthcare professional to subject's home were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here “Number of Subjects Analyzed” signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: visits				
arithmetic mean (standard deviation)	0 (± 0.11)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Times Subjects Visited Emergency Room due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Times Subjects Visited Emergency Room due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of times subjects visited emergency room due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects analyzed" signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: emergency room visits				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Days Subjects Hospitalized due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Days Subjects Hospitalized due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room,

consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of days subjects hospitalized due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: days				
arithmetic mean (standard deviation)	0.1 (± 0.75)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire -Number of Subjects Who Paid Someone to Assist Them due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire -Number of Subjects Who Paid Someone to Assist Them due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of subjects who paid someone to assist them due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: subjects	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Days per Week Assistant Worked For Subject due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Days per Week Assistant Worked For Subject due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of days per week assistant worked for subject due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure.Here "99999" signifies data was not available because standard deviation could not be estimated as there was only 1 subject analysed.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: days per week				
arithmetic mean (standard deviation)	2.5 (± 2.12)	2 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Hours per Day Assistant Worked for Subject due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Hours per Day Assistant Worked for Subject due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of hours per week assistant worked for subject due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure. Here "99999" signifies data was not available because standard deviation could not be estimated as there was only 1 subject analysed.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: hours per day				
arithmetic mean (standard deviation)	2 (± 1.41)	4 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Subjects Whose Relatives or Friends Missed Work due to Subjects Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Subjects Whose Relatives or Friends Missed Work due to Subjects Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of subjects whose relatives or friends missed work due to subjects' MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: subject	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Working Days Missed by Relative or Friend due to Subjects' Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Working Days Missed by Relative or Friend due to Subjects' Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of working days missed by relative or friend due to subjects' MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here “Number of Subjects Analyzed” signifies number of subjects evaluable for this outcome measure. Here "99999" signifies Standard deviation could not be estimated as there was only 1 subject analyzed.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: days				
arithmetic mean (standard deviation)	1 (± 99999)	3 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Subjects Who Missed any Full Days From Work due to Multiple Sclerosis (MS).

End point title	Healthcare Resource Utilization Questionnaire - Number of Subjects Who Missed any Full Days From Work due to Multiple Sclerosis (MS).

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of subjects who missed any full days from work due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here “Number of Subjects Analyzed” signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: subjects	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Full Days Missed From Work by Subjects

End point title	Healthcare Resource Utilization Questionnaire - Number of Full Days Missed From Work by Subjects

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of full days missed from work by subjects were presented. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: days				
arithmetic mean (standard deviation)	46.5 (± 61.52)	3.5 (± 2.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Subjects Who Missed any Partial Days From Work due to Multiple Sclerosis (MS).

End point title	Healthcare Resource Utilization Questionnaire - Number of Subjects Who Missed any Partial Days From Work due to Multiple Sclerosis (MS).

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of subjects who missed any partial days from work due to MS were

presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here “Number of Subjects Analyzed” signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: subjects	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Hours per day Missed From Work by Subjects

End point title	Healthcare Resource Utilization Questionnaire - Number of Hours per day Missed From Work by Subjects

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of hours per day missed from work by subjects were presented. Here “Number of Subjects Analyzed” signifies number of subjects evaluable for this outcome measure. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "99999" signifies data was not available because standard deviation could not be estimated as there was only 1 subject analysed.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: hours per day				
arithmetic mean (standard deviation)	8 (± 99999)	3 (± 2.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Subjects Accomplished Less Work due to Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Subjects Accomplished Less Work due to Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Number of subjects accomplished less work due to MS were presented. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	17		
Units: subjects	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization Questionnaire - Number of Subjects With Percentage of Work completed Despite of Multiple Sclerosis (MS)

End point title	Healthcare Resource Utilization Questionnaire - Number of Subjects With Percentage of Work completed Despite of Multiple Sclerosis (MS)

End point description:

Subjects was assessed at Month 12 utilizing the Health Resource Utilization Questionnaire (HRUQ), a subject self-report tool designed to evaluate the economic impact of MS. Healthcare resource utilization was collected in the following areas: admissions and stays in the hospital, emergency room, consultations with specialists, general practitioners, or other healthcare professionals, work productivity, health care financial impact. Amount of work done by subjects in spite of multiple sclerosis was presented under different percentages (0-100%). Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment. Here "Number of Subjects Analyzed" signifies number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects				
0% Work Completed	0	0		
10% Work Completed	1	0		
20% Work Completed	0	0		
30% Work Completed	1	0		
40% Work Completed	0	0		
50% Work Completed	0	0		
60% Work Completed	0	0		
70% Work Completed	0	0		
80% Work Completed	3	1		
90% Work Completed	2	0		
100% Work Completed	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Medication Adherence based on Morisky Medication Adherence Score

End point title	Number of subjects with Medication Adherence based on Morisky Medication Adherence Score

End point description:

The Morisky Medication Adherence Scale (MMAS) is a valid and reliable instrument that consists of 8 items that measure medication adherence. The scores of the MMAS-8 range from 0 to 8. This self-report scale consists of 7 items answered with a yes or no and 1 item with a 5-point Likert scale. A score below 6 indicates low adherence, a score between 6 to < 8 indicates medium adherence and a score of 8 indicates high adherence. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	17		
Units: subjects				
Low Adherence	23	3		
Medium Adherence	45	6		
High Adherence	21	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Event or Adverse Drug Reaction (AE/ADR), Serious AE/ADR, AE/ADR Leading to Death and AE/ADR Leading to Early Termination

End point title	Number of Subjects With Adverse Event or Adverse Drug Reaction (AE/ADR), Serious AE/ADR, AE/ADR Leading to Death and AE/ADR Leading to Early Termination

End point description:

An AE was any untoward medical occurrence in a subject or clinical investigation in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An ADR was any unfavourable or unintended response (adverse event) that could possibly be related to the drug treatment. An SAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. AE/ADR was planned to be reported for both the arms together. Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Rebif in RMS and CIS Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	106			
Units: subjects				
AE/ADR	30			
Serious AE/ADR	1			
AE/ADR Leading to Death	0			
AE/ADR Leading to Early Termination	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Expanded Disability Status Scale (EDSS) Score

End point title	Expanded Disability Status Scale (EDSS) Score

End point description:

EDSS is an ordinal scale in half-point increments that qualifies disability in participants with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS). Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Rebif In RMS Subjects	Rebif in CIS Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	17		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	1.87 (± 0.991)	1.24 (± 0.615)		
Month 12	1.8 (± 0.981)	1.13 (± 0.581)		

Statistical analyses

No statistical analyses for this end point

Secondary: Body Mass Index (BMI)

End point title	Body Mass Index (BMI)

End point description:

BMI was defined as weight in kilogram (kg) divided by height in square meter (m^2). Full analysis set included all subjects enrolled into the study and who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Rebif in RMS and CIS Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	106			
Units: Kg/m^2				
arithmetic mean (standard deviation)				
Baseline	23.57 (± 3.347)			
Month 12	23.51 (± 3.582)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 12 months	
Adverse event reporting additional description:	
AE/ADR was planned to be reported for both the arms together.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Rebif in RMS and CIS Subjects
Reporting group description:	
Rebif was administered in RMS and CIS subjects at a dose of 44 mcg subcutaneously using RebiSmart auto-injector three times a week for a total duration up to 12 months.	

Serious adverse events	Rebif in RMS and CIS Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 106 (0.94%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rebif in RMS and CIS Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 106 (14.15%)		
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	7 / 106 (6.60%)		
occurrences (all)	7		
General disorders and administration site conditions			

Influenza Like Illness subjects affected / exposed occurrences (all)	9 / 106 (8.49%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported