Clinical trial results:
Multicenter, open-label, 12 weeks, phase IV pRospectivE randomized study aimed at evaLuating whether sc IFN beta 1a (Rebif®) administered In the morning may affEct the severity of Flu-like syndrome and patient perceived invisible symptoms in subjects with relapsing multiple sclerosis (RELIEF)

Summary

EudraCT number	2013-004450-21
Trial protocol	IT
Global end of trial date	11 May 2017

Results information

Result version number	v1 (current)
This version publication date	06 April 2018
First version publication date	06 April 2018

Trial information

Trial identification

Sponsor protocol code	EMR200136-570

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02064816
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 Healthcare, a business of Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Merck KGaA Communication Center, Merck Healthcare, a business of Merck KGaA, Darmstadt, Germany, +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	13 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to assess the severity of flu like symptoms (FLS), as measured by Items 13 to 16 of the Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ), in subjects injecting Rebif 44 mcg in the morning versus the evening.

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	12 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	200
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 29 clinical trial sites in Italy.

Pre-assignment

Screening details:

A total of 200 subjects were enrolled in the study, of which 104 were randomized to Rebif morning treatment group, and 96 were randomized to Rebif evening treatment group. A subgroup of subjects also took part in a sub study assessing cytokines and other immunological biomarkers.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rebif Morning Administration

Arm description:

Subjects self-injected Rebif at a dose of 44 microgram (mcg) subcutaneously three times a week by using RebiSmart autoinjector device in the morning for 12 weeks.

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

Dosage and administration details:

Subjects self-injected Rebif at a dose of 44 microgram (mcg) subcutaneously three times a week by using RebiSmart autoinjector device in the morning for 12 weeks.

Arm title	Rebif Evening Administration

Arm description:

Subjects self-injected Rebif at a dose of 44 mcg subcutaneously three times a week by using RebiSmart autoinjector device in the evening for 12 weeks.

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

Dosage and administration details:

Subjects self-injected Rebif at a dose of 44 mcg subcutaneously three times a week by using RebiSmart autoinjector device in the evening for 12 weeks

Number of subjects in period 1	Rebif Morning Administration	Rebif Evening Administration
Started	104	96
Completed	96	88
Not completed	8	8
Consent withdrawn by subject	2	1
Adverse event, non-fatal	3	2
Therapeutic failure	-	1
Unspecified	1	3
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Rebif Morning Administration
Reporting group description:	
Subjects self-injected Rebif at a dose of 44 microgram (mcg) subcutaneously three times a week by using RebiSmart autoinjector device in the morning for 12 weeks.	
Reporting group title	Rebif Evening Administration
Reporting group description:	
Subjects self-injected Rebif at a dose of 44 mcg subcutaneously three times a week by using RebiSmart autoinjector device in the evening for 12 weeks.	

Reporting group values	Rebif Morning Administration	Rebif Evening Administration	Total
Number of subjects	104	96	200
Age Categorical Units: Subjects			
<18 years	0	0	0
>=18 years to 64 years	104	96	200
>64 years	0	0	0
Gender, Male/Female Units: Subjects			
Female	76	62	138
Male	28	34	62

End points

End points reporting groups

Reporting group title	Rebif Morning Administration
Reporting group description:	
Subjects self-injected Rebif at a dose of 44 microgram (mcg) subcutaneously three times a week by using RebiSmart autoinjector device in the morning for 12 weeks.	
Reporting group title	Rebif Evening Administration
Reporting group description:	
Subjects self-injected Rebif at a dose of 44 mcg subcutaneously three times a week by using RebiSmart autoinjector device in the evening for 12 weeks.	

Primary: Difference in Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Flu Like Symptom (FLS) Score Between Rebif Morning Administration and Rebif Evening Administration Groups at Week 12

End point title	Difference in Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Flu Like Symptom (FLS) Score Between Rebif Morning Administration and Rebif Evening Administration Groups at Week 12

End point description:

The MSTCQ was used as a tool to measure treatment satisfaction, focusing on the attributes specific to multiple sclerosis (MS) medications. The FLS subscale of MSTCQ was defined as the sum of the scores for questions 13 to 16 with a minimum possible total FLS score = 1 and a maximum possible total FLS score = 20. Lower score indicates lower flu like symptoms and better satisfaction. Difference between Rebif Morning Administration and Rebif Evening Administration groups at Week 12 is presented in statistical analysis section. The Intention to Treat Analysis Set (ITT) included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Missing data on FLS were imputed using the last observation carried forward (LOCF) method.

End point type	Primary

End point timeframe:

Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	88		
Units: units on scale				
arithmetic mean (standard deviation)	12.3 (± 3.87)	11.8 (± 3.02)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Rebif Morning Administration v Rebif Evening Administration

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.277763
Method	Mann-Whitney Non Parameteric test
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	1.56
Variability estimate	Standard deviation
Dispersion value	3.5

Secondary: Difference in Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Flu Like Symptom (FLS) Score Between Rebif Morning Administration and Rebif Evening Administration Groups at Week 4 and 8

End point title	Difference in Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Flu Like Symptom (FLS) Score Between Rebif Morning Administration and Rebif Evening Administration Groups at Week 4 and 8

End point description:

The MSTCQ was used as a tool to measure treatment satisfaction, focusing on the attributes specific to multiple sclerosis (MS) medications. The FLS subscale of MSTCQ was defined as the sum of the scores for questions 13 to 16 with a minimum possible total FLS score = 1 and a maximum possible total FLS score = 20. Lower score indicates lower flu like symptoms and better satisfaction. Difference between Rebif Morning Administration and Rebif Evening Administration groups at Week 4 and 8 is presented in statistical analysis section. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Week 4 and 8

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	88		
Units: units on scale				
least squares mean (confidence interval 95%)				
Week 4 (n= 81, 81)	12.4368 (11.7402 to 13.1333)	11.0876 (10.3705 to 11.8046)		
Week 8 (n= 97, 88)	13.0039 (12.3244 to 13.6834)	11.6672 (10.9565 to 12.3779)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0083
Method	linear mixed model for repeated measures
Parameter estimate	Least Square (LS) Mean difference
Point estimate	1.3492
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3495
upper limit	2.3489

Statistical analysis title	Statistical Analysis
Statistical analysis description: Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0079
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	1.3367
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3534
upper limit	2.32

Secondary: Difference in Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Subscale Scores Between Rebif Morning Administration and Rebif Evening Administration Groups at Week 4, 8 and 12

End point title	Difference in Multiple Sclerosis Treatment Concern Questionnaire (MSTCQ) Subscale Scores Between Rebif

	Morning Administration and Rebif Evening Administration Groups at Week 4, 8 and 12

End point description:

MSTCQ: a tool to measure treatment satisfaction, focusing on attributes specific to MS medications. Following sub-scales were assessed: Injection site reactions (ISRs), Global side-effects, Benefits, Pain, Visual Analog Scale (VAS), and Rating of Pain. ISR subscale: defined as sum of scores for questions 17 to 20 (minimum score 4 and maximum score of 20). Global side-effects subscale: defined as sum of scores for questions 21 to 23 (minimum score 3 and maximum score 15). Benefits (question 35); description of pain (question 36); VAS (question 37); rating of pain (question 38) subscales ranged from 1 to 5, with minimum score of 1 and maximum score of 5. For each of subscales, lower scores indicated better satisfaction. ITT population was used. "Number of Subjects Analyzed" = subjects who were evaluable for this outcome measure and "n" = subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Week 4, 8 and 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	93		
Units: units on scale				
least squares mean (confidence interval 95%)				
ISRs subscale Week 4 (n= 75; 66)	10.8459 (10.1609 to 11.5309)	10.4456 (9.7177 to 11.1735)		
ISRs subscale Week 8 (n= 80; 77)	11.5363 (10.8625 to 12.2101)	11.4515 (10.7540 to 12.1490)		
ISRs subscale Week 12 (n= 83; 75)	11.6380 (10.9720 to 12.3041)	11.9625 (11.2598 to 12.6652)		
Global side-effect subscale: Week 4 (n= 96; 91)	10.2144 (9.6771 to 10.7518)	10.2852 (9.7276 to 10.8429)		
Global side-effect subscale: Week 8 (n= 94; 87)	10.4111 (9.8698 to 10.9525)	10.2214 (9.6567 to 10.7862)		
Global side-effect subscale: Week 12 (n= 93; 87)	10.5879 (10.0456 to 11.1302)	10.1782 (9.6132 to 10.7432)		
Benefits: Week 4 (n= 76; 75)	3.1325 (2.7856 to 3.4794)	3.5408 (3.1912 to 3.8905)		
Benefits: Week 8 (n= 71; 74)	3.5779 (3.2207 to 3.9351)	3.7137 (3.3622 to 4.0652)		
Benefits: Week 12 (n= 70; 71)	3.6059 (3.2467 to 3.9652)	3.6640 (3.3062 to 4.0218)		
Description of pain: Week 4 (n= 89; 86)	4.3755 (3.2024 to 5.5485)	3.7846 (2.5846 to 4.9847)		
Description of pain: Week 8 (n= 85; 84)	5.3132 (4.1262 to 6.5003)	6.0821 (4.8767 to 7.2875)		

Description of pain: Week 12 (n= 88; 80)	5.7853 (4.6089 to 6.9617)	5.6431 (4.4239 to 6.8624)		
VAS: Week 4 (n= 96; 89)	11.8837 (7.6691 to 16.0983)	11.2293 (6.8280 to 15.6305)		
VAS: Week 8 (n= 91; 87)	17.2316 (12.9597 to 21.5035)	19.4610 (15.0359 to 23.8860)		
VAS: Week 12 (n= 91; 84)	16.1757 (11.9054 to 20.4460)	21.5953 (17.1359 to 26.0547)		
Rating of pain: Week 4 (n= 98; 90)	1.3073 (1.1008 to 1.5138)	1.3004 (1.0846 to 1.5162)		
Rating of pain: Week 8 (n= 93; 89)	1.5653 (1.3553 to 1.7753)	1.6522 (1.4356 to 1.8688)		
Rating of pain: Week 12 (n= 93; 86)	1.4994 (1.2895 to 1.7094)	1.7218 (1.5029 to 1.9407)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: ISRs subscale Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4311
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.4003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5992
upper limit	1.3998

Statistical analysis title	Statistical Analysis
Statistical analysis description: ISRs subscale Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8635
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.08479
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.885
upper limit	1.0546

Statistical analysis title	Statistical Analysis
Statistical analysis description: ISRs subscale Week 12	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5099
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.3245
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2927
upper limit	0.6437

Statistical analysis title	Statistical Analysis
Statistical analysis description: Global side-effect subscale: Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8574
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.07079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8452
upper limit	0.7036

Statistical analysis title	Statistical Analysis
Statistical analysis description: Global side-effect subscale: Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6338
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.1897
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5926
upper limit	0.972

Statistical analysis title	Statistical Analysis
Statistical analysis description: Global side-effect subscale: Week 12	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3042
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.4097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3734
upper limit	1.1929

Statistical analysis title	Statistical Analysis
Statistical analysis description: Benefits: Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1038
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.4083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9008
upper limit	0.08419

Statistical analysis title	Statistical Analysis
Statistical analysis description: Benefits: Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.594
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.1358
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.637
upper limit	0.3653

Statistical analysis title	Statistical Analysis
Statistical analysis description: Benefits: Week 12	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8217
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.05809
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5651
upper limit	0.4489

Statistical analysis title	Statistical Analysis
Statistical analysis description: Description of pain: Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.489
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.5909
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0873
upper limit	2.269

Statistical analysis title	Statistical Analysis
Statistical analysis description: Description of pain: Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3719
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.7689
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4607
upper limit	0.9229

Statistical analysis title	Statistical Analysis
Statistical analysis description: Description of pain: Week 12	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.869
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.1422
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5521
upper limit	1.8364

Statistical analysis title	Statistical Analysis
Statistical analysis description: VAS: Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8328
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.6544
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4393
upper limit	6.7482

Statistical analysis title	Statistical Analysis
Statistical analysis description: VAS: Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4764
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-2.2294
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.38
upper limit	3.9212

Statistical analysis title	Statistical Analysis
Statistical analysis description: VAS: Week 12	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0852
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-5.4196
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5939
upper limit	0.7547

Statistical analysis title	Statistical Analysis
Statistical analysis description: Rating of pain: Week 4	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9639
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	0.006873
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2918
upper limit	0.3055

Statistical analysis title	Statistical Analysis
Statistical analysis description: Rating of pain: Week 8	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5715
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.08689
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3886
upper limit	0.2148

Statistical analysis title	Statistical Analysis
Statistical analysis description: Rating of pain: Week 12	
Comparison groups	Rebif Morning Administration v Rebif Evening Administration
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1502
Method	linear mixed model for repeated measures
Parameter estimate	LS Mean difference
Point estimate	-0.2224
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5256
upper limit	0.0809

Secondary: Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Score at Week 4, 8 and 12

End point title	Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Score at Week 4, 8 and 12

End point description:

HADS was used to measure depression and anxiety in subjects. The scale was limited to 14 questions. Seven of the items related to anxiety and 7 related to depression. Each item on the questionnaire was scored from 0-3 giving a total score between 0 and 21 for either anxiety or depression where higher score indicates more anxiety/depression. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8 and 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	93		
Units: units on scale				
least squares mean (confidence interval 95%)				
Anxiety score: Change at Week 4 (n= 95; 90)	-0.6625 (-1.1976 to -0.1273)	-0.4604 (-1.0106 to 0.08968)		
Anxiety score: Change at Week 8 (n= 89; 88)	-0.7222 (-1.2688 to -0.1755)	-0.3763 (-0.9308 to 0.1782)		
Anxiety score: Change at Week 12 (n= 90; 86)	-0.6435 (-1.1879 to -0.09918)	0.05023 (-0.5081 to 0.6085)		
Depression score: Change at Week 4 (n= 97; 89)	-0.1539 (-0.8083 to 0.5005)	0.2211 (-0.4617 to 0.9038)		
Depression score: Change at Week 8 (n= 92; 89)	-0.2397 (-0.9062 to 0.4267)	0.1999 (-0.4835 to 0.8833)		
Depression score: Change at Week 12 (n= 91; 86)	0.1906 (-0.4778 to 0.8590)	0.1162 (-0.5741 to 0.8066)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fatigue Severity Scale (FSS) Score at Week 4, 8 and 12

End point title	Change From Baseline in Fatigue Severity Scale (FSS) Score at Week 4, 8 and 12

End point description:

FSS is a method designed to assess disabling fatigue in all the individuals. The Fatigue Severity Scale is a 9-item questionnaire developed to assess the level of fatigue due to neurological disease, were each item assessed on a 1-7 scale (1= no fatigue and 7= severe fatigue). The total score was calculated as the average of individual 9-items and ranged from 1 to 7 with a higher value indicating greater impairment due to fatigue. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8 and 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	94		
Units: units on scale				
least squares mean (confidence interval 95%)				
Change at Week 4 (n= 93; 92)	0.2089 (-0.05810 to 0.4759)	0.06901 (-0.2010 to 0.3391)		
Change at Week 8 (n= 92; 90)	0.2062 (-0.06211 to 0.4746)	0.1366 (-0.1354 to 0.4085)		
Change at Week 12 (n= 88; 87)	0.1464 (-0.1253 to 0.4182)	0.1942 (-0.08036 to 0.4688)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pittsburgh Sleep Quality Index (PSQI) Score at Week 4, 8 and 12

End point title	Change From Baseline in Pittsburgh Sleep Quality Index (PSQI) Score at Week 4, 8 and 12

End point description:

PSQI is a self-rated questionnaire which assess sleep quality and disturbances over a 1-month interval using seven clinically derived components of sleep difficulties: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. PSQI is a summary of 7 components. Each component is scored from 0 to 3, therefore PSQI has a range of 0 (better) to 21 (worse). Interpretation of the PSQI is that a score less than 5 is associated with good sleep quality and a score of 5 or greater is associated with poor sleep quality. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8 and 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	55		
Units: units on scale				
least squares mean (confidence interval 95%)				
Change at Week 4 (n= 58; 50)	-0.08889 (-0.7690 to 0.5912)	0.5747 (-0.1653 to 1.3147)		
Change at Week 8 (n= 62; 53)	-0.4513 (-1.1161 to 0.2136)	0.7092 (-0.01588 to 1.4343)		

Change at Week 12 (n= 53; 47)	0.07841 (-0.6265 to 0.7833)	0.4293 (-0.3270 to 1.1855)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple Sclerosis International Quality of Life (MusiQOL) Score at Week 4, 8 and 12

End point title	Change From Baseline in Multiple Sclerosis International Quality of Life (MusiQOL) Score at Week 4, 8 and 12

End point description:

MusiQoL: validated 31-item questionnaire describing 9 dimensions: activities of daily living; psychological well-being; symptoms; relationships with friends; relationships with family; relationship with healthcare system; sentimental and sexual life; coping; and rejection. Each of questions was answered using a 6-point Likert scale ranging from 1 (never/not at all) to 6 (always/very much). Scores of each dimension were obtained by computing mean of item scores of dimension with negatively worded item scores reversed so that higher scores indicated higher health-related quality of life (QoL). All 9 dimension scores were linearly transformed to 0 to 100 scale and average of 9 dimensions was used to give a Global Score ranging from 0 to 100 (higher scores indicated higher health-related QoL. ITT population was used. "Number of Subjects Analyzed" = subjects who were evaluable for this outcome measure and "n" = subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8 and 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: units on scale				
least squares mean (confidence interval 95%)				
Global Score: Change at Week 4 (n= 83; 81)	1.6283 (-0.3761 to 3.6326)	0.1174 (-1.9196 to 2.1544)		
Global Score: Change at Week 8 (n= 81; 78)	1.1439 (-0.8780 to 3.1658)	-2.2945 (-4.3568 to -0.2321)		
Global Score: Change at Week 12 (n= 78; 75)	0.9670 (-1.0753 to 3.0094)	-1.3948 (-3.4796 to 0.6900)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Adherence at Week 4, 8 and 12

End point title	Percentage of Subjects With Treatment Adherence at Week 4, 8 and 12

End point description:

Adherence to treatment was calculated as 100 x the number of completed injections the subject administered divided by the expected number of injections. Treatment adherence was divided in two categories: percentage of subjects with less than (<) 80 percent adherence and percentage of subjects with more than and equal to (>=) 80 percent adherence. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Week 4, 8 and 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	85		
Units: Percentage of subjects				
number (not applicable)				
< 80 percent adherence at Week 4 (n= 92; 85)	3.3	5.9		
>= 80 percent adherence at Week 4 (n= 92; 85)	96.7	94.1		
< 80 percent adherence at Week 8 (n= 69; 67)	2.9	1.5		
>= 80 percent adherence at Week 8 (n= 69; 67)	97.1	98.5		
< 80 percent adherence at Week 12 (n= 84; 79)	4.8	6.3		
>= 80 percent adherence at Week 12 (n= 84; 79)	95.2	93.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Circulating Levels of Cytokines at Week 12

End point title	Change From Baseline in Circulating Levels of Cytokines at Week 12

End point description:

Results are presented for three cytokines: leptin, resistin and adiponectin. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	77		
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Leptin: Change at Week 12	-2.6 (± 3.42)	-2.6 (± 3.90)		
Resistin: Change at Week 12	-3.1 (± 3.31)	-3.0 (± 3.77)		
Adiponectin: Change at Week 12	2.8 (± 6.38)	2.8 (± 5.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Change From Baseline in Circulating Levels of Cytokines and in Flu Like Symptom (FLS) Score at Week 12

End point title	Correlation Between Change From Baseline in Circulating Levels of Cytokines and in Flu Like Symptom (FLS) Score at Week 12

End point description:

Correlation was assessed by using Pearson correlation coefficient. The MSTCQ was used as a tool to measure treatment satisfaction, focusing on the attributes specific to MS medications. The FLS subscale of MSTCQ was defined as the sum of the scores for questions 13 to 16 with a minimum possible total FLS score = 1 and a maximum possible total FLS score = 20. Lower score indicates lower flu like symptoms and better satisfaction. The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	70		
Units: Correlation coefficient				
number (not applicable)				
Leptin: Change at Week 12	0.08822	0.03944		
Resistin: Change at Week 12	-0.20200	-0.01069		
Adiponectin: Change at Week 12	0.04616	-0.13571		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Change From Baseline in Circulating Levels of Cytokines and in Other MSTCQ Items, HADS, FSS, PSQI and MusiQOL Scores at Week 12

End point title	Correlation Between Change From Baseline in Circulating Levels of Cytokines and in Other MSTCQ Items, HADS, FSS, PSQI and MusiQOL Scores at Week 12

End point description:

Correlation was assessed by using Pearson correlation coefficient. MSTCQ, HADS, FSS, PSQI and MusiQOL are described in the above endpoints. Following abbreviations used in the categories: Global side-effects (GLOBSE); description of pain (PAINDESCR). The ITT included all subjects enrolled into the study and assigned to the RebiSmart device. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	77		
Units: Correlation Coefficient				
number (not applicable)				
Leptin and MSTCQ-ISR: Week 12(n= 76; 65)	0.00595	-0.10214		
Resistin and MSTCQ-ISR: Week 12(n= 76; 65)	-0.22380	0.04855		
Adiponectin and MSTCQ-ISR: Week 12 (n= 76; 65)	-0.13365	-0.14865		
Leptin and MSTCQ-GLOBSE: Week 12 (n= 85; 76)	0.03121	0.21425		
Resistin and MSTCQ-GLOBSE: Week 12 (n= 85; 76)	0.20285	-0.12730		
Adiponectin and MSTCQ-GLOBSE: Week 12 (n= 85; 76)	0.00169	-0.06398		
Leptin and MSTCQ-benefits: Week 12 (n= 63; 61)	0.13023	-0.10915		
Resistin and MSTCQ-benefits: Week 12 (n= 63; 61)	-0.13544	-0.15636		
Adiponectin and MSTCQ-benefits: Week 12(n= 63; 61)	0.10726	0.04081		
Leptin and MSTCQ-PAINDESCR: Week 12 (n= 82; 69)	0.09118	0.01165		
Resistin and MSTCQ-PAINDESCR: Week 12 (n= 82; 69)	-0.13918	0.04150		
Adiponectin and MSTCQ-PAINDESCR: Week12(n= 82;69)	0.07093	0.01535		
Leptin and MSTCQ-VAS: Week 12 (n= 84; 73)	0.34840	-0.01433		
Resistin and MSTCQ-VAS: Week 12 (n= 84; 73)	-0.15231	0.16220		
Adiponectin and MSTCQ-VAS: Week 12 (n= 84; 73)	-0.07840	0.02109		

Leptin and MSTCQ-pain rating: Week 12 (n= 85; 75)	0.16675	-0.14381		
Resistin and MSTCQ-pain rating: Week 12(n= 85;75)	-0.23531	0.12355		
Adiponectin and MSTCQ-pain rating: Week12(n=85;75)	-0.08060	-0.08718		
Leptin and HADS-anxiety: Week 12 (n= 83; 76)	0.00754	-0.06360		
Resistin and HADS-anxiety: Week 12 (n= 83; 76)	0.02447	0.07986		
Adiponectin and HADS-anxiety: Week 12 (n= 83; 76)	0.06295	0.08818		
Leptin and HADS-depression: Week 12 (n= 83; 76)	0.05226	-0.14953		
Resistin and HADS-depression: Week 12 (n= 83; 76)	0.01970	-0.04154		
Adiponectin and HADS-depression: Week 12(n= 83;76)	0.03228	0.19209		
Leptin and FSS: Week 12 (n= 81; 77)	0.04256	0.14284		
Resistin and FSS: Week 12 (n= 81; 77)	-0.23755	-0.10961		
Adiponectin and FSS: Week 12 (n= 81; 77)	-0.00326	0.03090		
Leptin and PSQI: Week 12 (n= 52; 43)	0.00873	0.00099		
Resistin and PSQI: Week 12 (n= 52; 43)	-0.03765	0.12085		
Adiponectin and PSQI: Week 12 (n= 52; 43)	0.25795	0.24406		
Leptin and MusiQoL- Global: Week 12 (n= 74; 64)	-0.25650	0.17917		
Resistin and MusiQoL-Global: Week 12 (n= 74; 64)	0.12190	0.21936		
Adiponectin and MusiQoL-Global: Week 12(n=74; 64)	0.07152	-0.05924		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cytokines (Leptin and Resistin) Levels at Week 12

End point title	Change From Baseline in Cytokines (Leptin and Resistin) Levels at Week 12

End point description:

Results are presented for cytokines: leptin and resistin. The Substudy Analysis Set (SSAS) included all subjects in the ITT who were enrolled in the substudy. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: Nanogram/milliliter (ng/mL)				
least squares mean (confidence interval 95%)				
Leptin: Change at Week 12	-2.7826 (-6.1880 to 0.6227)	-0.7936 (-4.4371 to 2.8499)		
Resistin: Change at Week 12	-3.6628 (-5.3424 to -1.9831)	-5.8360 (-7.6339 to -4.0381)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cytokine (Adiponectin) Level at Week 12

End point title	Change From Baseline in Cytokine (Adiponectin) Level at Week 12

End point description:

The SSAS included all subjects in the ITT who were enrolled in the substudy. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: microgram per milliliter (mcg/mL)				
least squares mean (confidence interval 95%)	2.7093 (-1.0663 to 6.4848)	4.3574 (0.3174 to 8.3975)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hormone-Like Cytokine (Interleukin-6, 10 and 12) Levels at Week 12

End point title	Change From Baseline in Hormone-Like Cytokine (Interleukin-6, 10 and 12) Levels at Week 12

End point description:

The SSAS included all subjects in the ITT who were enrolled in the substudy. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies

those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: Picogram/milliliter (pg/mL)				
least squares mean (confidence interval 95%)				
Interleukin-6: Change at Week 12 (n= 8, 7)	-0.5173 (-1.7940 to 0.7593)	-0.6970 (-2.0624 to 0.6683)		
Interleukin-10: Change at Week 12 (n= 5, 3)	-0.05819 (-0.5453 to 0.4290)	-0.6660 (-1.2999 to -0.03210)		
Interleukin-12: Change at Week 12 (n= 7, 7)	-0.3490 (-0.9115 to 0.2135)	-0.4384 (-0.9973 to 0.1204)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Sleep Time (TST) and Rapid Eye Movement (REM) Sleep Time at Week 12

End point title	Change From Baseline in Total Sleep Time (TST) and Rapid Eye Movement (REM) Sleep Time at Week 12

End point description:

Polysomnography (PSG) was performed for subjects who participated in the substudy. PSG is a multi-parametric test used in the study of sleep and as a diagnostic tool in sleep medicine. Total sleep time is the total of all REM and non-REM sleep in a sleep episode. The SSAS included all subjects in the ITT who were enrolled in the substudy. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: minutes				
median (full range (min-max))				

Total Sleep Time: Change at Week 12 (n= 7; 6)	10.0 (-73.0 to 117.0)	33.0 (-227.0 to 165.0)		
REM sleep: Change at Week 12 (n= 4; 5)	-3.0 (-207.0 to 9.0)	6.0 (-67.0 to 288.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Change From Baseline in Cytokines (Leptin, Resistin and Adiponectin) and Hormone-like Cytokine Levels (Interleukin-6, 10 and 12), and TST and REM Sleep Time at Week 12

End point title	Correlation Between Change From Baseline in Cytokines (Leptin, Resistin and Adiponectin) and Hormone-like Cytokine Levels (Interleukin-6, 10 and 12), and TST and REM Sleep Time at Week 12

End point description:

Correlations between change from baseline at Week 12 in TST or REM sleep and the area under the curve (AUC) calculated using the trapezoidal method for cytokine levels (ie, leptin, resistin, adiponectin, Interleukin (IL)-12, IL 10, and IL 6) were analyzed using Pearson's correlation coefficient. Polysomnography (PSG) was performed for subjects who participated in the substudy. The SSAS included all subjects in the ITT who were enrolled in the substudy. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure. Here "n" signifies those subjects who were evaluable for this outcome measure for specified category. Here 99999 signifies that Correlation Coefficient could not be estimated as there was only 1 subject analysed for this arm at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Correlation Coefficients				
number (not applicable)				
AUC Leptin and TST: Week 12 (n= 7; 6)	0.10816	0.46984		
AUC Resistin and TST: Week 12 (n= 7; 6)	-0.56278	-0.05056		
AUC Adiponectin and TST: Week 12 (n= 7; 5)	0.17402	0.58181		
AUC IL-12 and TST: Week 12 (n= 5; 5)	-0.44328	0.24717		
AUC IL-10 and TST: Week 12 (n= 2; 1)	1.00000	99999		
AUC IL-6 and TST: Week 12 (n= 7; 6)	0.18626	-0.51662		
AUC Leptin and REM: Week 12 (n= 4; 5)	0.99732	0.63155		
AUC Resistin and REM: Week 12 (n= 4; 5)	0.22684	-0.38234		
AUC Adiponectin and REM: Week 12 (n= 4; 4)	0.98335	-0.05732		
AUC IL-12 and REM: Week 12 (n= 2; 4)	1.00000	-0.76606		
AUC IL-10 and REM: Week 12 (n= 2; 1)	-1.00000	99999		

AUC IL-6 and REM: Week 12 (n= 4; 5)	0.06269	-0.34860		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Death and TEAEs Leading to Discontinuation

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Death and TEAEs Leading to Discontinuation

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the treatment. An AE was any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with use of a medicinal product, whether or not considered related to the medicinal product. A serious adverse event (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. The term TEAE is defined as AEs starting or worsening after the first intake of the study drug. The Safety Analysis Set (SAF) included all subjects in the ITT who received at least 1 dose of the planned study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Rebif Morning Administration	Rebif Evening Administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	96		
Units: Subjects				
TEAEs	82	77		
Serious TEAEs	1	2		
TEAEs Leading to Death	0	0		
TEAE leading to Discontinuation	6	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 12

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Rebif Morning Administration

Reporting group description:

Subjects self-injected Rebif at a dose of 44 microgram (mcg) subcutaneously three times a week by using RebiSmart autoinjector device in the morning for 12 weeks.

Reporting group title	Rebif Evening Administration

Reporting group description:

Subjects self-injected Rebif at a dose of 44 mcg subcutaneously three times a week by using RebiSmart autoinjector device in the evening for 12 weeks.

Serious adverse events	Rebif Morning Administration	Rebif Evening Administration	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 104 (0.96%)	2 / 96 (2.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 104 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	1 / 104 (0.96%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rebif Morning Administration	Rebif Evening Administration	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 104 (74.04%)	70 / 96 (72.92%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	4 / 104 (3.85%)	7 / 96 (7.29%)	
occurrences (all)	4	7	
Aspartate Aminotransferase Increased			
subjects affected / exposed	4 / 104 (3.85%)	5 / 96 (5.21%)	
occurrences (all)	4	5	
Transaminases Increased			
subjects affected / exposed	4 / 104 (3.85%)	6 / 96 (6.25%)	
occurrences (all)	4	6	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 104 (22.12%)	16 / 96 (16.67%)	
occurrences (all)	23	16	
Multiple Sclerosis Relapse			
subjects affected / exposed	3 / 104 (2.88%)	7 / 96 (7.29%)	
occurrences (all)	3	7	
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	52 / 104 (50.00%)	42 / 96 (43.75%)	
occurrences (all)	52	42	
Pyrexia			
subjects affected / exposed	15 / 104 (14.42%)	11 / 96 (11.46%)	
occurrences (all)	15	11	
Injection Site Erythema			
subjects affected / exposed	14 / 104 (13.46%)	8 / 96 (8.33%)	
occurrences (all)	14	8	

Fatigue			
subjects affected / exposed	9 / 104 (8.65%)	2 / 96 (2.08%)	
occurrences (all)	9	2	
Asthenia			
subjects affected / exposed	7 / 104 (6.73%)	4 / 96 (4.17%)	
occurrences (all)	7	4	
Injection Site Pain			
subjects affected / exposed	5 / 104 (4.81%)	5 / 96 (5.21%)	
occurrences (all)	5	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 104 (9.62%)	2 / 96 (2.08%)	
occurrences (all)	10	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 104 (1.92%)	9 / 96 (9.38%)	
occurrences (all)	2	9	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	10 / 104 (9.62%)	6 / 96 (6.25%)	
occurrences (all)	10	6	
Arthralgia			
subjects affected / exposed	5 / 104 (4.81%)	7 / 96 (7.29%)	
occurrences (all)	5	7	
Pain In Extremity			
subjects affected / exposed	4 / 104 (3.85%)	6 / 96 (6.25%)	
occurrences (all)	4	6	

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