Clinical trial results:
A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects With Relapsing Multiple Sclerosis

Summary

EudraCT number	2008-006333-27
Trial protocol	LV EE DE BE NL ES CZ BG GR GB
Global end of trial date	24 October 2013

Results information

Result version number	v1 (current)
This version publication date	04 February 2016
First version publication date	21 February 2015

Trial information

Trial identification

Sponsor protocol code	105MS301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00906399
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen Idec
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Idec Study Medical Director, Biogen Idec, Clinicaltrials@biogenidec.com
Scientific contact	Biogen Idec Study Medical Director, Biogen Idec, Clinicaltrials@biogenidec.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	24 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the efficacy of peginterferon beta-1a in reducing the annualized relapse rate (ARR) in subjects with relapsing multiple sclerosis (RMS) at 1 year. The secondary objectives of this study are to determine whether peginterferon beta-1a, at 1 year when compared with placebo, is effective in reducing the total number of new or newly enlarging T2 hyperintense lesions on brain magnetic resonance imaging (MRI) scans, reducing the proportion of subjects who relapse, and slowing the progression of disability.

Protection of trial subjects:

During the first 6 weeks of treatment year 1 and again in treatment year 2, subjects were to complete dosing in the clinic; thereafter, dosing was to occur at home, and subjects were asked to attend clinic visits for collection of assessment data. If subjects experienced disease progression or relapses and wished to discontinue study treatment, recommended rules for rescue medication (switching to open-label treatment alternative approved MS medications) were defined in the protocol. To mitigate flu-like symptoms, all subjects randomized to receive peginterferon beta-1a treatment started dosing with a lower dose (starting dose of 63 mcg) and increased the dose every 2 weeks to the target dose of 125 mcg. The titration was performed in a blinded fashion. In order to relieve flu-like symptoms for the first 26 weeks in the study, all subjects were instructed to take acetaminophen, ibuprofen, nonsteroidal anti-inflammatory drugs (NSAIDS) or naproxen prior to injection and for the 24 hours following each study treatment injection at the recommended doses and frequencies per local labels. Additional doses of these protocol-designated products could be taken after 24 hours within the maximum daily dosage recommended per local labels.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Colombia: 18
Country: Number of subjects enrolled	Croatia: 14
Country: Number of subjects enrolled	Georgia: 19
Country: Number of subjects enrolled	India: 170
Country: Number of subjects enrolled	Mexico: 25
Country: Number of subjects enrolled	New Zealand: 18
Country: Number of subjects enrolled	Peru: 25
Country: Number of subjects enrolled	Russian Federation: 145

Country: Number of subjects enrolled	Serbia: 134
Country: Number of subjects enrolled	Ukraine: 189
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 386
Country: Number of subjects enrolled	Romania: 48
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 70
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Estonia: 23
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Latvia: 9
Worldwide total number of subjects	1516
EEA total number of subjects	717

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)	1516
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Screening Visit was to occur within 6 weeks prior to randomization (Baseline). The Screening period was to start on the day the subject signed the informed consent form (ICF).

Period 1

Period 1 title	Treatment Year 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Year 1: Placebo

Arm description:

Placebo every 2 weeks for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL pre-filled syringes, self-administered by subcutaneous injection

Arm title	Year 1: Peginterferon Beta-1a Q4W

Arm description:

125 mcg peginterferon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).

Arm type	Experimental
Investigational medicinal product name	PEGylated interferon beta-1a
Investigational medicinal product code	BIIB017
Other name	interferon beta-1a, Plegridy, PEG IFN ß-1a
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL of 0.25 mg/mL (125 mcg dose), self-administered by subcutaneous injection

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL pre-filled syringes, self-administered by subcutaneous injection.

Arm title	Year 1: Peginterferon Beta-1a Q2W

Arm description:

125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	PEGylated interferon beta-1a
Investigational medicinal product code	BIIB017
Other name	interferon beta-1a, Plegridy, PEG IFN ß-1a
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL of 0.25 mg/mL (125 mcg dose), self administered by subcutaneous injection.

Number of subjects in period 1[1]	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W
Started	500	500	512
Completed Year 1 Study Treatment	456	438	438 [2]
Completed	456	438	439
Not completed	44	62	73
Adverse event, serious fatal	2	1	1
Consent withdrawn by subject	30	32	36
Physician decision	-	1	3
Adverse event, non-fatal	4	22	24
Not specified	4	2	7
Lost to follow-up	4	4	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All efficacy endpoints were evaluated on the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (peginterferon beta-1a or placebo). The 1512 subjects who received at least 1 dose of study treatment comprised the ITT and safety population, and are presented in this subject disposition.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 1 subject in the Year 1: Peginterferon Beta-1a Q2W arm discontinued treatment before end of study period but remained to complete follow-up.

Period 2

Period 2 title	Treatment Year 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Year 2: Placebo Followed by Peginterferon Beta-1a Q4W

Arm description:

Subjects from Year 1 Placebo group were re-randomized to receive peginterferon beta-1a treatment with 125 mcg peginterfeon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).

Arm type	Experimental
Investigational medicinal product name	PEGylated interferon beta-1a
Investigational medicinal product code	BIIB017
Other name	interferon beta-1a, Plegridy, PEG IFN ß-1a
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL of 0.25 mg/mL (125 mcg dose), self-administered by subcutaneous injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL pre-filled syringes, self-administered by subcutaneous injection.

Arm title	Year 2: Placebo Followed by Peginterferon Beta-1a Q2W

Arm description:

Subjects from Year 1 Placebo group were re-randomized to receive peginterferon beta-1a treatment with 125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	PEGylated interferon beta-1a
Investigational medicinal product code	BIIB017
Other name	interferon beta-1a, Plegridy, PEG IFN ß-1a
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL of 0.25 mg/mL (125 mcg dose), self administered by subcutaneous injection.

Arm title	Year 2: Peginterferon Beta-1a Q4W

Arm description:

125 mcg peginterferon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).

Arm type	Experimental
Investigational medicinal product name	PEGylated interferon beta-1a
Investigational medicinal product code	BIIB017
Other name	interferon beta-1a, Plegridy, PEG IFN ß-1a
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL of 0.25 mg/mL (125 mcg dose), self-administered by subcutaneous injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL pre-filled syringes, self-administered by subcutaneous injection

Arm title	Year 2: Peginterferon Beta-1a Q2W

Arm description:

125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	PEGylated interferon beta-1a
Investigational medicinal product code	BIIB017
Other name	interferon beta-1a, Plegridy, PEG IFN ß-1a
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL of 0.25 mg/mL (125 mcg dose), self administered by subcutaneous injection.

Number of subjects in period 2[3]	Year 2: Placebo Followed by Peginterferon Beta-1a Q4W	Year 2: Placebo Followed by Peginterferon Beta-1a Q2W	Year 2: Peginterferon Beta-1a Q4W
Started	228	228	438
Completed Year 2 Study Treatment	200	196	391
Completed	198	193	391
Not completed	30	35	47
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	17	18	27
Physician decision	-	2	6
Adverse event, non-fatal	9	8	11
Not specified	2	3	1
Lost to follow-up	1	4	2

Number of subjects in period 2[3]	Year 2: Peginterferon Beta-1a Q2W
Started	438
Completed Year 2 Study Treatment	411
Completed	409
Not completed	29
Adverse event, serious fatal	3
Consent withdrawn by subject	13
Physician decision	3
Adverse event, non-fatal	6
Not specified	-
Lost to follow-up	4

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 1 subject in the Year 1: Peginterferon Beta-1a Q2W arm discontinued treatment before end

of study period but remained to complete follow-up. This subject did not enter Year 2 treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Year 1: Placebo
Reporting group description:	
Placebo every 2 weeks for 48 weeks.	
Reporting group title	Year 1: Peginterferon Beta-1a Q4W
Reporting group description:	
125 mcg peginterferon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).	
Reporting group title	Year 1: Peginterferon Beta-1a Q2W
Reporting group description:	
125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.	

Reporting group values	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W
Number of subjects	500	500	512
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	500	500	512
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	36.3	36.4	36.5
standard deviation	± 9.74	± 9.87	± 9.8
Gender categorical Units: Subjects			
Female	358	352	361
Male	142	148	151
Expanded Disability Status Scale (EDSS)			
The EDSS measures the disability status of people with multiple sclerosis (MS) on a scale that ranges from 0 to 10. The range of main categories include 0 (normal neurologic exam), to 5 (ambulatory without aid or rest for 200 meters/disability severe enough to impair full daily activities), to 10 (death due to MS).			
Units: Units on a scale			
arithmetic mean	2.44	2.48	2.47
standard deviation	± 1.18	± 1.244	± 1.255

Reporting group values	Total		
Number of subjects	1512		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	1512		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1071		
Male	441		
Expanded Disability Status Scale (EDSS)			
The EDSS measures the disability status of people with multiple sclerosis (MS) on a scale that ranges from 0 to 10. The range of main categories include 0 (normal neurologic exam), to 5 (ambulatory without aid or rest for 200 meters/disability severe enough to impair full daily activities), to 10 (death due to MS).			
Units: Units on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Year 1: Placebo
Reporting group description:	
Placebo every 2 weeks for 48 weeks.	
Reporting group title	Year 1: Peginterferon Beta-1a Q4W
Reporting group description:	
125 mcg peginterferon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).	
Reporting group title	Year 1: Peginterferon Beta-1a Q2W
Reporting group description:	
125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.	
Reporting group title	Year 2: Placebo Followed by Peginterferon Beta-1a Q4W
Reporting group description:	
Subjects from Year 1 Placebo group were re-randomized to receive peginterferon beta-1a treatment with 125 mcg peginterfeon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).	
Reporting group title	Year 2: Placebo Followed by Peginterferon Beta-1a Q2W
Reporting group description:	
Subjects from Year 1 Placebo group were re-randomized to receive peginterferon beta-1a treatment with 125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.	
Reporting group title	Year 2: Peginterferon Beta-1a Q4W
Reporting group description:	
125 mcg peginterferon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).	
Reporting group title	Year 2: Peginterferon Beta-1a Q2W
Reporting group description:	
125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.	

Primary: Annualized Relapse Rate (ARR) at 1 Year

End point title	Annualized Relapse Rate (ARR) at 1 Year
End point description:	
A relapse is defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurologic findings. Only relapses confirmed by an independent neurology evaluation committee (INEC) are included in the analysis. Data after participants switched to alternative multiple sclerosis (MS) medications are exlcuded. Data were analyzed using negative binomial regression, adjusted for baseline Expanded Disability Status Scale (EDSS) score (<4 versus > or = 4), baseline age (<40 versus > or =40 years), and baseline relapse rate (number of relapses in 3 years prior to study entry divided by 3).	
End point type	Primary
End point timeframe:	
1 Year	

End point values	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500	500	512	
Units: Relapses per person-years				
number (confidence interval 95%)	0.397 (0.328 to 0.481)	0.288 (0.234 to 0.355)	0.256 (0.206 to 0.318)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q4W
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114
Method	Negative Binomial Regression
Parameter estimate	Rate Ratio
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.565
upper limit	0.93
Variability estimate	Standard error of the mean

Statistical analysis title	Statistical Analysis 2
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q2W
Number of subjects included in analysis	1012
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Negative Binomial Regression
Parameter estimate	Rate Ratio
Point estimate	0.644
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.831
Variability estimate	Standard error of the mean

Secondary: Number of New or Newly Enlarging T2 Hyperintense Lesions at 1 Year	
End point title	Number of New or Newly Enlarging T2 Hyperintense Lesions at

	1 Year

End point description:

Number of new or newly enlarging T2 hyperintense lesions on brain magnetic resonance imaging (MRI) scans. Data observed after participants switched to alternative MS medications are excluded. Adjusted mean is based on negative binomial regression, adjusted for baseline number of T2 lesions.

End point type	Secondary

End point timeframe:

1 Year

End point values	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	476[1]	462[2]	457[3]	
Units: lesions				
number (confidence interval 95%)	10.9 (9.6 to 12.5)	7.9 (6.9 to 9)	3.6 (3.1 to 4.2)	

Notes:

[1] - ITT population, with at least 1 post-baseline assessment.

[2] - ITT population, with at least 1 post-baseline assessment.

[3] - ITT population, with at least 1 post-baseline assessment.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q4W
Number of subjects included in analysis	938
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Negative Binomial Regression
Parameter estimate	Lesion Mean Ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.87
Variability estimate	Standard error of the mean

Statistical analysis title	Statistical Analysis 2
Comparison groups	Year 1: Peginterferon Beta-1a Q2W v Year 1: Placebo

Number of subjects included in analysis	933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative Binomial Regression
Parameter estimate	Lesion Mean Ratio
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.4
Variability estimate	Standard error of the mean

Secondary: Proportion of Subjects Relapsed at 1 Year

End point title	Proportion of Subjects Relapsed at 1 Year

End point description:

A relapse is defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurologic findings. Only relapses confirmed by INEC were included in the analysis. Estimated proportion of subjects relapsed is based on the Kaplan-Meier product limit method.

End point type	Secondary

End point timeframe:

Year 1

End point values	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500	500	512	
Units: Proportion of participants				
number (not applicable)	0.291	0.222	0.187	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q4W
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [4]
Method	Cox Proportion Hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.95
Variability estimate	Standard error of the mean

Notes:

[4] - Based on Cox Proportion Hazards model, adjusted for baseline EDSS (<4 versus > or = 4), age (<40 versus > or = 40 years), baseline relapse rate, and baseline Gd enhancing lesions (presence versus absence).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q2W
Number of subjects included in analysis	1012
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [5]
Method	Cox Proportion Hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.8
Variability estimate	Standard error of the mean

Notes:

[5] - Based on Cox Proportion Hazards model, adjusted for baseline EDSS (<4 versus > or = 4), age (<40 versus > or = 40 years), baseline relapse rate, and baseline Gd enhancing lesions (presence versus absence).

Secondary: Estimated Proportion of Subjects With Sustained Disability Progression at 1 Year

End point title	Estimated Proportion of Subjects With Sustained Disability Progression at 1 Year

End point description:

Sustained disability progression is defined as: at least a 1.0 point increase on the EDSS from baseline EDSS > or = 1.0 that is sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks. The EDSS measures the disability status of people with MS on a scale that ranges from 0 to 10. The range of main categories include 0 (normal neurologic examination), to 5 (ambulatory without aid or rest for 200 meters/disability severe enough to impair full daily activities), to 10 (death due to MS). Estimated proportion of subjects with progression based on the Kaplan-Meier product limit method.

End point type	Secondary

End point timeframe:

1 Year

End point values	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500	500	512	
Units: Proportion of participants				
number (not applicable)	0.105	0.068	0.068	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q4W
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038 [6]
Method	Cox Proportion Hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.97
Variability estimate	Standard error of the mean

Notes:

[6] - Based on Cox Proportion Hazards model, adjusted for baseline EDSS (<4 versus > or = 4), age (<40 versus > or = 40 years).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Year 1: Placebo v Year 1: Peginterferon Beta-1a Q2W
Number of subjects included in analysis	1012
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0383 [7]
Method	Cox Proportion Hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.97
Variability estimate	Standard error of the mean

Notes:

[7] - Based on Cox Proportion Hazards model, adjusted for baseline EDSS (<4 versus > or = 4), age (<40 versus > or = 40 years).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening through Week 96 (treatment period), plus 4 weeks (+/- 5 days) follow-up

Adverse event reporting additional description:

One subject, randomized to placebo followed by Q4W, received 1 wrong dosing kit during Year 1, and was mistakenly distributed with 1 Q2W kit, therefore receiving study drug in Weeks 20 and 22 instead of placebo. For Year 1 safety tables, this subject was grouped with Q2W, and for Year 2 safety tables, this subject was grouped with Q4W.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Year 1: Placebo

Reporting group description:

Placebo every 2 weeks for 48 weeks.

Reporting group title	Year 1: Peginterferon Beta-1a Q4W

Reporting group description:

125 mcg peginterferon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).

Reporting group title	Year 1: Peginterferon Beta-1a Q2W

Reporting group description:

125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.

Reporting group title	Year 2: Placebo Followed by Peginterferon Beta-1a Q4W

Reporting group description:

Subjects from Year 1 Placebo group were re-randomized to receive peginterferon beta-1a treatment with 125 mcg peginterfeon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).

Reporting group title	Year 2: Placebo Followed by Peginterferon Beta-1a Q2W

Reporting group description:

Subjects from Year 1 Placebo group were re-randomized to receive peginterferon beta-1a treatment with 125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.

Reporting group title	Year 2: Peginterferon Beta-1a Q4W

Reporting group description:

125 mcg peginterfeon beta-1a subcutaneously every 4 weeks (Q4W) for 48 weeks. Subjects received a placebo injection 2 weeks after each active injection (in order to maintain the blind with the Q2W arm).

Reporting group title	Year 2: Peginterferon Beta-1a Q2W

Reporting group description:

125 mcg peginterferon beta-1a subcutaneously every 2 weeks (Q2W) for 48 weeks.

Serious adverse events	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 499 (15.23%)	70 / 500 (14.00%)	55 / 513 (10.72%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign vulval neoplasm			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Venous thrombosis limb			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic pregnancy			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gait disturbance			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperpyrexia			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritability			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcoidosis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectropion of cervix			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endometrial hyperplasia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymal cyst			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic adhesions			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cervical erosion			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality disorder			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 499 (0.20%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Bile duct stone			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transaminases increased			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Avulsion fracture			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus lesion			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple injuries			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital cystic kidney disease			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocardial infarction			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Bulbar palsy			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complex partial seizures			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	57 / 499 (11.42%)	47 / 500 (9.40%)	34 / 513 (6.63%)
occurrences causally related to treatment / all	1 / 76	2 / 61	0 / 37
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuritis cranial			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuromyelitis optica			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uhthoff's phenomenon			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal strangulation			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition disorder			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Basedow's disease			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enthesopathy			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 499 (0.20%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteonecrosis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacroiliitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial diarrhoea			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis gangrenous			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometritis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myometritis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 499 (0.20%)	2 / 500 (0.40%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 499 (0.20%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhoid fever			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 499 (0.20%)	2 / 500 (0.40%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	1 / 513 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pharyngitis			
subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral tracheitis			

subjects affected / exposed	0 / 499 (0.00%)	0 / 500 (0.00%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 499 (0.00%)	1 / 500 (0.20%)	0 / 513 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Year 2: Placebo Followed by Peginterferon Beta-1a Q4W	Year 2: Placebo Followed by Peginterferon Beta-1a Q2W	Year 2: Peginterferon Beta-1a Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 227 (18.50%)	36 / 228 (15.79%)	67 / 439 (15.26%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign vulval neoplasm			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip and/or oral cavity cancer			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Uterine leiomyoma			

subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic pregnancy			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperpyrexia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritability			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sarcoidosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectropion of cervix			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymal cyst			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic adhesions			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cervical erosion			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality disorder			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Bile duct stone			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Avulsion fracture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Facial bones fracture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	2 / 439 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus lesion			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

Congenital cystic kidney disease			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Bulbar palsy			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebrovascular insufficiency			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complex partial seizures			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	27 / 227 (11.89%)	21 / 228 (9.21%)	45 / 439 (10.25%)
occurrences causally related to treatment / all	3 / 31	0 / 22	2 / 50
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuritis cranial			

subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuromyelitis optica			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uhthoff's phenomenon			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Constipation			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal strangulation			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition disorder			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enthesopathy			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc disorder			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacroiliitis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial diarrhoea			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis gangrenous			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometritis			

subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	1 / 227 (0.44%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myometritis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			

subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	1 / 227 (0.44%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 227 (0.44%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhoid fever			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	3 / 227 (1.32%)	1 / 228 (0.44%)	1 / 439 (0.23%)
occurrences causally related to treatment / all	1 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 227 (0.00%)	1 / 228 (0.44%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pharyngitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral tracheitis			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Year 2: Peginterferon Beta-1a Q2W		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 438 (8.90%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign vulval neoplasm			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			

subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			

Abortion incomplete				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abortion spontaneous				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ectopic pregnancy				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gait disturbance				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperpyrexia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injection site reaction				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Irritability				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sarcoidosis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Cervical dysplasia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ectropion of cervix				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endometrial hyperplasia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endometriosis				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Epididymal cyst				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic adhesions				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine cervical erosion				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Organising pneumonia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Conversion disorder				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Personality disorder				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Bile duct stone				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Avulsion fracture			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Facial bones fracture			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meniscus lesion			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			

subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Congenital cystic kidney disease				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure congestive				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Myocardial infarction				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Bulbar palsy				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ataxia			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carpal tunnel syndrome			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Complex partial seizures			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Extrapyramidal disorder			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Monoparesis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis			

subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	25 / 438 (5.71%)		
occurrences causally related to treatment / all	0 / 29		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuritis cranial			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuromyelitis optica			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraparesis			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Partial seizures with secondary generalisation			

subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Trigeminal neuralgia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uhthoff's phenomenon				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				

subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal strangulation			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Proctalgia			

subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis toxic			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decubitus ulcer			

subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dermatitis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Micturition disorder			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Bursitis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enthesopathy			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemarthrosis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc disorder			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoporosis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Patellofemoral pain syndrome			

subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sacroiliitis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Acute sinusitis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial diarrhoea				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis gangrenous				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cervicitis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				

subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometritis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myometritis			

subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic inflammatory disease				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis chronic				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salpingo-oophoritis				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 438 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	0 / 438 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				

subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Typhoid fever			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral pharyngitis			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral tracheitis			
subjects affected / exposed	1 / 438 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Year 1: Placebo	Year 1: Peginterferon Beta-1a Q4W	Year 1: Peginterferon Beta-1a Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	378 / 499 (75.75%)	466 / 500 (93.20%)	472 / 513 (92.01%)
Investigations			
Body temperature increased			
subjects affected / exposed	27 / 499 (5.41%)	51 / 500 (10.20%)	60 / 513 (11.70%)
occurrences (all)	24	142	228
Alanine aminotransferase increased			
subjects affected / exposed	13 / 499 (2.61%)	19 / 500 (3.80%)	29 / 513 (5.65%)
occurrences (all)	13	22	34
Nervous system disorders			
Headache			
subjects affected / exposed	165 / 499 (33.07%)	206 / 500 (41.20%)	225 / 513 (43.86%)
occurrences (all)	778	1143	1415
Multiple sclerosis relapse			
subjects affected / exposed	154 / 499 (30.86%)	111 / 500 (22.20%)	90 / 513 (17.54%)
occurrences (all)	200	133	123
Dizziness			
subjects affected / exposed	30 / 499 (6.01%)	22 / 500 (4.40%)	35 / 513 (6.82%)
occurrences (all)	45	49	85
Paraesthesia			
subjects affected / exposed	23 / 499 (4.61%)	22 / 500 (4.40%)	26 / 513 (5.07%)
occurrences (all)	42	31	35
Hypoaesthesia			
subjects affected / exposed	30 / 499 (6.01%)	29 / 500 (5.80%)	17 / 513 (3.31%)
occurrences (all)	46	39	38
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	33 / 499 (6.61%)	282 / 500 (56.40%)	315 / 513 (61.40%)
occurrences (all)	67	1716	3300
Influenza like illness			
subjects affected / exposed	63 / 499 (12.63%)	234 / 500 (46.80%)	238 / 513 (46.39%)
occurrences (all)	335	1629	2492

Pyrexia			
subjects affected / exposed	75 / 499 (15.03%)	218 / 500 (43.60%)	227 / 513 (44.25%)
occurrences (all)	211	1150	1578
Chills			
subjects affected / exposed	23 / 499 (4.61%)	92 / 500 (18.40%)	88 / 513 (17.15%)
occurrences (all)	67	419	379
Injection site pain			
subjects affected / exposed	15 / 499 (3.01%)	67 / 500 (13.40%)	78 / 513 (15.20%)
occurrences (all)	18	148	287
Asthenia			
subjects affected / exposed	38 / 499 (7.62%)	70 / 500 (14.00%)	68 / 513 (13.26%)
occurrences (all)	117	248	316
Injection site pruritus			
subjects affected / exposed	6 / 499 (1.20%)	56 / 500 (11.20%)	70 / 513 (13.65%)
occurrences (all)	19	130	328
Fatigue			
subjects affected / exposed	49 / 499 (9.82%)	55 / 500 (11.00%)	52 / 513 (10.14%)
occurrences (all)	87	125	153
Pain			
subjects affected / exposed	16 / 499 (3.21%)	29 / 500 (5.80%)	25 / 513 (4.87%)
occurrences (all)	77	84	69
Hyperthermia			
subjects affected / exposed	5 / 499 (1.00%)	26 / 500 (5.20%)	22 / 513 (4.29%)
occurrences (all)	25	155	132
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	43 / 499 (8.62%)	32 / 500 (6.40%)	27 / 513 (5.26%)
occurrences (all)	74	46	73
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	31 / 499 (6.21%)	43 / 500 (8.60%)	45 / 513 (8.77%)
occurrences (all)	52	88	105
Vomiting			
subjects affected / exposed	11 / 499 (2.20%)	37 / 500 (7.40%)	26 / 513 (5.07%)
occurrences (all)	15	63	35
Diarrhoea			

subjects affected / exposed	23 / 499 (4.61%)	22 / 500 (4.40%)	18 / 513 (3.51%)
occurrences (all)	28	26	19
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	31 / 499 (6.21%)	26 / 500 (5.20%)	34 / 513 (6.63%)
occurrences (all)	44	37	56
Cough			
subjects affected / exposed	28 / 499 (5.61%)	26 / 500 (5.20%)	21 / 513 (4.09%)
occurrences (all)	34	35	29
Psychiatric disorders			
Depression			
subjects affected / exposed	21 / 499 (4.21%)	25 / 500 (5.00%)	22 / 513 (4.29%)
occurrences (all)	21	28	28
Insomnia			
subjects affected / exposed	19 / 499 (3.81%)	18 / 500 (3.60%)	28 / 513 (5.46%)
occurrences (all)	29	28	49
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	30 / 499 (6.01%)	97 / 500 (19.40%)	99 / 513 (19.30%)
occurrences (all)	96	396	661
Back pain			
subjects affected / exposed	57 / 499 (11.42%)	64 / 500 (12.80%)	62 / 513 (12.09%)
occurrences (all)	126	132	132
Arthralgia			
subjects affected / exposed	35 / 499 (7.01%)	54 / 500 (10.80%)	58 / 513 (11.31%)
occurrences (all)	54	170	296
Pain in extremity			
subjects affected / exposed	48 / 499 (9.62%)	53 / 500 (10.60%)	44 / 513 (8.58%)
occurrences (all)	87	107	110
Muscular weakness			
subjects affected / exposed	18 / 499 (3.61%)	23 / 500 (4.60%)	22 / 513 (4.29%)
occurrences (all)	20	45	33
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	77 / 499 (15.43%)	69 / 500 (13.80%)	54 / 513 (10.53%)
occurrences (all)	121	105	95

Urinary tract infection			
subjects affected / exposed	20 / 499 (4.01%)	28 / 500 (5.60%)	28 / 513 (5.46%)
occurrences (all)	29	39	38
Upper respiratory tract infection			
subjects affected / exposed	27 / 499 (5.41%)	16 / 500 (3.20%)	28 / 513 (5.46%)
occurrences (all)	41	22	37

Non-serious adverse events	Year 2: Placebo Followed by Peginterferon Beta-1a Q4W	Year 2: Placebo Followed by Peginterferon Beta-1a Q2W	Year 2: Peginterferon Beta-1a Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 227 (83.70%)	206 / 228 (90.35%)	373 / 439 (84.97%)
Investigations			
Body temperature increased			
subjects affected / exposed	5 / 227 (2.20%)	10 / 228 (4.39%)	19 / 439 (4.33%)
occurrences (all)	22	63	67
Alanine aminotransferase increased			
subjects affected / exposed	13 / 227 (5.73%)	14 / 228 (6.14%)	17 / 439 (3.87%)
occurrences (all)	16	15	26
Nervous system disorders			
Headache			
subjects affected / exposed	70 / 227 (30.84%)	64 / 228 (28.07%)	122 / 439 (27.79%)
occurrences (all)	278	516	699
Multiple sclerosis relapse			
subjects affected / exposed	50 / 227 (22.03%)	52 / 228 (22.81%)	95 / 439 (21.64%)
occurrences (all)	57	63	125
Dizziness			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	13 / 227 (5.73%)	11 / 228 (4.82%)	10 / 439 (2.28%)
occurrences (all)	27	17	22
General disorders and administration site conditions			

Injection site erythema			
subjects affected / exposed	119 / 227 (52.42%)	135 / 228 (59.21%)	211 / 439 (48.06%)
occurrences (all)	773	1521	1426
Influenza like illness			
subjects affected / exposed	95 / 227 (41.85%)	106 / 228 (46.49%)	199 / 439 (45.33%)
occurrences (all)	733	1290	1526
Pyrexia			
subjects affected / exposed	66 / 227 (29.07%)	66 / 228 (28.95%)	138 / 439 (31.44%)
occurrences (all)	362	434	804
Chills			
subjects affected / exposed	28 / 227 (12.33%)	29 / 228 (12.72%)	52 / 439 (11.85%)
occurrences (all)	91	157	252
Injection site pain			
subjects affected / exposed	25 / 227 (11.01%)	25 / 228 (10.96%)	32 / 439 (7.29%)
occurrences (all)	73	71	77
Asthenia			
subjects affected / exposed	24 / 227 (10.57%)	10 / 228 (4.39%)	39 / 439 (8.88%)
occurrences (all)	105	48	137
Injection site pruritus			
subjects affected / exposed	17 / 227 (7.49%)	26 / 228 (11.40%)	24 / 439 (5.47%)
occurrences (all)	58	130	63
Fatigue			
subjects affected / exposed	10 / 227 (4.41%)	21 / 228 (9.21%)	26 / 439 (5.92%)
occurrences (all)	18	71	88
Pain			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Hyperthermia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 227 (3.96%)	11 / 228 (4.82%)	17 / 439 (3.87%)
occurrences (all)	18	17	29
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	9 / 227 (3.96%)	14 / 228 (6.14%)	16 / 439 (3.64%)
occurrences (all)	18	37	24
Vomiting			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	6 / 227 (2.64%)	13 / 228 (5.70%)	18 / 439 (4.10%)
occurrences (all)	6	14	19
Insomnia			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	27 / 227 (11.89%)	27 / 228 (11.84%)	60 / 439 (13.67%)
occurrences (all)	89	481	154
Back pain			
subjects affected / exposed	11 / 227 (4.85%)	19 / 228 (8.33%)	31 / 439 (7.06%)
occurrences (all)	130	18	69
Arthralgia			
subjects affected / exposed	23 / 227 (10.13%)	14 / 228 (6.14%)	33 / 439 (7.52%)
occurrences (all)	114	61	58
Pain in extremity			
subjects affected / exposed	10 / 227 (4.41%)	14 / 228 (6.14%)	23 / 439 (5.24%)
occurrences (all)	17	53	45

Muscular weakness			
subjects affected / exposed	12 / 227 (5.29%)	12 / 228 (5.26%)	18 / 439 (4.10%)
occurrences (all)	25	34	40
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 227 (9.69%)	17 / 228 (7.46%)	45 / 439 (10.25%)
occurrences (all)	29	32	56
Urinary tract infection			
subjects affected / exposed	10 / 227 (4.41%)	11 / 228 (4.82%)	31 / 439 (7.06%)
occurrences (all)	11	18	37
Upper respiratory tract infection			
subjects affected / exposed	0 / 227 (0.00%)	0 / 228 (0.00%)	0 / 439 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Year 2: Peginterferon Beta-1a Q2W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	367 / 438 (83.79%)		
Investigations			
Body temperature increased			
subjects affected / exposed	24 / 438 (5.48%)		
occurrences (all)	128		
Alanine aminotransferase increased			
subjects affected / exposed	13 / 438 (2.97%)		
occurrences (all)	19		
Nervous system disorders			
Headache			
subjects affected / exposed	126 / 438 (28.77%)		
occurrences (all)	1000		
Multiple sclerosis relapse			
subjects affected / exposed	63 / 438 (14.38%)		
occurrences (all)	81		
Dizziness			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Paraesthesia			

subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	11 / 438 (2.51%)		
occurrences (all)	20		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	212 / 438 (48.40%)		
occurrences (all)	2981		
Influenza like illness			
subjects affected / exposed	192 / 438 (43.84%)		
occurrences (all)	2384		
Pyrexia			
subjects affected / exposed	136 / 438 (31.05%)		
occurrences (all)	1070		
Chills			
subjects affected / exposed	41 / 438 (9.36%)		
occurrences (all)	203		
Injection site pain			
subjects affected / exposed	45 / 438 (10.27%)		
occurrences (all)	172		
Asthenia			
subjects affected / exposed	40 / 438 (9.13%)		
occurrences (all)	226		
Injection site pruritus			
subjects affected / exposed	47 / 438 (10.73%)		
occurrences (all)	323		
Fatigue			
subjects affected / exposed	32 / 438 (7.31%)		
occurrences (all)	150		
Pain			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Hyperthermia			

subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	14 / 438 (3.20%)		
occurrences (all)	22		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	27 / 438 (6.16%)		
occurrences (all)	102		
Vomiting			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	17 / 438 (3.88%)		
occurrences (all)	24		
Insomnia			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	58 / 438 (13.24%)		
occurrences (all)	309		
Back pain			

subjects affected / exposed	32 / 438 (7.31%)		
occurrences (all)	69		
Arthralgia			
subjects affected / exposed	33 / 438 (7.53%)		
occurrences (all)	254		
Pain in extremity			
subjects affected / exposed	31 / 438 (7.08%)		
occurrences (all)	64		
Muscular weakness			
subjects affected / exposed	13 / 438 (2.97%)		
occurrences (all)	33		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	47 / 438 (10.73%)		
occurrences (all)	64		
Urinary tract infection			
subjects affected / exposed	29 / 438 (6.62%)		
occurrences (all)	39		
Upper respiratory tract infection			
subjects affected / exposed	0 / 438 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2009	The protocol was revised primarily to clarify study procedures and some of the description of the statistical analysis methods.
16 April 2010	The protocol was revised primarily to adjust the holding and stopping rules for study treatment dosing. The language regarding the monitoring of hepatic safety was strengthened following an in depth review of the safety experience for interferons, including interferon beta-1a. Thus, the guidelines (Table 1, Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Blinded Study Treatment with BIIB017/Placebo) for re-starting study treatment after a >5 fold elevation in transaminases (ALT and AST) were added to the study Holding and Stopping rules.
14 March 2011	The protocol was revised primarily to increase the study sample size. The number of planned subjects was increased from 1260 subjects to approximately 1500 subjects. As permitted by the protocol, the pooled 1-year annualized relapse rate was monitored and the placebo 1-year annualized relapse rate was estimated by back-calculating from the pooled annualized relapse rate, and the assumed treatment effect. As a result of this monitoring, the sample size was increased from 420 to 500 subjects per treatment group. The planned sample sizes for PK/PD sample collections were accordingly increased. Inclusion Criterion No. 2 was updated. The age limit for subject inclusion into the study was increased to optimize enrollment and to better reflect the age range of the treated MS population. The Exclusion Criterion No. 11, known history or positive test results for hepatitis was updated in order to prevent the inappropriate exclusion of patients from the study. Testing for HBsAb was added as a screening assessment to determine if a patient had cleared a hepatitis B infection. Based on the CDC's interpretation of the hepatitis B serology panel (CDC, 2007), subjects who were positive for HBcAb would now only be excluded if they were also negative for HBsAb IgG. Subjects who were positive for HCV Ab were to continue to be excluded from the study, as were all subjects who were positive for HBsAg. Exclusion Criterion No. 16, which provides a table of treatment agents that were prohibited for eligibility, was modified to include the recently approved MS therapy, fingolimod.
27 March 2012	The protocol was revised primarily to move the MSIS-29 outcome measure from the secondary objectives to the additional objectives. Unlike the other specified primary and secondary objectives and endpoints (measures of relapses, MRI lesions, and disease progression), the MSIS-29, a patient reported measure of health status, has not yet been fully established as a direct measure of MS disease activity. As such, inclusion of this assessment in the key secondary endpoints may not be appropriate. Analysis for Primary Endpoint, EDSS (≤3.5 or >3.5) was changed to (<4 and ≥4) for clarity. Given the ordinal nature of the EDSS scale, the revised cutoff is logically equivalent to that previously described; therefore, this change doesn't affect the analysis methods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24794721