



Clinical trial results:

Multicenter, Double-blind, Randomized, Parallel-group, Monotherapy, Active-control Study to Determine the Efficacy and Safety of Daclizumab High Yield Process (DAC HYP) Versus Avonex® (Interferon Beta-1a) in Patients With Relapsing-Remitting Multiple Sclerosis

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2009-012500-11
Trial protocol	IE FR DE CZ HU FI SE ES GB GR IT DK SI
Global end of trial date	28 July 2014

Results information

Result version number	v2 (current)
This version publication date	19 February 2016
First version publication date	12 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Data correction due to a system error in EudraCT – Results

Trial information

Trial identification

Sponsor protocol code	205MS301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01064401
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.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	28 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective is to test the superiority of Daclizumab High Yield Process (DAC HYP) compared with interferon β -1a (IFN β -1a) in preventing multiple sclerosis (MS) relapse in participants with relapsing remitting multiple sclerosis.

The secondary study objectives are to test the superiority of DAC HYP compared with IFN β -1a in slowing functional decline and disability progression and maintaining quality of life in this participant population.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 May 2010
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	Poland: 451
Country: Number of subjects enrolled	United States: 217
Country: Number of subjects enrolled	Russian Federation: 198
Country: Number of subjects enrolled	Ukraine: 129
Country: Number of subjects enrolled	Serbia: 111
Country: Number of subjects enrolled	Italy: 97
Country: Number of subjects enrolled	Czech Republic: 85
Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	India: 50

Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Sweden: 31
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	Argentina: 24
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Moldova, Republic of: 17
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Georgia: 5
Country: Number of subjects enrolled	Finland: 3
Worldwide total number of subjects	1841
EEA total number of subjects	994

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)	1841
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a 4-week screening period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Interferon beta-1a
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Arm description:

Interferon beta-1a (IFN β -1a) 30 μ g IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks

Arm type	Active comparator
Investigational medicinal product name	Interferon beta-1A
Investigational medicinal product code	
Other name	Avonex
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Avonex was supplied in treatment kits that were dispensed to subjects at each visit and contained a sufficient supply of Avonex prefilled syringes and IM needles for each dosing interval. Subjects were instructed on how to perform injections at home.

Investigational medicinal product name	Placebo to DAC HYP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo to DAC HYP was prepared and administered in an identical manner to DAC HYP.

Arm title	Daclizumab High Yield Process
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Arm description:

DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β -1a intramuscular (IM) injection once weekly for 96 to 144 weeks

Arm type	Experimental
Investigational medicinal product name	Daclizumab HYP
Investigational medicinal product code	BIIB019
Other name	DAC HYP
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The individual preparing the DAC HYP carefully reviewed the instructions provided in the Directions for Handling and Administration, which superseded all other references (e.g., the DAC HYP Investigator Brochure), and DAC HYP was administered by staff in the clinic at the monthly visits. Subjects received SC injections of DAC HYP in one or more of the following locations: the back of the upper arm, the thigh,

or the abdomen.

Investigational medicinal product name	Placebo to Avonex
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo to Avonex was supplied in treatment kits, which was dispensed to subjects at each visit and contained a sufficient supply of Avonex placebo prefilled syringes and IM needles for each dosing interval. Subjects were instructed on how to perform injections at home.

Number of subjects in period 1	Interferon beta-1a	Daclizumab High Yield Process
Started	922	919
Completed	694	724
Not completed	228	195
Consent withdrawn by subject	98	80
Physician decision	4	6
Death	4	-
Not specified	2	1
Pregnancy	4	7
Adverse event	47	56
Non-compliance	7	8
Lost to follow-up	12	9
Site closure	4	5
Lack of efficacy	46	23

Baseline characteristics

Reporting groups

Reporting group title	Interferon beta-1a
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Reporting group description:

Interferon beta-1a (IFN β -1a) 30 μ g IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks

Reporting group title	Daclizumab High Yield Process
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Reporting group description:

DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β -1a intramuscular (IM) injection once weekly for 96 to 144 weeks

Reporting group values	Interferon beta-1a	Daclizumab High Yield Process	Total
Number of subjects	922	919	1841
Age categorical Units: Subjects			
18 to 19 years	25	14	39
20 to 29 years	227	236	463
30 to 39 years	327	322	649
40 to 49 years	256	250	506
50 to 55 years	86	96	182
> 55 years	1	1	2
Age Continuous Units: years			
arithmetic mean	36.2	36.4	
standard deviation	\pm 9.32	\pm 9.36	-
Gender, Male/Female Units: participants			
Female	627	625	1252
Male	295	294	589

End points

End points reporting groups

Reporting group title	Interferon beta-1a
Reporting group description: Interferon beta-1a (IFN β -1a) 30 μ g IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks	
Reporting group title	Daclizumab High Yield Process
Reporting group description: DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β -1a intramuscular (IM) injection once weekly for 96 to 144 weeks	

Primary: Adjusted Annualized Relapse Rate (ARR)

End point title	Adjusted Annualized Relapse Rate (ARR)
End point description: Relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. Only relapses confirmed by Independent Neurology Evaluation Committee (INEC) are included in this analysis. Adjusted ARR was estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline Expanded Disability Status Scale (EDSS; ≤ 2.5 vs > 2.5) and baseline age (≤ 35 vs > 35). Data after subjects switched to alternative MS medications are excluded.	
End point type	Primary
End point timeframe: Up to 144 weeks	

End point values	Interferon beta-1a	Daclizumab High Yield Process		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392 ^[1]	260 ^[2]		
Units: relapses per person-years				
number (confidence interval 95%)	0.393 (0.353 to 0.438)	0.216 (0.191 to 0.244)		

Notes:

[1] - subject with a relapse; number of relapses analyzed = 643

[2] - subject with a relapse; number of relapses analyzed = 402

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Daclizumab High Yield Process v Interferon beta-1a
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	negative binomial regression
Parameter estimate	rate ratio
Point estimate	0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.469
upper limit	0.645

Notes:

[3] - Estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (≤ 2.5 vs > 2.5) and baseline age (≤ 35 vs > 35).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon beta-1a v Daclizumab High Yield Process
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	percent reduction
Point estimate	45
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.5
upper limit	53.1

Secondary: Adjusted Mean Number of New or Newly Enlarging T2 Hyperintense Lesions up to Week 96

End point title	Adjusted Mean Number of New or Newly Enlarging T2 Hyperintense Lesions up to Week 96
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End point description:

Assessed by brain magnetic resonance imaging (MRI). Estimated from a negative binomial regression model, adjusted for baseline volume of T2 hyperintense lesions, history of prior IFN beta use and baseline age (≤ 35 vs > 35). To account for the timing of the MRI measurement, the logarithmic transformation of the scan number of the MRI assessment was included in the model as the 'offset' parameter. Observed data after subjects switched to alternative MS medications are excluded. Missing data are not imputed. Only observed new or newly enlarging T2 lesions at the last visit of the subject up to Week 96 visit are used in this analysis.

End point type	Secondary
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End point timeframe:

up to 96 weeks

End point values	Interferon beta-1a	Daclizumab High Yield Process		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	841 ^[4]	864 ^[5]		
Units: lesions				
arithmetic mean (confidence interval 95%)	9.44 (8.46 to 10.54)	4.31 (3.85 to 4.81)		

Notes:

[4] - subjects with baseline and at least 1 post-baseline MRI measurement

[5] - subjects with baseline and at least 1 post-baseline MRI measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Sustained Disability Progression at 144 Weeks

End point title	Proportion of Subjects With Sustained Disability Progression at 144 Weeks
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End point description:

Sustained disability progression is defined as: at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from Baseline EDSS ≥ 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 multiple sclerosis on a scale that ranges from 0 to 10, with higher scores indicating more disability. Estimated proportion of subjects with progression is based on the Kaplan-Meier product limit method. Subjects were censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression. Subjects with a tentative progression at the End of Treatment Period Visit (or the last EDSS assessment prior to alternative MS start date) and no confirmation assessment were censored at their last EDSS assessment.

End point type	Secondary
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End point timeframe:

Baseline through 144 weeks

End point values	Interferon beta-1a	Daclizumab High Yield Process		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	922	919		
Units: proportion of participants				
number (not applicable)	0.203	0.162		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Relapse-free at Week 144

End point title	Proportion of Subjects Relapse-free at Week 144
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End point description:

Relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist. Only relapses confirmed by INEC are included in this analysis. Data after subjects switched to alternative MS medications are excluded. The estimated proportion of subjects relapse-free at Week 144 is based on the Kaplan-Meier product limit method.

End point type	Secondary
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End point timeframe:

144 weeks

End point values	Interferon beta-1a	Daclizumab High Yield Process		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	922	919		
Units: proportion of participants				
number (not applicable)	0.508	0.673		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a ≥ 7.5 Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at 96 Weeks

End point title	Percentage of Subjects With a ≥ 7.5 Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at 96 Weeks
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End point description:

The MSIS-29 is a 29-item disease-specific patient-reported outcome measure that has been developed and validated to examine the physical and psychological impact of MS from a patient's perspective; it measures physical and psychological items. Worsening in the MSIS-29 physical score is defined as an increase of ≥ 7.5 points in the MSIS-29 physical score at 96 weeks compared to baseline. If a subject was missing data for less than 10 of the 20 items that make up the physical score, then the mean of the non-missing items were used for the missing items. If a subject was missing 10 or more of the 20 items that make up the physical score, or missing the questionnaire entirely, or if the questionnaire was completed after the subject switched to alternative MS medication, a random effects model was used to estimate the MSIS-29 physical score.

End point type	Secondary
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End point timeframe:

Baseline and 96 weeks

End point values	Interferon beta-1a	Daclizumab High Yield Process		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	912 ^[6]	906 ^[7]		
Units: percentage of subjects				
number (not applicable)	23	19		

Notes:

[6] - subjects with an assessment at baseline and Week 96

[7] - subjects with an assessment at baseline and Week 96

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All events were collected from Baseline through Week 164 (end of Post-dosing period).

Adverse event reporting additional description:

Treatment emergent events are reported. Events are considered treatment emergent if they occurred on or after the first dosing date and up to 180 days after the last dosing date.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	IFN beta-1a 30 mcg
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Reporting group description:

IFN β -1a 30 μ g IM injection once weekly plus placebo to DAC HYP SC once every 4 weeks for 96 to 144 weeks

Reporting group title	DAC HYP 150 mg
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Reporting group description:

DAC HYP 150 mg subcutaneous (SC) injection once every 4 weeks plus placebo to IFN β -1a intramuscular (IM) injection once weekly for 96 to 144 weeks

Serious adverse events	IFN beta-1a 30 mcg	DAC HYP 150 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	194 / 922 (21.04%)	221 / 919 (24.05%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ovarian tumour			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Benign salivary gland neoplasm subjects affected / exposed	0 / 922 (0.00%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm malignant subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			

subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Squamous cell carcinoma		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of the cervix		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Testicular seminoma (pure)		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thyroid cancer		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Transitional cell carcinoma		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine leiomyoma		

subjects affected / exposed	1 / 922 (0.11%)	3 / 919 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kawasaki's disease			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Abortion induced			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioplasty			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cystectomy			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal decompression			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 922 (0.11%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	3 / 922 (0.33%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial disorder			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 922 (0.11%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleurisy			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 922 (0.00%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder with mixed disturbance of emotion and conduct			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 922 (0.22%)	3 / 919 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depression suicidal			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional distress			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorder due to a general medical condition			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance abuse			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	2 / 922 (0.22%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	3 / 922 (0.33%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 922 (0.11%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 922 (0.22%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 922 (0.22%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Smear cervix abnormal			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 922 (0.22%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 922 (0.22%)	4 / 919 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 922 (0.11%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail avulsion			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	2 / 922 (0.22%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 922 (0.33%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Palpitations			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 922 (0.11%)	4 / 919 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			

subjects affected / exposed	3 / 922 (0.33%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	124 / 922 (13.45%)	97 / 919 (10.55%)	
occurrences causally related to treatment / all	1 / 206	3 / 150	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasticity			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing-remitting multiple sclerosis			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uhthoff's phenomenon			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 922 (0.00%)	5 / 919 (0.54%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 922 (0.00%)	3 / 919 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoid tissue hyperplasia			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 922 (0.00%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cystoid macular oedema			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 922 (0.11%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth cyst			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oroantral fistula			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 922 (0.00%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dermal cyst			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 922 (0.00%)	3 / 919 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytoclastic vasculitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichenoid keratosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pityriasis rubra pilaris			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pustular psoriasis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 922 (0.00%)	3 / 919 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus-like syndrome			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Plica syndrome			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondyloarthropathy			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 922 (0.00%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 922 (0.00%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis a		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral discitis		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lobar pneumonia		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ludwig angina		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lyme disease		
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Neuroborreliosis		

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 922 (0.22%)	5 / 919 (0.54%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Reiter's syndrome		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis acute		
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Strongyloidiasis		
subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Varicella		
subjects affected / exposed	1 / 922 (0.11%)	1 / 919 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	2 / 922 (0.22%)	8 / 919 (0.87%)
occurrences causally related to treatment / all	0 / 2	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Viral myocarditis		

subjects affected / exposed	1 / 922 (0.11%)	0 / 919 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 922 (0.11%)	2 / 919 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetany			
subjects affected / exposed	0 / 922 (0.00%)	1 / 919 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IFN beta-1a 30 mcg	DAC HYP 150 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	783 / 922 (84.92%)	731 / 919 (79.54%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	66 / 922 (7.16%)	69 / 919 (7.51%)	
occurrences (all)	86	96	
Aspartate aminotransferase			

increased subjects affected / exposed occurrences (all)	44 / 922 (4.77%) 51	48 / 919 (5.22%) 69	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	37 / 922 (4.01%) 58	48 / 919 (5.22%) 66	
Headache subjects affected / exposed occurrences (all)	175 / 922 (18.98%) 925	159 / 919 (17.30%) 443	
Hypoaesthesia subjects affected / exposed occurrences (all)	54 / 922 (5.86%) 76	54 / 919 (5.88%) 71	
Multiple sclerosis relapse subjects affected / exposed occurrences (all)	428 / 922 (46.42%) 748	293 / 919 (31.88%) 480	
Paraesthesia subjects affected / exposed occurrences (all)	57 / 922 (6.18%) 101	42 / 919 (4.57%) 59	
Blood and lymphatic system disorders			
Lymphadenopathy subjects affected / exposed occurrences (all)	7 / 922 (0.76%) 7	46 / 919 (5.01%) 58	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	55 / 922 (5.97%) 232	37 / 919 (4.03%) 66	
Fatigue subjects affected / exposed occurrences (all)	76 / 922 (8.24%) 125	69 / 919 (7.51%) 103	
Influenza like illness subjects affected / exposed occurrences (all)	345 / 922 (37.42%) 3172	88 / 919 (9.58%) 166	
Injection site pain subjects affected / exposed occurrences (all)	102 / 922 (11.06%) 376	96 / 919 (10.45%) 331	

Injection site erythema subjects affected / exposed occurrences (all)	47 / 922 (5.10%) 243	40 / 919 (4.35%) 62	
Pyrexia subjects affected / exposed occurrences (all)	134 / 922 (14.53%) 624	104 / 919 (11.32%) 170	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	55 / 922 (5.97%) 71	67 / 919 (7.29%) 82	
Nausea subjects affected / exposed occurrences (all)	46 / 922 (4.99%) 60	46 / 919 (5.01%) 80	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	46 / 922 (4.99%) 56	53 / 919 (5.77%) 68	
Oropharyngeal pain subjects affected / exposed occurrences (all)	41 / 922 (4.45%) 53	69 / 919 (7.51%) 86	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	26 / 922 (2.82%) 29	64 / 919 (6.96%) 80	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	56 / 922 (6.07%) 68	72 / 919 (7.83%) 85	
Insomnia subjects affected / exposed occurrences (all)	54 / 922 (5.86%) 62	42 / 919 (4.57%) 52	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	62 / 922 (6.72%) 113	71 / 919 (7.73%) 96	
Back pain			

subjects affected / exposed occurrences (all)	70 / 922 (7.59%) 106	86 / 919 (9.36%) 146	
Myalgia subjects affected / exposed occurrences (all)	49 / 922 (5.31%) 167	42 / 919 (4.57%) 67	
Pain in extremity subjects affected / exposed occurrences (all)	58 / 922 (6.29%) 134	55 / 919 (5.98%) 90	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	43 / 922 (4.66%) 48	61 / 919 (6.64%) 76	
Nasopharyngitis subjects affected / exposed occurrences (all)	197 / 922 (21.37%) 319	226 / 919 (24.59%) 499	
Influenza subjects affected / exposed occurrences (all)	56 / 922 (6.07%) 77	82 / 919 (8.92%) 113	
Oral herpes subjects affected / exposed occurrences (all)	44 / 922 (4.77%) 63	57 / 919 (6.20%) 106	
Pharyngitis subjects affected / exposed occurrences (all)	69 / 922 (7.48%) 89	77 / 919 (8.38%) 109	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	124 / 922 (13.45%) 183	148 / 919 (16.10%) 259	
Urinary tract infection subjects affected / exposed occurrences (all)	96 / 922 (10.41%) 136	92 / 919 (10.01%) 150	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2011	<p>The primary reasons for this amendment to Protocol 205MS301 were to:</p> <ul style="list-style-type: none">- Increase subject monitoring for laboratory signals related to hepatic function (liver function tests [LFTs] will be assessed monthly throughout the treatment period), and update criteria for temporary suspension and discontinuation of study treatment for subjects who develop elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin. Subjects who must permanently discontinue study treatment due to elevated LFTs will be evaluated for possible toxicological, infectious, immunological, and metabolic causes of liver injury.- Provide additional guidance to Investigators on the evaluation and management of cutaneous events.- Increase the sample size for the study from 1500 to 1800 subjects based on recent clinical studies that suggested a lower annualized relapse rate for the IFN β-1a group.
10 March 2012	<p>The primary reasons for this amendment to Protocol 205MS301 were to:</p> <ul style="list-style-type: none">- Prohibit concomitant treatment with medications that have an established association with hepatotoxicity or cutaneous hypersensitivity reactions.- Provide monthly liver function testing results to the Treating Neurologist prior to administration of study treatment.
29 April 2013	<p>The primary reasons for this amendment to Protocol 205MS301 were to:</p> <ul style="list-style-type: none">- Modify the definition and rank ordering of some secondary and additional endpoints- Update the statistical analysis section in the protocol: In the protocol version 1 for Study 205MS301, it was stated that efficacy analyses in the trial would first be tested at the 0.04 significance level, and if they were negative, they would then be tested at the 0.01 significance level in the subgroup of subjects who were positive at Baseline for the DAC HYP response signature. Based on the results from exploratory analyses that were performed on Study 205MS201 biomarker data, and in accordance with the original design of Study 205MS301, the sponsor then amended protocol for Study 205MS301 on 29 April 2013 (approximately 11 months prior to the end of Study 205MS301 Treatment Period) to document this result, removed the reference to the response signature from the analysis plan, and clarified that all efficacy analyses in Study 205MS301 would be performed at the standard 0.05 significance level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported