Clinical trial results:
Multi-centre, randomized, double-blind, placebo-controlled, parallel-group, 9 month, equivalence trial comparing the efficacy and safety and tolerability of GTR (Synthon BV) to Copaxone® (Teva) in subjects with relapsing remitting multiple sclerosis followed by an open-label 15 month GTR treatment part evaluating the long-term GTR treatment effects

Summary

EudraCT number	2011-000888-27
Trial protocol	CZ BG GB DE EE GR IT RO
Global end of trial date	16 July 2015

Results information

Result version number	v1 (current)
This version publication date	10 July 2016
First version publication date	10 July 2016

Trial information

Trial identification

Sponsor protocol code	GTR001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01489254
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Synthon BV
Sponsor organisation address	Microweg 22, Nijmegen, Netherlands, 6545 CM
Public contact	Clinical Development, Synthon BV, +31 24 3727700, clinicaltrials@synthon.com
Scientific contact	Clinical Development, Synthon BV, +31 24 3727700, clinicaltrials@synthon.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	16 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 July 2015
Global end of trial reached?	Yes
Global end of trial date	16 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the efficacy of Synthon’s glatiramer acetate (GTR) is equivalent to Copaxone® (TEVA) in subjects with relapsing remitting multiple sclerosis (RRMS) as measured by the number of gadolinium-enhancing lesions on T1-weighted MRIs during the months 7-9.

Protection of trial subjects:

The study was conducted in accordance with the principles of the “Declaration of Helsinki” and Good Clinical Practice according to the regulations and procedures described in the protocol. Written informed consent was obtained from each participant in the study. Approval from the independent Ethics Committees/Institutional Review Board was obtained before starting the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
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	Belarus: 65
Country: Number of subjects enrolled	Croatia: 16
Country: Number of subjects enrolled	Serbia: 62
Country: Number of subjects enrolled	Bosnia and Herzegovina: 24
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Russian Federation: 188
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Ukraine: 195
Country: Number of subjects enrolled	Moldova, Republic of: 26
Country: Number of subjects enrolled	Georgia: 32
Country: Number of subjects enrolled	South Africa: 15
Country: Number of subjects enrolled	Poland: 72
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Bulgaria: 31
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Estonia: 3
Worldwide total number of subjects	796
EEA total number of subjects	175

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)	796
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1549 patients were assessed for eligibility of whom 796 subjects were randomized in a 4.3:4.3:1 ratio to receive generic glatiramer acetate (GTR), brand glatiramer acetate (Copaxone) or matching placebo.

Pre-assignment

Screening details:

Overall 1549 subjects were screened of whom 796 subjects were randomized into the study, two subjects were randomized to the generic glatiramer acetate group but did not start treatment

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Glatiramer 20 mg

Arm description:

Glatiramer Acetate (GTR) 20 mg daily for 9 months

Arm type	Experimental
Investigational medicinal product name	Glatiramer Acetate 20 mg
Investigational medicinal product code	GTR
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

20 mg/mL, 1 mL syringe, daily injections

Arm title	Copaxone 20 mg

Arm description:

Glatiramer Acetate (Copaxone) 20 mg daily for 9 months

Arm type	Active comparator
Investigational medicinal product name	Copaxone 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

20 mg/mL, 1 mL syringe, daily injections

Arm title	Placebo

Arm description:

Placebo daily for 9 months

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:

1 mL syringe, daily injections

Number of subjects in period 1	Glatiramer 20 mg	Copaxone 20 mg	Placebo
Started	355	357	84
Completed	330	324	81
Not completed	25	33	3
Consent withdrawn by subject	12	20	1
Adverse event, non-fatal	7	2	2
Other	4	6	-
Pregnancy	1	3	-
Lost to follow-up	1	2	-

Period 2

Period 2 title	Open-label Extension Part
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Extension glatiramer 20 mg

Arm description:

Glatiramer Acetate (GTR) 20 mg daily for 15 months

Arm type	Experimental
Investigational medicinal product name	Glatiramer Acetate 20 mg
Investigational medicinal product code	GTR
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

20 mg/mL, 1 mL syringe, daily injections

Number of subjects in period 2[1]	Extension glatiramer 20 mg
Started	728
Completed	670
Not completed	58
Consent withdrawn by subject	30
Adverse event, non-fatal	10
Other	5
Pregnancy	3
Lost to follow-up	9
Protocol deviation	1

Notes:

[1] - 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: 735 completed the DB part, 729 were eligible to continue in the OL part, 1 opted not to continue

Baseline characteristics

Reporting groups	
Reporting group title	Glatiramer 20 mg
Reporting group description:	
Glatiramer Acetate (GTR) 20 mg daily for 9 months	
Reporting group title	Copaxone 20 mg
Reporting group description:	
Glatiramer Acetate (Copaxone) 20 mg daily for 9 months	
Reporting group title	Placebo
Reporting group description:	
Placebo daily for 9 months	

Reporting group values	Glatiramer 20 mg	Copaxone 20 mg	Placebo
Number of subjects	355	357	84
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	32.6	33.8	32.6
standard deviation	± 8.6	± 9	± 8.7
Gender categorical Units: Subjects			
Female	234	238	57
Male	121	119	27
Time from onset of symptoms to randomization (y) Units: Years			
arithmetic mean	5.5	6.4	5.7
standard deviation	± 5.3	± 6	± 6
No. of relapses in prior 2 y Units: Relapses			
arithmetic mean	1.9	1.8	1.9
standard deviation	± 0.9	± 0.9	± 0.9

Reporting group values	Total		
Number of subjects	796		

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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	529		
Male	267		
Time from onset of symptoms to randomization (y) Units: Years			
arithmetic mean			
standard deviation	-		
No. of relapses in prior 2 y Units: Relapses			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups	
Reporting group title	Glatiramer 20 mg
Reporting group description: Glatiramer Acetate (GTR) 20 mg daily for 9 months	
Reporting group title	Copaxone 20 mg
Reporting group description: Glatiramer Acetate (Copaxone) 20 mg daily for 9 months	
Reporting group title	Placebo
Reporting group description: Placebo daily for 9 months	
Reporting group title	Extension glatiramer 20 mg
Reporting group description: Glatiramer Acetate (GTR) 20 mg daily for 15 months	

Primary: The number of T1-Gadolinium enhancing lesions during months 7-9	
End point title	The number of T1-Gadolinium enhancing lesions during months 7-9
End point description:	
End point type	Primary
End point timeframe: 9 months	

End point values	Glatiramer 20 mg	Copaxone 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	353	357	84	
Units: Number of Gd lesions				
arithmetic mean (confidence interval 95%)				
Number of Gd lesions (study sensitivity)	0.42 (0.31 to 0.57)	0.38 (0.28 to 0.52)	0.82 (0.57 to 1.2)	
Number of Gd lesions (equivalence)	0.45 (0.34 to 0.59)	0.41 (0.31 to 0.54)	0 (0 to 0)	

Statistical analyses

Statistical analysis title	Study sensitivity

Statistical analysis description:

Estimates represent the mean total lesions during months 7 through 9 and were estimated from the fitted random effect generalized linear model (longitudinal model) with a negative binomial distribution and logaritmic link function. To assess study sensitivity, data of the active treatment groups and placebo were included in the model, resulting in the ratios and 95% CIs for the combined Glatiramer 20 mg and Copaxone 20 mg treatment group and the individual treatments over placebo.

Comparison groups	Copaxone 20 mg v Placebo v Glatiramer 20 mg
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Ratio (or Ratio of estimated means)
Point estimate	0.488
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.365
upper limit	0.651

Notes:

[1] - To conclude study sensitivity the combined active treatment groups Glatiramer 20 mg and Copaxone 20 mg needed to be superior to placebo.

Statistical analysis title	Equivalence

Statistical analysis description:

Estimates represent the mean total lesions during months 7 through 9 and were estimated from the fitted random effect generalized linear model (longitudinal model) with a negative binomial distribution and logaritmic link function including Glatiramer 20 mg and Copaxone 20 mg treatment groups to assess study equivalence.

Comparison groups	Glatiramer 20 mg v Copaxone 20 mg
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Ratio (or Ratio of estimated means)
Point estimate	1.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.883
upper limit	1.36

Notes:

[2] - To conclude equivalence between Glatiramer 20 mg and Copaxone 20 mg, efficacy in the combined active treatment groups needed to be superior to placebo (confirming
study sensitivity) and the 2-sided 95% CI for the estimated ratio of Glatiramer 20 mg to Copaxone 20 mg needed to be fully enclosed in the prespecified equivalence margin (0.727 - 1.375). Study sensitivity was already concluded in statistical analysis "Study sensitivity".

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Total trial period	
Adverse event reporting additional description:	
The safety population consisted of all subjects who received at least 1 injection with study treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Glatiramer Acetate 20 mg
Reporting group description: -	
Reporting group title	Copaxone 20 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Extension Glatiramer 20 mg
Reporting group description: -	

Serious adverse events	Glatiramer Acetate 20 mg	Copaxone 20 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 353 (3.40%)	17 / 357 (4.76%)	2 / 84 (2.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous sytem			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Glioblastoma multiforme			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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

Benign hydatidiform mole			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Small intestine carcinoma			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
General disorders and administration site conditions			
Immediate post-injection reaction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 353 (0.28%)	1 / 357 (0.28%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Anaphylactic reaction			

subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Ovarian cyst			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Depression			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Anxiety			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Bipolar disorder			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Injury, poisoning and procedural complications			
Tibia fracture			

subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Brain contusion			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Fibula fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Joint dislocation			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 353 (0.57%)	4 / 357 (1.12%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Sciatica			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Status epilepticus			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Radiculitis cervical			

subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Secondary progressive multiple sclerosis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Uveitis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Pancreatitis acute			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Hepatitis toxic			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Cholecystitis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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	1 / 353 (0.28%)	1 / 357 (0.28%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Urinary retention			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Renal colic			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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
Nephrolithiasis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Osteoarthritis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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			
Pneumonia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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

Respiratory tract infection viral			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	0 / 84 (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
Bronchitis			
subjects affected / exposed	0 / 353 (0.00%)	2 / 357 (0.56%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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	0 / 353 (0.00%)	0 / 357 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 353 (0.00%)	1 / 357 (0.28%)	0 / 84 (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
Appendicitis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	0 / 84 (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	Extension Glatiramer 20 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 728 (3.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous sytem			

subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	2 / 728 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glioblastoma multiforme			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign hydatidiform mole			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestine carcinoma			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Immediate post-injection reaction			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaphylactic reaction			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometriosis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety			

subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain contusion			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	2 / 728 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	5 / 728 (0.69%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Sciatica				
subjects affected / exposed	0 / 728 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	0 / 728 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radiculitis cervical				
subjects affected / exposed	1 / 728 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Secondary progressive multiple sclerosis				
subjects affected / exposed	1 / 728 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Uveitis				
subjects affected / exposed	1 / 728 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Constipation				
subjects affected / exposed	0 / 728 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 728 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatitis toxic				

subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psoriasis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Patellofemoral pain syndrome			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salpingo-oophoritis			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Glatiramer Acetate 20 mg	Copaxone 20 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 353 (49.58%)	190 / 357 (53.22%)	47 / 84 (55.95%)
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 353 (4.53%)	12 / 357 (3.36%)	7 / 84 (8.33%)
occurrences (all)	21	12	11
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	58 / 353 (16.43%)	62 / 357 (17.37%)	6 / 84 (7.14%)
occurrences (all)	79	86	8
Immediate post-injection reaction			
subjects affected / exposed	24 / 353 (6.80%)	17 / 357 (4.76%)	0 / 84 (0.00%)
occurrences (all)	48	23	0
Injection site swelling			
subjects affected / exposed	14 / 353 (3.97%)	12 / 357 (3.36%)	3 / 84 (3.57%)
occurrences (all)	26	15	4
Injection site pain			
subjects affected / exposed	11 / 353 (3.12%)	13 / 357 (3.64%)	1 / 84 (1.19%)
occurrences (all)	17	21	1
Injection site haematoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 357 (0.00%)	3 / 84 (3.57%)
occurrences (all)	1	0	4
Injection site bruising			
subjects affected / exposed	0 / 353 (0.00%)	0 / 357 (0.00%)	3 / 84 (3.57%)
occurrences (all)	0	0	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 353 (3.68%)	23 / 357 (6.44%)	6 / 84 (7.14%)
occurrences (all)	20	28	9
Upper respiratory tract infection			
subjects affected / exposed	6 / 353 (1.70%)	6 / 357 (1.68%)	3 / 84 (3.57%)
occurrences (all)	7	6	3
Respiratory tract infection			

subjects affected / exposed	2 / 353 (0.57%)	4 / 357 (1.12%)	4 / 84 (4.76%)
occurrences (all)	2	4	7

Non-serious adverse events	Extension Glatiramer 20 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	252 / 728 (34.62%)		
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 728 (2.20%)		
occurrences (all)	19		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	15 / 728 (2.06%)		
occurrences (all)	18		
Immediate post-injection reaction			
subjects affected / exposed	11 / 728 (1.51%)		
occurrences (all)	16		
Injection site swelling			
subjects affected / exposed	4 / 728 (0.55%)		
occurrences (all)	6		
Injection site pain			
subjects affected / exposed	7 / 728 (0.96%)		
occurrences (all)	12		
Injection site haematoma			
subjects affected / exposed	0 / 728 (0.00%)		
occurrences (all)	0		
Injection site bruising			
subjects affected / exposed	1 / 728 (0.14%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	39 / 728 (5.36%)		
occurrences (all)	52		
Upper respiratory tract infection			
subjects affected / exposed	5 / 728 (0.69%)		
occurrences (all)	6		

Respiratory tract infection subjects affected / exposed occurrences (all)	4 / 728 (0.55%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2012	As per Protocol Amendment 1 (i) a local tolerance assessment was added at the start of the open label phase (month 9), (ii) subjects with active disease who experienced a relapse after being found eligible were allowed to be randomized and, (iii) subjects who could not start day 1 assessments due to logistical reasons beyond their control were allowed an extended screening window of maximally 90 days.
31 May 2013	As per Protocol Amendment 2 additional requirements were formulated in the protocol related to the inclusion criteria and characteristics for patients or volunteers undergoing an MRI test scan to qualify each imaging site prior to the start of screening trial participants.

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/26458034