Clinical trial results:
CONFIDENCE: A Multinational, Multicenter, Randomized, Parallel Group, Open-Label Study to Assess Medication Satisfaction in Patients with Relapsing Remitting Multiple Sclerosis (RRMS) Treated with Subcutaneous Injections of Copaxone® (Glatiramer Acetate) 40 mg/mL Three Times a Week Compared to 20 mg/mL Daily

Summary

EudraCT number	2015-000922-12
Trial protocol	BE AT DE IE PL FI ES HR FR IT
Global end of trial date	02 June 2017

Results information

Result version number	v1 (current)
This version publication date	18 August 2018
First version publication date	18 August 2018

Trial information

Trial identification

Sponsor protocol code	TV44400-CNS-40083

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02499900
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries, Ltd.
Sponsor organisation address	12 Hatrufa St., P.O. Box 8077, Sapir Industrial Zone, Netanya, Israel, 42504
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 888-483-8279 , info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 001 888-483-8279 , info.era-clinical@teva.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare patient medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ) scores between the Copaxone 40 mg/mL three times a week (TIW) group and the Copaxone 20 mg/mL once daily (QD) group over 6 months of treatment.

Protection of trial subjects:

For adult subjects, written informed consent signed and dated by the subject before conducting any study-related procedures; for minor subjects, written informed consent signed and dated by the parent/legal guardian and written assent signed and dated by the subject before conducting any study related procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 142
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Croatia: 88
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 95
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 109
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	Puerto Rico: 4
Country: Number of subjects enrolled	Russian Federation: 198
Country: Number of subjects enrolled	Turkey: 22
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	861
EEA total number of subjects	527

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)	846
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 876 patients with RRMS were screened for enrollment into this study. Of the 876 patients screened, 861 patients at 88 centers in Russian Federation, Poland, Italy, France, Croatia, US, Mexico, Spain, Austria, Turkey, Belgium, Argentina, Germany, Finland, & Puerto Rico met entry criteria and were considered to be eligible for enrollment.

Pre-assignment

Screening details:

Of the 15 patients who were not enrolled, 2 patients were excluded on the basis of inclusion criteria not met, 4 patients were excluded on the basis of exclusion criteria met, 7 patients withdrew consent, and 2 patients were lost to follow-up before the baseline visit.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Copaxone® 20 mg/mL QD

Arm description:

Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Arm type	Experimental
Investigational medicinal product name	Copaxone®
Investigational medicinal product code	
Other name	glatiramer acetate
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients administered Copaxone at home at the required frequency and according to the appropriate product instructions.

Arm title	Copaxone® 40 mg/mL TIW

Arm description:

Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Arm type	Experimental
Investigational medicinal product name	Copaxone®
Investigational medicinal product code	
Other name	glatiramer acetate
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients administered Copaxone at home at the required frequency and according to the appropriate product instructions.

Number of subjects in period 1	Copaxone® 20 mg/mL QD	Copaxone® 40 mg/mL TIW
Started	430	431
Safety Analysis Set	427	430
Completed	395	399
Not completed	35	32
Consent withdrawn by subject	11	10
Per sponsor request	-	1
Death	-	1
Not specified	1	4
Pregnancy	1	-
Adverse event	18	14
Lost to follow-up	1	2
Protocol deviation	3	-

Period 2	
Period 2 title	Completed Core, Continued Into Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Copaxone® 20 mg/mL QD
Arm description:	
Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.	
Arm type	Experimental
Investigational medicinal product name	Copaxone®
Investigational medicinal product code	
Other name	glatiramer acetate
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Patients administered Copaxone at home at the required frequency and according to the appropriate product instructions.	
Arm title	Copaxone® 40 mg/mL TIW
Arm description:	
Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.	
Arm type	Experimental

Investigational medicinal product name	Copaxone®	
Investigational medicinal product code		
Other name	glatiramer acetate	
Pharmaceutical forms	Solution for injection in pre-filled injector	
Routes of administration	Subcutaneous use	

Dosage and administration details:

Patients administered Copaxone at home at the required frequency and according to the appropriate product instructions.

Number of subjects in period 2	Copaxone® 20 mg/mL QD	Copaxone® 40 mg/mL TIW
Started	395	399
Completed	392	397
Not completed		

Arm type	Experimental
Investigational medicinal product name	Copaxone®
Investigational medicinal product code	
Other name	glatiramer acetate
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients administered Copaxone at home at the required frequency and according to the appropriate product instructions.

Number of subjects in period 3	Copaxone® 20 mg/mL QD	Copaxone® 40 mg/mL TIW
Started	392	397
Completed	380	377
Not completed	12	20
Consent withdrawn by subject	5	2
Physician decision	2	5
Not specified	-	2
Pregnancy	1	2
Adverse event	2	4
Lost to follow-up	2	5

Baseline characteristics

Reporting groups	
Reporting group title	Copaxone® 20 mg/mL QD
Reporting group description:	
Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.	
Reporting group title	Copaxone® 40 mg/mL TIW
Reporting group description:	
Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.	

Reporting group values	Copaxone® 20 mg/mL QD	Copaxone® 40 mg/mL TIW	Total
Number of subjects	430	431	861
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 40.1 ± 10.67	 41.0 ± 11.15	 -
Gender categorical Units: Subjects			
Female	307	288	595
Male	123	143	266
Race/Ethnicity, Customized Units: Subjects			
White	363	359	722
Black or African American	4	3	7
American Indian or Alaskan Native	1	0	1
Other	59	63	122
Missing	3	6	9
Weight			
n=425, 424; some subjects were missing a baseline weight.			
Units: kg arithmetic mean standard deviation	 70.49 ± 16.471	 71.85 ± 16.265	 -
Body Mass Index (BMI)			
n=425, 424; due to the missing baseline weight assessments, BMI could not be calculated for those subjects.			
Units: kg/m^2 arithmetic mean standard deviation	 24.62 ± 5.272	 24.93 ± 4.879	 -
Height			
n=425, 425; some subjects were missing baseline height data.			
Units: cm arithmetic mean standard deviation	 168.6 ± 9.24	 169.4 ± 8.56	 -

End points

End points reporting groups

Reporting group title	Copaxone® 20 mg/mL QD

Reporting group description:

Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Reporting group title	Copaxone® 40 mg/mL TIW

Reporting group description:

Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Reporting group title	Copaxone® 20 mg/mL QD

Reporting group description:

Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Reporting group title	Copaxone® 40 mg/mL TIW

Reporting group description:

Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Reporting group title	Copaxone® 20 mg/mL QD

Reporting group description:

Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Reporting group title	Copaxone® 40 mg/mL TIW

Reporting group description:

Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12.

Subject analysis set title	Full Analysis Set: Copaxone® 20 mg/mL QD
Subject analysis set type	Full analysis

Subject analysis set description:

Subcutaneous injections of 20 mg/mL QD for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12. The full analysis set included those patients in the intention to treat (ITT) analysis set [all randomized subjects] who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment.

Subject analysis set title	Full Analysis Set: Copaxone® 40 mg/mL TIW
Subject analysis set type	Full analysis

Subject analysis set description:

Subcutaneous injections of 40 mg/mL TIW for the core period, which lasted 6 months. In the extension period, patients were administered Copaxone® 40 mg/mL for Months 7 - 12. The full analysis set included those patients in the ITT analysis set [all randomized subjects] who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment.

Subject analysis set title	Safety Analysis Set: Copaxone® 20 mg/mL QD (Core)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subcutaneous injections of Copaxone 20 mg/mL QD for the core period from Day 1 to Month 6. The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Subject analysis set title	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Core)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subcutaneous injections of Copaxone 40 mg/mL TIW for the core period from Day 1 to Month 6. The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Subject analysis set title	Safety Analysis Set:Copaxone® 40 mg/mL TIW (Switch-Extension)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who were administered daily Copaxone 20 mg/mL daily injections during the core period, and were switched to 40 mg/mL TIW injections for the extension period (Months 7-12). The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Subject analysis set title	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Extension)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who were administered Copaxone 40 mg/mL TIW injections during the core period, and continued Copaxone at that same dosage for the extension period (Months 7-12). The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Primary: Change From Baseline in the MSQ to Month 6 Using a Repeated Measures Analysis of Covariance (ANCOVA)

End point title	Change From Baseline in the MSQ to Month 6 Using a Repeated Measures Analysis of Covariance (ANCOVA)

End point description:

Patient satisfaction with the study medication was assessed using the MSQ, a 1-item, global, patient-rated scale. Patients were asked to respond on a 7-point scale, ranging from extremely dissatisfied (1) to extremely satisfied (7), to the following: "Overall, how satisfied are you with your current medication?". Positive change from baseline score indicates greater satisfaction with the medication. Estimates and p-value are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: MSQ=baseline MSQ score+treatment+visit+treatment by visit interaction.

End point type	Primary

End point timeframe:

Baseline (Month 0), Months 1, 3 and 6

End point values	Full Analysis Set: Copaxone® 20 mg/mL QD	Full Analysis Set: Copaxone® 40 mg/mL TIW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	221[1]	235[2]		
Units: units on a scale				
least squares mean (standard error)	5.396 (± 0.0889)	5.717 (± 0.0879)		

Notes:

[1] - Treatment naïve patients do not have a MSQ score at baseline so are not included.

[2] - Treatment naïve patients do not have a MSQ score at baseline so are not included.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimates and p-value are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: MSQ=baseline MSQ core+treatment+visit+treatment by visit interaction. Treatment-naïve patients are not included in this analysis as MSQ is not measured at baseline for these patients.

Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW

Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.321
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1615
upper limit	0.4814

Notes:

[3] - 0.05 level of significance

Secondary: Change From Baseline in the Treatment Satisfaction Questionnaire for Medication 9-item Version (TSQM-9) Convenience Score to Month 6 Using a Repeated Measures ANCOVA

End point title	Change From Baseline in the Treatment Satisfaction Questionnaire for Medication 9-item Version (TSQM-9) Convenience Score to Month 6 Using a Repeated Measures ANCOVA

End point description:

Convenience perception was measured by the 3 convenience items (items 4 to 6) within the validated TSQM-9. The responses to each of the 3 convenience items are reported on a 1-to-7 scale. The TSQM-9 convenience scale is computed, for each subject, by adding the 3 items loading on each response with the lowest possible total score (1*3 on the 3 items) subtracted from this composite score, and divided by the greatest possible score (3*7) minus the lowest possible score (3), i.e., 21-3=18. This provides a transformed score between 0 and 1 that was multiplied by 100. The final scale is 0 (Extremely Difficult/Inconvenient) to 100 (Extremely Easy/Convenient). If more than one item is missing, then the convenience scale was considered invalid for that patient. Estimates and p-value are obtained from baseline-adjusted repeated measures ANCOVA with treatment, visit, and Country/Geographical Region as main factors, visit by treatment as the interaction term, and baseline score as the covariate.

End point type	Secondary

End point timeframe:

Baseline (Month 0), Months 1, 3 and 6

End point values	Full Analysis Set: Copaxone® 20 mg/mL QD	Full Analysis Set: Copaxone® 40 mg/mL TIW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	216[4]	223[5]		
Units: units on a scale				
least squares mean (standard error)	69.740 (± 1.1999)	79.189 (± 1.2347)		

Notes:

[4] - Treatment naïve patients do not have TSQM-9 convenience scores at baseline and are not included.

[5] - Treatment naïve patients do not have TSQM-9 convenience scores at baseline and are not included.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimates and p-value are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: TSQM-9 convenience score=baseline TSQM-9 convenience score+treatment+CGR+treatment by visit interaction. Treatment-naïve patients are not included in this analysis as TSQM-9 is not measured at baseline for these patients.

Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.448
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9538
upper limit	11.9429

Notes:

[6] - 0.05 level of significance

Secondary: Change From Baseline in the Modified Fatigue Impact Scale (MFIS) Total Score and Subscales to Month 6 Using a Repeated Measures ANCOVA

End point title	Change From Baseline in the Modified Fatigue Impact Scale (MFIS) Total Score and Subscales to Month 6 Using a Repeated Measures ANCOVA

End point description:

MFIS is a modified form of the Fatigue Impact Scale based on items derived from interviews with MS patients concerning how fatigue impacts their lives. It is a structured, self-report questionnaire consisting of 21 items assessing the effects of fatigue. All 21 items are scaled 0 to 4, with higher scores indicating a greater impact of fatigue on patient's activities. The Total MFIS score ranges from 0 to 84, the Physical Subscale from 0 to 36, the Cognitive Subscale from 0 to 40, and the Psychosocial Subscale from 0 to 8. A score of 0 indicates fatigue has no impact on activities and the high-end score indicates fatigue has extreme impact on activities. Negative change from baseline values indicate improvement in the effects of fatigue. Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MFIS score=baseline MFIS score+treatment+visit +Country/Geographical Region+treatment by visit interaction.

End point type	Secondary

End point timeframe:

Baseline (Month 0), Months 1, 3 and 6

End point values	Full Analysis Set: Copaxone® 20 mg/mL QD	Full Analysis Set: Copaxone® 40 mg/mL TIW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	422[7]	425[8]		
Units: units on a scale				
least squares mean (standard error)				
MFIS Total Score	-2.811 (± 0.5166)	-3.613 (± 0.5052)		

MFIS Physical Subscale	-1.483 (± 0.2599)	-1.714 (± 0.2535)		
MFIS Cognitive Subscale	-0.965 (± 0.2553)	-1.604 (± 0.2503)		
MFIS Psychosocial Subscale	-0.306 (± 0.0704)	-0.204 (± 0.0685)		

Notes:

[7] - The subject was considered invalid for MFIS if any of the items were missing.

[8] - The subject was considered invalid for MFIS if any of the items were missing.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MFIS Total Score Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MFIS score=baseline MFIS score+treatment+visit +country/geographical region (CGR)+treatment by visit interaction.

Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	847
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208 [9]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	0.4461

Notes:

[9] - 0.05 level of significance

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

MFIS Physical Subscale Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MFIS score=baseline MFIS score+treatment+visit +CGR+treatment by visit interaction.

Comparison groups	Full Analysis Set: Copaxone® 40 mg/mL TIW v Full Analysis Set: Copaxone® 20 mg/mL QD
Number of subjects included in analysis	847
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47 [10]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8588
upper limit	0.3962

Notes:

[10] - 0.05 level of significance

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
MFIS Cognitive Subscale Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MFIS score=baseline MFIS score+treatment+visit +CGR+treatment by visit interaction.	
Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	847
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [11]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.639
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2564
upper limit	-0.0214

Notes:

[11] - 0.05 level of significance

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
MFIS Psychosocial Subscale Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MFIS score=baseline MFIS score+treatment+visit +CGR+treatment by visit interaction.	
Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	847
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237 [12]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0672
upper limit	0.2711

Notes:

[12] - 0.05 level of significance

Secondary: Change From Baseline in the Mental Health Index (MHI) Total Score and Anxiety and Depression Subscales to Month 6 Using a Repeated Measures ANCOVA

End point title	Change From Baseline in the Mental Health Index (MHI) Total Score and Anxiety and Depression Subscales to Month 6 Using a Repeated Measures ANCOVA

End point description:

The MHI consists of 18 items and provides an assessment of 4 subscales of mental health, including Anxiety (5 items), Depression (4 items), Behavioral Control (4 items), and Positive Affect (4 items), and 1 Total Score. The subscales and Total Score for analyses range from 0 to 100 each, with 0 indicating not mentally healthy and 100 indicating superior mental health. Positive change from baseline scores indicate improved mental health. Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MHI score=baseline MHI Total Score +treatment +visit +country/geographic region +treatment by visit interaction. If a participant skipped x items of y items, the scale was not computed: MHI Total Score, 9 of 19; Anxiety subscale, 2 of 5; Depression subscale, 2 of 4; Behavioral Control subscale, 2 of 4; MHI Positive Affect subscale, 2 of 4.

End point type	Secondary

End point timeframe:

Baseline (Month 0), Months 1, 3 and 6

End point values	Full Analysis Set: Copaxone® 20 mg/mL QD	Full Analysis Set: Copaxone® 40 mg/mL TIW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	422[13]	426[14]		
Units: units on a scale				
least squares mean (standard deviation)				
MHI Total Score	3.136 (± 0.5381)	3.842 (± 0.5249)		
Anxiety subscale	5.468 (± 0.6861)	5.609 (± 0.6695)		
Depression subscale	3.773 (± 0.6433)	4.253 (± 0.6270)		

Notes:

[13] - subjects with an assessment

[14] - subjects with an assessment

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Total Score Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MHI score=baseline MHI Total Score +treatment +visit +country/geographic region +treatment by visit interaction.

Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287 [15]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.706
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5947
upper limit	1.0074

Notes:

[15] - 0.05 level of significance

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Anxiety subscale Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MHI score=baseline MHI Total Score +treatment +visit +country/geographic region +treatment by visit interaction.	
Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868 [16]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5179
upper limit	1.7991

Notes:

[16] - 0.05 level of significance

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Depression subscale Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MHI depression subscale=baseline MHI depression subscale+treatment+visit+CGR+treatment by visit interaction.	
Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.544 [17]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.481
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0734
upper limit	2.0348

Notes:

[17] - 0.05 level of significance

Secondary: Change From Baseline in the MHI Behavioral Control and Positive Affect Subscales to Month 6 Using a Repeated Measures ANCOVA

End point title	Change From Baseline in the MHI Behavioral Control and Positive Affect Subscales to Month 6 Using a Repeated Measures ANCOVA

End point description:

The MHI consists of 18 items and provides an assessment of 4 subscales of mental health, including Anxiety (5 items), Depression (4 items), Behavioral Control (4 items), and Positive Affect (4 items), and 1 Total Score. The subscales and Total Score for analyses range from 0 to 100 each, with 0 indicating not mentally healthy and 100 indicating superior mental health. Positive change from baseline scores indicate improved mental health. Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MHI score=baseline MHI Total Score +treatment +visit +country/geographic region +treatment by visit interaction. If a participant skipped x items of y items, the scale was not computed: MHI Total Score, 9 of 19; Anxiety subscale, 2 of 5; Depression subscale, 2 of 4; Behavioral Control subscale, 2 of 4; MHI Positive Affect subscale, 2 of 4.

End point type	Secondary

End point timeframe:

Baseline (Month 0), Months 1, 3 and 6

End point values	Full Analysis Set: Copaxone® 20 mg/mL QD	Full Analysis Set: Copaxone® 40 mg/mL TIW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	423[18]	426[19]		
Units: units on a scale				
least squares mean (standard error)				
Behavioral Control	0.659 (± 0.6133)	2.526 (± 0.6000)		
MHI Positive Affect	3.024 (± 0.7306)	2.932 (± 0.7126)		

Notes:

[18] - subjects with an assessment

[19] - subjects with an assessment

Notes:

[20] - 0.05 level of significance

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Behavioral Control subscale Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline MHI score=baseline MHI Total Score +treatment +visit +country/geographic region +treatment by visit interaction.	
Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	849
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919 [21]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8565
upper limit	1.6728

Notes:

[21] - 0.05 level of significance

Secondary: Change From Baseline in the Beck Depression Inventory II (BDI-II) Total Score to Month 6 Using a Repeated Measures ANCOVA

End point title	Change From Baseline in the Beck Depression Inventory II (BDI-II) Total Score to Month 6 Using a Repeated Measures ANCOVA
End point description:	
Depressive symptoms were measured by the BDI-II, a 21-item, self-reported rating inventory that measures characteristic attitudes and symptoms of depression. The BDI-II assesses mood, pessimism, sense of failure, self dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, sadness, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. Each of the 21 items is rated on a 4-point scale ranging from 0 to 3. BDI-II Total Score indicates the severity of depression and has a total range of 0 to 63. For those clinically diagnosed, scores from 0-13 represent minimal depressive symptoms, scores of 14-19 indicate mild depression, scores of 20-28 indicate moderate depression, and scores of 30-63 indicate severe depression. Negative change from baseline scores indicate improvement.	
End point type	Secondary
End point timeframe:	
Baseline (Month 0), Months 1, 3 and 6	

End point values	Full Analysis Set: Copaxone® 20 mg/mL QD	Full Analysis Set: Copaxone® 40 mg/mL TIW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	422[22]	426[23]		
Units: units on a scale				
least squares mean (standard error)	-1.525 (± 0.2560)	-1.585 (± 0.2495)		

Notes:

[22] - subjects with an assessment

[23] - subjects with an assessment

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Estimates and p-values are obtained from baseline-adjusted repeated measures ANCOVA model with visit as a repeated effect: change from baseline BDI-II total score=baseline BDIII total score+treatment+visit+country/geographic region +treatment by visit interaction.	
Comparison groups	Full Analysis Set: Copaxone® 20 mg/mL QD v Full Analysis Set: Copaxone® 40 mg/mL TIW
Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.851 [24]
Method	Repeated Measures ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6777
upper limit	0.5592

Notes:

[24] - 0.05 level of significance

Secondary: Subjects With Treatment-Emergent Adverse Events (TEAEs) During Both the Core Period and Extension Periods

End point title	Subjects With Treatment-Emergent Adverse Events (TEAEs) During Both the Core Period and Extension Periods
End point description:	
An adverse event (AE) is defined as any study-related event that represents a change (positive or negative) in frequency or severity from a baseline (prestudy) event (if any), regardless of the presence of causal relationship or medical significance. Treatment-emergent adverse events are defined as any adverse event with a start date on or after the first study dose date. The investigator determined relation to study drug. A severe AE is defined as an inability to carry out usual activities. A serious AE (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Although a subject may have had 2 or more adverse experiences the subject is counted only once in a category. The same subject may appear in different categories.	
End point type	Secondary
End point timeframe:	
Core: Day 1 to Month 6; Extension: Month 7 to Month 12	

End point values	Safety Analysis Set: Copaxone® 20 mg/mL QD (Core)	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Core)	Safety Analysis Set:Copaxone ® 40 mg/mL TIW (Switch-Extension)	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Extension)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	427	430	392	396
Units: subjects				
>= 1 TEAE	219	231	132	129
>= 1 serious TEAE	8	13	3	2
>= 1 serious fatal TEAE	0	0	0	0
>= 1 serious and related TEAE	1	2	0	0
>= 1 Severe TEAE	4	3	1	0
>= 1 injection-related TEAE	149	146	38	25
>=1 TEAE leading to withdrawal	18	13	2	3

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Core study period: Day 1 to Month 6; Extension study period: Month 7 to Month 12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Safety Analysis Set: Copaxone® 20 mg/mL QD (Core)

Reporting group description:

Subcutaneous injections of Copaxone 20 mg/mL QD for the core period from Day 1 to Month 6. The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Reporting group title	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Core)

Reporting group description:

Subcutaneous injections of Copaxone 40 mg/mL TIW for the core period from Day 1 to Month 6. The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Reporting group title	Safety Analysis Set:Copaxone® 40 mg/mL TIW (Switch-Extension)

Reporting group description:

Subjects who were administered daily Copaxone 20 mg/mL daily injections during the core period, and were switched to 40 mg/mL TIW injections for the extension period (Months 7-12). The Safety Analysis Set included all randomized patients who received at least 1 dose of Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Reporting group title	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Extension)

Reporting group description:

Subjects who were administered Copaxone 40 mg/mL TIW injections during the core period, and continued Copaxone at that same dosage for the extension period (Months 7-12). The Safety Analysis Set included all randomized patients who received at least 1 dose of
Copaxone, based on the treatment patients actually received regardless of the treatment to which they were randomized.

Serious adverse events	Safety Analysis Set: Copaxone® 20 mg/mL QD (Core)	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Core)	Safety Analysis Set:Copaxone® 40 mg/mL TIW (Switch-Extension)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 427 (1.87%)	13 / 430 (3.02%)	3 / 392 (0.77%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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

Malignant melanoma			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Brain neoplasm			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 427 (0.00%)	0 / 430 (0.00%)	0 / 392 (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
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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
Rib fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Clavicle fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Intentional overdose			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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

Scapula fracture			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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
Atrial fibrillation			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Coronary artery disease			
subjects affected / exposed	0 / 427 (0.00%)	0 / 430 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			

subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Pneumothorax			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Depression			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 427 (0.00%)	2 / 430 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Nephrolithiasis			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Pituitary hyperplasia			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Arthropathy			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 427 (0.23%)	0 / 430 (0.00%)	0 / 392 (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
Escherichia sepsis			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (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

Pneumonia			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 427 (0.00%)	1 / 430 (0.23%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 427 (0.00%)	0 / 430 (0.00%)	0 / 392 (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	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Extension)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 396 (0.51%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			

subjects affected / exposed	1 / 396 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scapula fracture			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysfunctional uterine bleeding			

subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 396 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

subjects affected / exposed	1 / 396 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis Set: Copaxone® 20 mg/mL QD (Core)	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Core)	Safety Analysis Set:Copaxone® 40 mg/mL TIW (Switch-Extension)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 427 (28.34%)	117 / 430 (27.21%)	22 / 392 (5.61%)
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	34 / 427 (7.96%)	32 / 430 (7.44%)	1 / 392 (0.26%)
occurrences (all)	34	32	1
Injection site pain			
subjects affected / exposed	84 / 427 (19.67%)	89 / 430 (20.70%)	10 / 392 (2.55%)
occurrences (all)	92	109	11
Injection site erythema			
subjects affected / exposed	71 / 427 (16.63%)	61 / 430 (14.19%)	10 / 392 (2.55%)
occurrences (all)	75	65	10
Injection site pruritus			
subjects affected / exposed	58 / 427 (13.58%)	37 / 430 (8.60%)	5 / 392 (1.28%)
occurrences (all)	61	40	5
Injection site bruising			
subjects affected / exposed	24 / 427 (5.62%)	17 / 430 (3.95%)	5 / 392 (1.28%)
occurrences (all)	24	17	5
Injection site haemorrhage			
subjects affected / exposed	20 / 427 (4.68%)	22 / 430 (5.12%)	2 / 392 (0.51%)
occurrences (all)	23	26	2

Non-serious adverse events	Safety Analysis Set: Copaxone® 40 mg/mL TIW (Extension)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 396 (3.79%)		
General disorders and administration site conditions			

Injection site swelling			
subjects affected / exposed	1 / 396 (0.25%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	5 / 396 (1.26%)		
occurrences (all)	6		
Injection site erythema			
subjects affected / exposed	4 / 396 (1.01%)		
occurrences (all)	4		
Injection site pruritus			
subjects affected / exposed	4 / 396 (1.01%)		
occurrences (all)	4		
Injection site bruising			
subjects affected / exposed	4 / 396 (1.01%)		
occurrences (all)	4		
Injection site haemorrhage			
subjects affected / exposed	3 / 396 (0.76%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2015	The primary reason for this amendment was to revise inclusion criterion (e) regarding birth control methods, in accordance with the Clinical Trial Facilitation Group "Recommendations related to contraception and pregnancy testing in clinical trials" (dated 15 September 2014).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported