Clinical trial results:
SATIVEX® AS ADD-ON THERAPY VS. FURTHER OPTIMIZED FIRST-LINE ANTISPASTICS: THE SAVANT TRIAL

Summary

EudraCT number	2015-004451-40
Trial protocol	CZ AT
Global end of trial date	23 May 2017

Results information

Result version number	v1 (current)
This version publication date	02 May 2018
First version publication date	02 May 2018

Trial information

Trial identification

Sponsor protocol code	H15/02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Almirall Hermal GmbH
Sponsor organisation address	Ronda General Mitre 151, Barcelona, Spain, 08022
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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	23 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of Sativex (tetrahydrocannabinol [THC]:cannabidiol [CBD] oromucosal spray) as add-on therapy compared to further optimized standard antispastic therapy with oral baclofen and/or tizanidine and/or dantrolene (mono- or combination therapy) in subjects with moderate to severe spasticity due to multiple sclerosis (MS) who have not gained adequate relief through 2 optimized standard antispastic drugs.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2016
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	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 190
Worldwide total number of subjects	191
EEA total number of subjects	191

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)	185
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 14 centers in the Czech Republic and 1 center in Austria between 25 April 2016 (first subject first visit) and 23 May 2017 (last subject last visit).

Pre-assignment

Screening details:

A total of 210 subjects were screened, 191 entered the study and 190 received treatment while 15 were screen failure, 2 withdrawn consent, 2 withdrawn due to technical reasons and 1 due to non-TEAE.

Period 1

Period 1 title	Phase A
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Phase A: Sativex

Arm description:

Subjects received up-titrated Sativex up to 12 sprays per day for 4 weeks as add-on to their optimized standard antispastic medication (oral baclofen and/or tizanidine and/or dantrolene) until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Arm type	Experimental
Investigational medicinal product name	Sativex
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received oromucosal spray of Sativex for 4 weeks.

Number of subjects in period 1	Phase A: Sativex
Started	191
Treated	190
Completed	134
Not completed	57
Physician decision	1
Adverse event, non-fatal	4
Noncompliance with study drug	1
Lack of efficacy	49
Protocol deviation	1
Not treated	1

Period 2	
Period 2 title	Washout Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Phase A: Sativex Washout

Arm description:

Subjects who qualified as Sativex initial responders received their underlying optimized standard antispastic medication (oral baclofen and/or tizanidine and/or dantrolene) but not Sativex. The washout phase was to last for a minimum of 1 week and a maximum of 4 weeks, until the subject's Phase A-improvement in MS spasticity numerical rating scale (NRS) score had been reduced by at least 80%.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Phase A: Sativex Washout
Started	134
Completed	106
Not completed	28
Consent withdrawn by subject	3
Failed to meet Inclusion criteria	22
Adverse event, non-fatal	1
Technical problems	2

Period 3	
Period 3 title	Phase B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes

Arm title	Phase B: Sativex

Arm description:

Subjects who were initial responders and whose Phase A-improvement in MS spasticity NRS score had been reduced by at least 80% during the washout phase received up-titrated Sativex to the dose identified during Phase A as being their optimal dose (up to 12 sprays per day) for 12 weeks as add-on to their optimized standard antispastic medication until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Arm type	Experimental
Investigational medicinal product name	Sativex
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received oromucosal spray (up to 12 sprays per day) of optimal dose of Sativex for 12 weeks.

Arm title	Phase B: Placebo

Arm description:

Subjects who were initial responders and whose Phase A-improvement in MS spasticity NRS score had been reduced by at least 80% during the washout phase received matched placebo for 12 weeks as add-on to their optimized standard antispastic medication until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Subjects received matched placebo for 12 weeks.

Number of subjects in period 3	Phase B: Sativex	Phase B: Placebo
Started	53	53
Completed	50	46
Not completed	3	7
Consent withdrawn by subject	3	4
Physician decision	-	1
Didn't meet inclusion criteria#14 (screen failure)	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase A: Sativex

Reporting group description:

Subjects received up-titrated Sativex up to 12 sprays per day for 4 weeks as add-on to their optimized standard antispastic medication (oral baclofen and/or tizanidine and/or dantrolene) until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Reporting group values	Phase A: Sativex	Total	
Number of subjects	191	191	
Age categorical Units: Subjects			

Age continuous			
Phase A safety set included all screened subjects who took at least 1 dose of study medication.			
Units: years arithmetic mean standard deviation	 51.3 ± 10.2	 -	
Gender categorical Units: Subjects			
Female	134	134	
Male	57	57	

End points reporting groups

Reporting group title	Phase A: Sativex

Reporting group description:

Subjects received up-titrated Sativex up to 12 sprays per day for 4 weeks as add-on to their optimized standard antispastic medication (oral baclofen and/or tizanidine and/or dantrolene) until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Reporting group title	Phase A: Sativex Washout

Reporting group description:

Subjects who qualified as Sativex initial responders received their underlying optimized standard antispastic medication (oral baclofen and/or tizanidine and/or dantrolene) but not Sativex. The washout phase was to last for a minimum of 1 week and a maximum of 4 weeks, until the subject's Phase A-improvement in MS spasticity numerical rating scale (NRS) score had been reduced by at least 80%.

Reporting group title	Phase B: Sativex

Reporting group description:

Subjects who were initial responders and whose Phase A-improvement in MS spasticity NRS score had been reduced by at least 80% during the washout phase received up-titrated Sativex to the dose identified during Phase A as being their optimal dose (up to 12 sprays per day) for 12 weeks as add-on to their optimized standard antispastic medication until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Reporting group title	Phase B: Placebo

Reporting group description:

Subjects who were initial responders and whose Phase A-improvement in MS spasticity NRS score had been reduced by at least 80% during the washout phase received matched placebo for 12 weeks as add-on to their optimized standard antispastic medication until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Subject analysis set title	Phase B: Intent To Treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT set included all randomized subjects in Phase B who took at least 1 dose of study medication and had at least a baseline and 1 post-dose efficacy value (N=106).

Primary: Percentage of Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) Responders After 12 Weeks of Randomized Treatment in Phase B

End point title	Percentage of Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) Responders After 12 Weeks of Randomized Treatment in Phase B

End point description:

MS Spasticity was measured based on a scale of 0 to 10, 0 as "No spasticity" and 10 as "Worst possible spasticity". A responder was defined as a subject who achieved an improvement in NRS score of greater than or equal to (>=) 30% (i.e. clinically important difference [CID]) from baseline.

End point type	Primary

End point timeframe:

Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[1]	53[2]		
Units: Percentage of responders				
number (not applicable)				
Logistic Regression Analysis (LOCF)	77.4	32.1		
Generalized Linear Mixed Models (GLMM) Analysis	67.9	30.2		

Notes:

[1] - Phase B: ITT

[2] - Phase B: ITT

Statistical analyses

Statistical analysis title	LOCF: Phase B- Sativex vs Placebo

Statistical analysis description:

The adjusted statistics were computed using Logistic regression model with Phase B baseline mean value as co-variate and treatment group as factor.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Adjusted Odds ratio
Point estimate	7.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.953
upper limit	16.738

Statistical analysis title	GLMM Analysis: Phase B- Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	6.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.75
upper limit	17.023

Secondary: Percentage of Subjects Who Achieve an Improvement From Baseline in Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) Score of Greater Than or Equal to (>=) 30% Clinically Important Difference (CID) After 4 and 8 Weeks of Treatment

End point title	Percentage of Subjects Who Achieve an Improvement From Baseline in Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) Score of Greater Than or Equal to (>=) 30% Clinically Important Difference (CID) After 4 and 8 Weeks of Treatment

End point description:

MS Spasticity was measured based on a scale of 0 to 10, 0 as "No spasticity" and 10 as "Worst possible spasticity".

End point type	Secondary

End point timeframe:

Week 4, Week 8

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[3]	53[4]		
Units: Percentage of subjects				
number (not applicable)				
Week 4	66.0	32.1		
Week 8	71.7	28.3		

Notes:

[3] - Phase B: ITT

[4] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as covariate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0013
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	4.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.747
upper limit	9.233

Statistical analysis title	Week 8: Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with Phase B baseline mean value as covariate and treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted Odds ratio
Point estimate	6.663
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.736
upper limit	16.225

Secondary: Percentage of Subjects Who Achieve an Improvement From Phase B Baseline in Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) Score of Greater Than 18% Minimum Clinically Important Difference (MCID) After 4, 8 and 12 Weeks of Treatment

End point title	Percentage of Subjects Who Achieve an Improvement From Phase B Baseline in Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) Score of Greater Than 18% Minimum Clinically Important Difference (MCID) After 4, 8 and 12 Weeks of Treatment
End point description:	
MS Spasticity was measured based on a scale of 0 to 10, 0 as “No spasticity” and 10 as “Worst possible spasticity”.	
End point type	Secondary
End point timeframe:	
Week 4, Week 8 and Week 12	

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[5]	53[6]		
Units: Percentage of subjects				
number (not applicable)				
Week 4	81.1	45.3		
Week 8	83.0	34.0		
Week 12	77.4	35.8		

Notes:
[5] - Phase B: ITT
[6] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Adjusted Odds ratio
Point estimate	4.911
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.999
upper limit	12.064

Statistical analysis title	Week 8: Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted Odds ratio
Point estimate	10.186
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.687
upper limit	28.139

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted Odds ratio
Point estimate	9.353
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.381
upper limit	25.875

Notes:

[7] - General Linear Mixed Model for binary repeated data with Phase B baseline mean value as covariate and treatment, week and treatment by week interaction as fixed effect factors.

Secondary: Change From Phase B Baseline in Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in Multiple Sclerosis (MS) Spasticity 0-10 Numerical Rating Scale (NRS) After 4, 8 and 12 Weeks of Treatment

End point description:

MS Spasticity was measured based on a scale of 0 to 10, 0 as "No spasticity" and 10 as "Worst possible spasticity".

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[8]	53[9]		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Change at Week 4	-3.04 (-3.58 to -2.50)	-1.51 (-2.06 to -0.97)		
Change at Week 8	-3.33 (-3.92 to -2.75)	-1.54 (-2.12 to -0.95)		
Change at Week 12	-3.49 (-4.08 to -2.91)	-1.60 (-2.19 to -1.00)		

Notes:

[8] - Phase B: ITT

[9] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.76

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	-0.97

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	-1.06

Secondary: Change From Phase B Baseline in the Frequency of Spasm After 4, 8 and

12 Weeks of Treatment

End point title	Change From Phase B Baseline in the Frequency of Spasm After 4, 8 and 12 Weeks of Treatment

End point description:

Frequency of Spasm was calculated by a daily review (at bedtime) as"number of spasms in the last 24 hours" and gave a best estimate if a large number of spasms occurred. '0' was recorded if no spasms were experienced.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[10]	53[11]		
Units: Frequency of spasm				
least squares mean (confidence interval 95%)				
Change at Week 4	-18.39 (-29.40 to -7.38)	-15.34 (-26.40 to -4.27)		
Change at Week 8	-19.82 (-30.91 to -8.73)	-17.80 (-29.10 to -6.50)		
Change at Week 12	-20.58 (-31.80 to -9.36)	-17.75 (-29.10 to -6.41)		

Notes:

[10] - Phase B: ITT

[11] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7002
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.67
upper limit	12.56

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8016
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.87
upper limit	13.82

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7278
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.79
upper limit	13.14

Secondary: Change From Phase B Baseline in the Severity of Spasm After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in the Severity of Spasm After 4, 8 and 12 Weeks of Treatment

End point description:

Subjects made a qualitative assessment of the severity of the spasms in a 3 levels categorical scale, i.e. mild, moderate, severe. Least square means and 95% confidence interval values of severity score were reported.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[12]	53[13]		
Units: Severity of spasms				
least squares mean (confidence interval 95%)				
Change at Week 4	-0.61 (-0.75 to -0.48)	-0.34 (-0.47 to -0.21)		
Change at Week 8	-0.67 (-0.82 to -0.52)	-0.36 (-0.51 to -0.21)		
Change at Week 12	-0.72 (-0.87 to -0.58)	-0.38 (-0.52 to -0.24)		

Notes:

[12] - Phase B: ITT

[13] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0052
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.08

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	-0.1

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0012
Method	Mixed Model for Repeated Measure (MMRM).
Parameter estimate	LS Mean Difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.14

Secondary: Change From Phase B Baseline in Sleep Disruption 0-10 Numerical Rating Scale (NRS) After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in Sleep Disruption 0-10 Numerical Rating Scale (NRS) After 4, 8 and 12 Weeks of Treatment

End point description:

Sleep disruption was measured based on a scale of 0 to 10, 0 as"did not disrupt sleep" and 10 as "completely disrupted (unable to sleep at all)".

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[14]	53[15]		
Units: Score on a Scale				
least squares mean (confidence interval 95%)				
Change at Week 4	-2.77 (-3.28 to -2.27)	-1.58 (-2.09 to -1.07)		
Change at Week 8	-3.14 (-3.70 to -2.58)	-1.62 (-2.18 to -1.05)		
Change at Week 12	-3.21 (-3.77 to -2.65)	-1.78 (-2.35 to -1.21)		

Notes:

[14] - Phase B: ITT

[15] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	-0.47

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	-0.73

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0006
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	-0.63

Secondary: Change From Phase B Baseline in the Spasticity Modified Ashworth Scale

After 4, 8 and 12 Weeks of Treatment (Overall Score)

End point title	Change From Phase B Baseline in the Spasticity Modified Ashworth Scale After 4, 8 and 12 Weeks of Treatment (Overall Score)

End point description:

The modified Ashworth scale had 5 categories to classify muscle spasticity by the healthcare professional as-
0) No increase in muscle tone.
1) Slight increase in muscle tone with a catch and release or minimal resistance at end of the range.
2) As 1 but minimal resistance through range following catch.
3) More marked increase in tone through range of motion (ROM).
4) Considerable increase in tone, passive movement is difficult.
5) Affected part rigid in flexion or extension.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[16]	53[17]		
Units: Score on a Scale				
least squares mean (confidence interval 95%)				
Change at Week 4	-0.26 (-0.34 to -0.17)	-0.02 (-0.11 to 0.07)		
Change at Week 8	-0.30 (-0.39 to -0.21)	-0.05 (-0.15 to 0.04)		
Change at Week 12	-0.30 (-0.39 to -0.21)	-0.06 (-0.16 to 0.04)		

Notes:

[16] - Phase B: ITT

[17] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.11

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.11

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.1

Secondary: Change From Phase B Baseline in Expanded Disability Status Scale (EDSS) Score After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in Expanded Disability Status Scale (EDSS) Score After 4, 8 and 12 Weeks of Treatment

End point description:

Expanded disability status scale quantifies disability in 8 functional systems and allows neurologists to assign a Functional System Score. EDSS steps 1.0 to 4.5 refer to subjects with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[18]	53[19]		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Change at Week 4	0.00 (-0.02 to 0.02)	0.00 (-0.02 to 0.02)		
Change at Week 8	-0.02 (-0.04 to 0.00)	0.00 (-0.02 to 0.02)		
Change at Week 12	-0.02 (-0.04 to 0.00)	-0.01 (-0.04 to 0.01)		

Notes:

[18] - Phase B: ITT

[19] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9878
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.03

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1706
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.01

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6259
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.03

Secondary: Change From Phase B Baseline in the Barthel Activities of Daily Living (ADL) Index After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in the Barthel Activities of Daily Living (ADL) Index After 4, 8 and 12 Weeks of Treatment

End point description:

The Barthel ADL index analysed the subject´s abilities to perform daily living activities quantitatively. The short form of Barthel ADL index was used in this study, which included 10 elements with a maximum total score of 20. Two elements (grooming and bathing) were on a scale of 0 to 1; 6 elements (bowels, bladder, toilet use, feeding, dressing, and stairs) were on a 0 to 2; and 2 elements (mobility and transfer) were on a scale of 0 to 3. Total possible scores range from 0 to 20, with lower scores indicating increased disability.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[20]	53[21]		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Change at Week 4	-0.08 (-0.31 to 0.15)	0.09 (-0.16 to 0.33)		
Change at Week 8	-0.10 (-0.39 to 0.18)	0.13 (-0.17 to 0.43)		
Change at Week 12	0.04 (-0.23 to 0.30)	0.11 (-0.17 to 0.39)		

Notes:

[20] - Phase B: ITT

[21] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3273
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.17

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2721
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.18

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.709
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.31

Secondary: Percentage of Subjects who Achieve the Minimum Clinically Important Difference (MCID) Improvement From Phase B Baseline in Barthel Activities of Daily Living (ADL) Index After 4, 8 and 12 Weeks of Treatment

End point title	Percentage of Subjects who Achieve the Minimum Clinically Important Difference (MCID) Improvement From Phase B Baseline in Barthel Activities of Daily Living (ADL) Index After 4, 8 and 12 Weeks of Treatment

End point description:

The Barthel ADL index analysed the subject´s abilities to perform activities of daily living quantitatively. The short form was used in this study, which included 10 elements with a maximum total score of 20. Two elements (grooming and bathing) were on a scale of 0 to 1; 6 elements (bowels, bladder, toilet use, feeding, dressing, and stairs) were on a 0 to 2; and 2 elements (mobility and transfer) were on a scale of 0 to 3. Total possible scores range from 0 to 20, with lower scores indicating increased disability. The MCID of the Barthel ADL index is 1.85 points.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[22]	53[23]		
Units: Percentage of subjects				
number (not applicable)				
Week 4	1.9	5.7		
Week 8	3.8	7.5		
Week 12	5.7	5.7		

Notes:

[22] - Phase B: ITT

[23] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2043
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	0.278

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	2.027

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3249
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	0.413
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	2.434

Statistical analysis title	Week 12: Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8834
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	0.879
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.153
upper limit	5.035

Secondary: Change From Phase B Baseline in Short Form 36 (SF-36) Scores After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in Short Form 36 (SF-36) Scores After 4, 8 and 12 Weeks of Treatment

End point description:

The SF-36 differentiates between physical and mental health and consists of 8 different dimensions (physical functioning, vitality, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health) and is validated for bodily pain and physical function. The SF-36 scores for each dimension could range between 0 and 100. Higher score indicates better functional health and well being.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[24]	53[25]		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Change at Week 4: General health	3.14 (0.02 to 6.25)	1.69 (-1.58 to 4.96)		
Change at Week 8: General health	2.73 (-0.60 to 6.07)	2.27 (-1.23 to 5.78)		
Change at Week 12: General health	0.31 (-3.71 to 4.34)	1.90 (-2.34 to 6.15)		
Change at Week 4: Physical role	9.05 (5.40 to 12.70)	4.26 (0.42 to 8.10)		
Change at Week 8: Physical role	12.25 (8.22 to 16.27)	5.90 (1.65 to 10.14)		
Change at Week 12: Physical role	7.44 (2.99 to 11.89)	4.77 (0.08 to 9.46)		
Change at Week 4: Vitality	7.93 (4.08 to 11.79)	2.55 (-1.50 to 6.60)		
Change at Week 8: Vitality	6.88 (2.83 to 10.92)	3.98 (-0.27 to 8.24)		
Change at Week 12: Vitality	8.34 (3.89 to 12.78)	3.00 (-1.69 to 7.68)		
Change at Week 4: Social functioning	8.08 (3.28 to 12.89)	3.49 (-1.56 to 8.54)		
Change at Week 8: Social functioning	7.90 (2.98 to 12.82)	5.35 (0.16 to 10.54)		
Change at Week 12: Social functioning	7.68 (3.12 to 12.24)	4.27 (-0.54 to 9.08)		
Change at Week 4: Emotional role	5.85 (0.77 to 10.93)	7.46 (2.12 to 12.80)		
Change at Week 8: Emotional role	9.38 (4.42 to 14.33)	3.84 (-1.40 to 9.07)		
Change at Week 12: Emotional role	6.21 (1.32 to 11.11)	4.99 (-0.18 to 10.16)		
Change at Week 4: Mental health	5.23 (2.19 to 8.26)	4.34 (1.15 to 7.53)		
Change at Week 8: Mental health	6.62 (3.02 to 10.23)	3.85 (0.06 to 7.65)		
Change at Week 12: Mental health	5.52 (2.09 to 8.95)	3.38 (-0.23 to 7.00)		
Change at Week 4: Bodily pain	18.05 (13.81 to 22.28)	6.02 (1.57 to 10.47)		

Change at Week 8: Bodily pain	19.52 (14.63 to 24.42)	9.84 (4.68 to 15.00)		
Change at Week 12: Bodily pain	19.71 (14.34 to 25.09)	10.41 (4.74 to 16.08)		
Change at Week 4: Physical functioning	3.90 (0.87 to 6.93)	2.63 (-0.55 to 5.82)		
Change at Week 8: Physical functioning	5.31 (2.05 to 8.57)	2.68 (-0.75 to 6.12)		
Change at Week 12: Physical functioning	4.08 (0.57 to 7.59)	3.65 (-0.05 to 7.35)		

Notes:

[24] - Phase B: ITT

[25] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: General Health- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.526
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.07
upper limit	5.97

Statistical analysis title	Week 8: General Health- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8507
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.38
upper limit	5.3

Statistical analysis title	Week 12: General Health- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5909
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.44
upper limit	4.26

Statistical analysis title	Week 4: Physical role- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0762
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	4.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	10.1

Statistical analysis title	Week 8: Physical role- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.034
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	6.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	12.21

Statistical analysis title	Week 12: Physical role- Sativex vs Placebo

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4148
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	9.13

Statistical analysis title	Week 4: Vitality- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0592
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	5.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	10.98

Statistical analysis title	Week 8: Vitality- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3306
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	8.77

Statistical analysis title	Week 12: Vitality- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1044
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	5.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	11.8

Statistical analysis title	Week 4: Social functioning- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1946
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	4.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	11.57

Statistical analysis title	Week 8: Social functioning- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.481
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.61
upper limit	9.71

Statistical analysis title	Week 12: Social functioning- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3109
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	10.04

Statistical analysis title	Week 4: Emotional role- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6653
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.99
upper limit	5.76

Statistical analysis title	Week 8: Emotional role- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1304
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	5.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	12.75

Statistical analysis title	Week 12: Emotional role- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7336
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	8.35

Statistical analysis title	Week 4: Mental health- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6914
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.52
upper limit	5.29

Statistical analysis title	Week 8: Mental health- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2964
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	2.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.47
upper limit	8.01

Statistical analysis title	Week 12: Mental health- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3976
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	7.12

Statistical analysis title	Week 4: Bodily pain- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	12.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.88
upper limit	18.18

Statistical analysis title	Week 8: Bodily pain- Sativex vs Placebo

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0082
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	9.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.57
upper limit	16.8

Statistical analysis title	Week 12: Bodily pain- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0201
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.49
upper limit	17.12

Statistical analysis title	Week 4: Physical functioning- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5699
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	5.66

Statistical analysis title	Week 8: Physical functioning- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2746
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	7.36

Statistical analysis title	Week 12: Physical functioning- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.868
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	5.53

Secondary: Percentage of Subjects With an Minimum Clinically Important Difference (MCID) Improvement From Phase B Baseline in Short Form 36 Quality of Life (SF-36 Qol) Scale Scores After 4, 8 and 12 Weeks of Treatment in Phase B

End point title	Percentage of Subjects With an Minimum Clinically Important Difference (MCID) Improvement From Phase B Baseline in Short Form 36 Quality of Life (SF-36 Qol) Scale Scores After 4, 8 and 12 Weeks of Treatment in Phase B

End point description:

The SF-36 differentiates between physical and mental health and consists of 8 different dimensions (physical functioning, vitality, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health) and is validated for bodily pain and physical function. The SF-36 scores for each dimension could range between 0 and 100. Higher score indicates better functional health and well being.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[26]	53[27]		
Units: Percentage of subjects				
number (not applicable)				
Week 4: Bodily pain	77.4	35.8		
Week 8: Bodily pain	79.2	47.2		
Week 12: Bodily pain	69.8	47.2		
Week 4: Physical functioning	49.1	34.0		
Week 8: Physical functioning	52.8	26.4		
Week 12: Physical functioning	47.2	35.8		

Notes:

[26] - Phase B: ITT

[27] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Bodily pain- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0008
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	6.264
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.196
upper limit	17.871

Statistical analysis title	Week 8: Bodily pain- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0016
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	5.078

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.884
upper limit	13.685

Statistical analysis title	Week 12: Bodily pain- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0543
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.983
upper limit	6.669

Statistical analysis title	Week 4: Physical functioning- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2454
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.619
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.714
upper limit	3.672

Statistical analysis title	Week 8: Physical functioning- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.015
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds Ratio
Point estimate	2.948
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	7.01

Statistical analysis title	Week 12: Physical functioning- Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.424
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds Ratio
Point estimate	1.393
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.614
upper limit	3.159

Secondary: Percentage of Subjects With Change From Baseline in Global Assessment Of Clinical Change (7-Item Categorical Scales) by the Subject (SGIC) and the Doctor (PGIC) After 4, 8 and 12 Weeks of Treatment

End point title	Percentage of Subjects With Change From Baseline in Global Assessment Of Clinical Change (7-Item Categorical Scales) by the Subject (SGIC) and the Doctor (PGIC) After 4, 8 and 12 Weeks of Treatment

End point description:

Subject global impression of change (SGIC) indicated the change in ability to function due to MS. The SGIC was assessed using a 7-point scale: Very much better, Much better, Minimally better, No change, Minimally worse, Much worse and Very much worse. The Physician/doctor Global assessment of clinical change (PGIC) was assessed by the physician, using the same 7-point scale used to assess the SGIC.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[28]	53[29]		
Units: Percentage of subjects				
number (not applicable)				
Week 4: SGIC- Very much better	1.9	0		
Week 4: SGIC- Much better	11.3	1.9		
Week 4: SGIC- Minimally better	41.5	15.1		
Week 4: SGIC- No change	20.8	39.6		
Week 4: SGIC- Minimally worse	13.2	22.6		
Week 4: SGIC- Much worse	11.3	11.3		
Week 4: SGIC- Very much worse	0	0		
Week 8: SGIC- Very much better	3.8	0		
Week 8: SGIC- Much better	13.2	9.4		
Week 8: SGIC- Minimally better	32.1	13.2		
Week 8: SGIC- No change	18.9	34.0		
Week 8: SGIC- Minimally worse	9.4	24.5		
Week 8: SGIC- Much worse	13.2	3.8		
Week 8: SGIC- Very much worse	5.7	1.9		
Week 12: SGIC- Very much better	0	0		
Week 12: SGIC- Much better	15.1	3.8		
Week 12: SGIC- Minimally better	28.3	22.6		
Week 12: SGIC- No change	32.1	41.5		
Week 12: SGIC- Minimally worse	5.7	17.0		
Week 12: SGIC- Much worse	13.2	1.9		
Week 12: SGIC- Very much worse	1.9	0		
Week 4: PGIC- Very much better	0	0		
Week 4: PGIC- Much better	20.8	1.9		
Week 4: PGIC- Minimally better	37.7	13.2		
Week 4: PGIC- No change	15.1	41.5		
Week 4: PGIC- Minimally worse	17.0	24.5		
Week 4: PGIC- Much worse	9.4	9.4		
Week 4: PGIC- Very much worse	0	0		
Week 8: PGIC- Very much better	3.8	0		
Week 8: PGIC- Much better	11.3	7.5		
Week 8: PGIC- Minimally better	34.0	11.3		
Week 8: PGIC- No change	26.4	39.6		
Week 8: PGIC- Minimally worse	9.4	26.4		
Week 8: PGIC- Much worse	11.3	0		
Week 8: PGIC- Very much worse	0	1.9		
Week 12: PGIC- Very much better	3.8	0		
Week 12: PGIC- Much better	11.3	5.7		
Week 12: PGIC- Minimally better	32.1	20.8		
Week 12: PGIC- No change	35.8	49.1		
Week 12: PGIC- Minimally worse	5.7	9.4		
Week 12: PGIC- Much worse	7.5	1.9		
Week 12: PGIC- Very much worse	0	0		

Notes:
[28] - Phase B: ITT
[29] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: SGIC- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for ordinal repeated data with treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0035
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.852
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	5.768

Statistical analysis title	Week 8: SGIC- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for ordinal repeated data with treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1331
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	1.823
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.833
upper limit	3.993

Statistical analysis title	Week 12: SGIC- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for ordinal repeated data with treatment, week and treatment by week	

interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3515
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	1.384
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.699
upper limit	2.741

Statistical analysis title	Week 4: PGIC- Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for ordinal repeated data with treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0005
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	3.972
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.834
upper limit	8.604

Statistical analysis title	Week 8: PGIC- Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for ordinal repeated data with treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.418

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.111
upper limit	5.262

Statistical analysis title	Week 12: PGIC- Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for ordinal repeated data with treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1615
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	1.623
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.824
upper limit	3.198

Secondary: Percentage of Subjects With an Minimum Clinically Important Difference (MCID) Improvement From Phase B Baseline in Global Assessment of Clinical Change by the Subject (SGIC) and the Doctor (PGIC) After 4, 8 and 12 Weeks of Treatment (Responder Analysis)

End point title	Percentage of Subjects With an Minimum Clinically Important Difference (MCID) Improvement From Phase B Baseline in Global Assessment of Clinical Change by the Subject (SGIC) and the Doctor (PGIC) After 4, 8 and 12 Weeks of Treatment (Responder Analysis)

End point description:

Subject global impression of change (SGIC) indicated the change in ability to function due to MS. The SGIC was assessed using a 7-point scale: Very much better, Much better, Minimally better, No change, Minimally worse, Much worse and Very much worse. The PGIC was assessed by the physician, using the same 7-point scale used to assess the SGIC.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[30]	53[31]		
Units: Percentage of subjects				
number (not applicable)				
Week 4: SGIC	54.7	17.0		
Week 8: SGIC	49.1	22.6		
Week 12: SGIC	43.4	26.4		
Week 4: PGIC	58.5	15.1		
Week 8: PGIC	49.1	18.9		
Week 12: PGIC	47.2	26.4		

Notes:

[30] - Phase B: ITT

[31] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: SGIC- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0006 [32]
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	5.236
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.077
upper limit	13.201

Notes:

[32] - General Linear Mixed Model for binary repeated data with treatment, week and treatment by week interaction as fixed effect factors.

Statistical analysis title	Week 8: SGIC- Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0152
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.238
upper limit	7.076

Statistical analysis title	Week 12: SGIC- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1568
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	1.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.786
upper limit	4.345

Statistical analysis title	Week 4: PGIC- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	7.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.707
upper limit	18.334

Statistical analysis title	Week 8: PGIC- Sativex vs Placebo
Statistical analysis description:	
General Linear Mixed Model for binary repeated data with treatment, week and treatment by week interaction as fixed effect factors.	
Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0045
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	3.777
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.524
upper limit	9.363

Statistical analysis title	Week 12: PGIC- Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.072
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.931
upper limit	5.119

Notes:

[33] - General Linear Mixed Model for binary repeated data with treatment, week and treatment by week interaction as fixed effect factors.

Secondary: Change From Phase B Baseline in Pain (0-10 NRS) After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in Pain (0-10 NRS) After 4, 8 and 12 Weeks of Treatment

End point description:

Pain was measured based on a scale of 0 to 10, 0 as “No pain”and 10 as“Worst possible pain”.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[34]	53[35]		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Change at Week 4	-2.85 (-3.37 to -2.32)	-1.65 (-2.18 to -1.12)		
Change at Week 8	-3.08 (-3.66 to -2.51)	-1.64 (-2.22 to -1.05)		
Change at Week 12	-3.21 (-3.81 to -2.62)	-1.80 (-2.41 to -1.20)		

Notes:

[34] - Phase B: ITT

[35] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0019
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	-0.45

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	-0.62

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	-0.56

Secondary: Percentage of Subjects With an Minimum Clinically Important Difference (MCID) Improvement in Pain (0-10 NRS) After 4, 8 And 12 Weeks of Treatment in Phase B

End point title	Percentage of Subjects With an Minimum Clinically Important Difference (MCID) Improvement in Pain (0-10 NRS) After 4, 8 And 12 Weeks of Treatment in Phase B

End point description:

Pain was measured based on a scale of 0 to 10, 0 as "No pain"and 10 as"Worst possible pain".

End point type	Secondary

End point timeframe:

Week 4, Week 8 And Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[36]	53[37]		
Units: Percentage of subjects				
number (not applicable)				
Week 4	77.4	62.3		
Week 8	83.0	54.7		
Week 12	73.6	58.5		

Notes:

[36] - Phase B: ITT

[37] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1104
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.842
upper limit	5.236

Statistical analysis title	Week 8: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0042
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	5.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.693
upper limit	15.396

Statistical analysis title	Week 12: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0571
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.688

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	7.447

Secondary: Change From Phase B Baseline in Timed 10 Minute Walk Test, After 4, 8 and 12 Weeks of Treatment

End point title	Change From Phase B Baseline in Timed 10 Minute Walk Test, After 4, 8 and 12 Weeks of Treatment

End point description:

The timed 10 minute walk test assessed walking speed in meters per second over a short distance.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[38]	53[39]		
Units: Meter per second				
least squares mean (confidence interval 95%)				
Change at Week 4	-2.09 (-3.16 to -1.03)	-1.10 (-2.25 to 0.05)		
Change at Week 8	-1.74 (-3.35 to -0.13)	-1.31 (-3.03 to 0.40)		
Change at Week 12	-2.79 (-4.25 to -1.32)	-1.08 (-2.65 to 0.48)		

Notes:

[38] - Phase B: ITT

[39] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2111
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	0.57

Statistical analysis title	Week 8: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7158
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	1.92

Statistical analysis title	Week 12: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1174
Method	Mixed Model for Repeated Measure (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.84
upper limit	0.44

Secondary: Percentage of Subjects With a Clinically Important Difference (CID) Improvement in Timed 10m Walk Test, After 4, 8 and 12 Weeks of Treatment

End point title	Percentage of Subjects With a Clinically Important Difference (CID) Improvement in Timed 10m Walk Test, After 4, 8 and 12 Weeks of Treatment

End point description:

The timed 10 m walk test assessed walking speed in meters per second over a short distance.

End point type	Secondary

End point timeframe:

Week 4, Week 8 and Week 12

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[40]	53[41]		
Units: Percentage of subjects				
number (not applicable)				
Week 4	15.1	11.3		
Week 8	17.0	13.2		
Week 12	18.9	7.5		

Notes:

[40] - Phase B: ITT

[41] - Phase B: ITT

Statistical analyses

Statistical analysis title	Week 4: Sativex vs Placebo
Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.7698
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	1.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.358
upper limit	3.983

Notes:

[42] - General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Statistical analysis title	Week 8: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7819
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	1.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.373
upper limit	3.69

Statistical analysis title	Week 12: Sativex vs Placebo

Statistical analysis description:

General Linear Mixed Model for binary repeated data with Phase B baseline mean value as co-variate and treatment, week and treatment by week interaction as fixed effect factors.

Comparison groups	Phase B: Sativex v Phase B: Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1537
Method	Generalized Linear Mixed model
Parameter estimate	Adjusted Odds ratio
Point estimate	2.596
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.695
upper limit	9.701

Secondary: Percentage of Subjects With Changes in Concomitant/Underlying Antispastic Standard Therapy Between Visit 4 and Visit 7

End point title	Percentage of Subjects With Changes in Concomitant/Underlying Antispastic Standard Therapy Between Visit 4 and Visit 7

End point description:

Any changes in concomitant medication - particularly any changes in antispastic medication – during the study period was recorded in the eCRF.

End point type	Secondary

End point timeframe:

Phase B: Start of study drug administration up to 12 weeks

End point values	Phase B: Sativex	Phase B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[43]	53[44]		
Units: Percentage of subjects				
number (not applicable)				
Baclofen	3.8	7.5		
Tizanidine	0	0		
Dantrolene	0	0		
Benzodiazepine derivatives	1.9	0		

Notes:

[43] - Phase B: ITT

[44] - Phase B: ITT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 20 weeks

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Phase A: Sativex

Reporting group description:

Subjects received up-titrated Sativex up to 12 sprays per day for 4 weeks as add-on to their optimized standard antispastic medication (oral baclofen and/or tizanidine and/or dantrolene) until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Reporting group title	Phase B: Sativex

Reporting group description:

Subjects who were initial responders and whose Phase A-improvement in MS spasticity NRS score had been reduced by at least 80% during the washout phase received up-titrated Sativex to the dose identified during Phase A as being their optimal dose (up to 12 sprays per day) for 12 weeks as add-on to their optimized standard antispastic medication until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Reporting group title	Phase B: Placebo

Reporting group description:

Subjects who were initial responders and whose Phase A-improvement in MS spasticity NRS score had been reduced by at least 80% during the washout phase received matched placebo for 12 weeks as addon to their optimized standard antispastic medication until they achieved optimized symptom relief and maintained this optimal dose. At least a 15-minute gap was maintained between sprays.

Reporting group title	Phase A: Sativex Washout

Reporting group description:

Subjects who qualified as Sativex initial responders received their underlying optimized standard antispastic medication (oral baclofen and/or tizanidine and/or
dantrolene) but not Sativex up to 4 weeks, until the subject’s Phase A-gain in MS spasticity NRS score had been reduced by at least 80%.

Serious adverse events	Phase A: Sativex	Phase B: Sativex	Phase B: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 191 (1.05%)	1 / 53 (1.89%)	1 / 53 (1.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (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 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (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

Serious adverse events	Phase A: Sativex Washout		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 134 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase A: Sativex	Phase B: Sativex	Phase B: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 191 (24.08%)	19 / 53 (35.85%)	8 / 53 (15.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Paraesthesia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 191 (1.57%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 191 (1.57%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	3	0	0
Asthenia			
subjects affected / exposed	2 / 191 (1.05%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Administration site pain			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hunger			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Prostatic neoplasms and hypertrophy			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Dry throat			
subjects affected / exposed	2 / 191 (1.05%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Throat tightness			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 191 (2.09%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	4	0	0
Somnolence			
subjects affected / exposed	3 / 191 (1.57%)	2 / 53 (3.77%)	0 / 53 (0.00%)
occurrences (all)	6	2	0
Dysaesthesia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			

subjects affected / exposed	1 / 191 (0.52%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Multiple sclerosis relapse			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Disturbance in attention			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hypotonia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Muscle spasticity			
subjects affected / exposed	1 / 191 (0.52%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Dysgeusia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Tremor			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hypogeusia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Psychomotor skills impaired			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	14 / 191 (7.33%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	15	1	0
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	4 / 191 (2.09%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	4	0	0
Diarrhoea			
subjects affected / exposed	4 / 191 (2.09%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	4	0	0
Dry mouth			
subjects affected / exposed	3 / 191 (1.57%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	3	1	0
Abdominal pain upper			
subjects affected / exposed	2 / 191 (1.05%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Oral pain			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Hydronephrosis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Obstructive nephropathy			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Muscular weakness			
subjects affected / exposed	2 / 191 (1.05%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Bursitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 191 (1.05%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	2	1	0
Erysipelas			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2
Gastroenteritis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	0 / 191 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 191 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Phase A: Sativex Washout		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 134 (8.96%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paraesthesia			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences (all)	1		
Asthenia			

subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Administration site pain			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Hunger			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Prostatic neoplasms and hypertrophy			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences (all)	2		
Throat tightness			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Psychotic disorder subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Somnolence subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Dysaesthesia subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Multiple sclerosis relapse subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Hypotonia subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		

Muscle spasticity subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Tremor subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Hypogeusia subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Psychomotor skills impaired subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1		
Dry mouth subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Oral pain subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Hepatobiliary disorders			

Hepatic cyst subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		
Renal and urinary disorders Tubulointerstitial nephritis subjects affected / exposed occurrences (all) Hydronephrosis subjects affected / exposed occurrences (all) Obstructive nephropathy subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0 0 / 134 (0.00%) 0 0 / 134 (0.00%) 0 0 / 134 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Bursitis subjects affected / exposed occurrences (all) Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0 1 / 134 (0.75%) 1 0 / 134 (0.00%) 0 0 / 134 (0.00%) 0		
Infections and infestations Cystitis			

subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Erysipelas			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Pulpitis dental			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			

Dehydration subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2016	- The investigational medicinal product (IMP) was not to be weighed - Subjects were to be withdrawn from the study if they had a relapse of MS. - Systemic corticosteroids were not to be prohibited. - Addition of a secondary efficacy variable: CID improvement in timed 10 minute walk test after 4, 8 and 12 weeks

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported