Clinical trial results:
NEUROPHYSIOLOGIC STUDY AIMED AT EVALUATING ON EFFECT OF SATIVEX® ON SPASTICITY IN PROGRESSIVE MULTIPLE SCLEROSIS

Summary

EudraCT number	2011-002258-30
Trial protocol	IT
Global end of trial date	30 August 2013

Results information

Result version number	v1 (current)
This version publication date	29 June 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	M/SATIVX/01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01538225
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Almirall S.A.
Sponsor organisation address	General Mitre 151 , Barcelona, Spain,
Public contact	Global Medical Affairs, ALMIRALL S.A., 0034 932913490, carlos.vila@almirall.com
Scientific contact	Global Medical Affairs, ALMIRALL S.A., 0034 932913490, carlos.vila@almirall.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2013
Global end of trial reached?	Yes
Global end of trial date	30 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of Sativex (THC:CBD 1:1 ratio oromucosal spray) compared to placebo in modifying neurophysiological measures of spasticity (H/M ratio scores at baseline and at week 4) in patients affected by lower limbs spasticity in Progressive Multiple Sclerosis

Protection of trial subjects:

Insurance policy available.
Informed consent and informative sheet for patients about study procedures.
Telephone conntacts at weeks 2 and 8 for Sativex dose fixation.
Presential visits at weeks 0, 4, 6, 10.

Background therapy:

Approved antispastic medication

Evidence for comparator:

Not applicable, Placebo comparator

Actual start date of recruitment	19 April 2012
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	Italy: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	43

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Following the protocol selection criteria

Pre-assignment

Screening details:

Patients fulfilling the protocol selection criteria, including Sativex approved label requirements and providing informed consent. Subjects affected by Secondary or Primary-Progressive MS. Sativex has been gradually titrated. Subjects recieved in a random order each treatment (Sativex/Placebo) during 2 subsequent 4-weeks period divided by a washout

Pre-assignment period milestones

Number of subjects started	44
Number of subjects completed	44

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	4 weeks Sativex and 4 weeks Placebo

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sativex and Placebo
Investigational medicinal product code	
Other name	THC:CDB oromucosal spray, Namiximols (USAN name)
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Spray containing, for 100 microliters, 2.7mg THC and 2.5mg CBD OR Placebo gradually titrated during the first 2 weeks of treatment, increasing the number of sprays until they reached and individualized sprayed dose (maximum 12 sprays)

Arm title	4 weeks Placebo and 4 weeks Sativex

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sativex and Placebo
Investigational medicinal product code	
Other name	THC:CBD oromucosal spray, Namiximols (USAN name)
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Spray containing, for 100 microliters, 2.7mg THC and 2.5mg CBD OR Placebo gradually titrated during the first 2 weeks of treatment, increasing the number of sprays until they reached and individualized sprayed dose (maximum 12 sprays)

Number of subjects in period 1	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex
Started	22	22
Completed	17	21
Not completed	5	1
Adverse event, non-fatal	2	-
Intolerance to TMS	-	1
Serious Adverse Event, non-fatal	1	-
Personal Reasons	1	-
Starting neurorehabilitation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	4 weeks Sativex and 4 weeks Placebo
Reporting group description: -	
Reporting group title	4 weeks Placebo and 4 weeks Sativex
Reporting group description: -	

Reporting group values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex	Total
Number of subjects	22	22	44
Age categorical Units: Subjects			
Aged 18 years or above	22	22	44
Age continuous Units: years			
arithmetic mean	48.5	47.6	
standard deviation	± 7.8	± 8.4	-
Gender categorical Units: Subjects			
Female	12	8	20
Male	10	14	24

End points

End points reporting groups

Reporting group title	4 weeks Sativex and 4 weeks Placebo
Reporting group description: -	
Reporting group title	4 weeks Placebo and 4 weeks Sativex
Reporting group description: -	

Primary: The treatment effect on the H reflex/Motor response ratio (H/M ratio)

End point title	The treatment effect on the H reflex/Motor response ratio (H/M ratio)
End point description:	
End point type	Primary
End point timeframe:	
H/M ratio scores at baseline and at week 4 for each treatment	

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: H/M ratio value				
arithmetic mean (standard deviation)				
Baseline sativex	0.37 (± 0.19)	0.3 (± 0.18)		
After 4 weeks sativex treatment	0.34 (± 0.17)	0.29 (± 0.16)		
Baseline placebo	0.31 (± 0.17)	0.31 (± 0.18)		
After 4 weeks placebo treatment	0.32 (± 0.18)	0.29 (± 0.15)		

Statistical analyses

Statistical analysis title	H reflex/Motor response H/M ratio values evolution
Comparison groups	4 weeks Sativex and 4 weeks Placebo v 4 weeks Placebo and 4 weeks Sativex
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.405
Method	T-test

Notes:

[1] - There was no significant difference between change from baseline to week 4 in the H/M ratio score (p=0.405) under treatment with Sativex or placebo. No significant effect of sequence of treatment was observed

Secondary: Resting Motor Thershold (RMT) at First Dorsal Interosseus (FDI)

End point title	Resting Motor Thershold (RMT) at First Dorsal Interosseus (FDI)

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: RMT at FDI				
arithmetic mean (standard deviation)				
Baseline Sativex	60.71 (± 16.31)	54.83 (± 12.45)		
Week 4 Sativex	61.14 (± 15.58)	55.78 (± 14.79)		
Baseline Placebo	58.71 (± 13.73)	54.26 (± 11.36)		
Week 4 Placebo	63.92 (± 13.77)	54 (± 11.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Motor Evoked Potentials (MEP)

End point title	Motor Evoked Potentials (MEP)

End point description:

End point type	Secondary

End point timeframe:

Frome baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: MEP value evolution				
arithmetic mean (standard deviation)				
Baseline Sativex	0.23 (± 0.15)	0.32 (± 0.3)		
week 4 Sativex	0.24 (± 0.17)	0.24 (± 0.16)		
Baseline Placebo	0.21 (± 0.1)	0.26 (± 0.15)		

Week 4 Placebo	0.34 (± 0.42)	0.24 (± 0.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: MEP/Muscle potential ratios at APB and AH muscles evolution

End point title	MEP/Muscle potential ratios at APB and AH muscles evolution

End point description:

Motos Evoked Potentials (MEP)/ Muscles potentials ratios at APB (Abductor Pollicis Brevis) and AH (Abductor Hallucis) left (L) and right (R) muscles.

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: MEP/M				
arithmetic mean (standard deviation)				
Baseline R APB Sativex	0.21 (± 0.1)	0.23 (± 0.19)		
Week 4 R APB Sativex	0.21 (± 0.14)	0.23 (± 0.17)		
Baseline L APB Sativex	0.17 (± 0.13)	0.23 (± 0.21)		
Week 4 L APB Sativex	0.2 (± 0.14)	0.22 (± 0.21)		
Baseline R AH Sativex	0.04 (± 0.02)	0.06 (± 0.06)		
Week 4 R AH Sativex	0.05 (± 0.03)	0.08 (± 0.08)		
Baseline L AH Sativex	0.04 (± 0.02)	0.06 (± 0.04)		
Week 4 L AH Sativex	0.04 (± 0.02)	0.06 (± 0.04)		
Baseline R APB Placebo	0.22 (± 0.13)	0.23 (± 0.16)		
Week 4 R APB Placebo	0.19 (± 0.12)	0.21 (± 0.15)		
Baseline L APB Placebo	0.17 (± 0.14)	0.22 (± 0.17)		
Week 4 L APB Placebo	0.19 (± 0.16)	0.24 (± 0.19)		
Baseline R AH Placebo	0.04 (± 0.02)	0.06 (± 0.03)		
Week 4 R AH Placebo	0.04 (± 0.02)	0.06 (± 0.03)		
Baseline L AH Placebo	0.04 (± 0.02)	0.05 (± 0.05)		
Week 4 L AH Placebo	0.04 (± 0.02)	0.06 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Spasticity Modified Ashworth Scale (MAS)

End point title	Spasticity Modified Ashworth Scale (MAS)

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: MAS score evolution				
arithmetic mean (standard deviation)				
Baseline Sativex	8.03 (± 4.26)	6.79 (± 1.87)		
Week 4 Sativex	7.67 (± 4.53)	6.37 (± 1.74)		
Baseline Placebo	7.4 (± 1.4)	7 (± 1.63)		
Week 4 Placebo	7.33 (± 1.84)	6.58 (± 2.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Spasticity Numeric Rating Scale (NRS)

End point title	Spasticity Numeric Rating Scale (NRS)

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 Weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: Numeric Rating Scale evolution				
arithmetic mean (standard deviation)				
Baseline Sativex	7.27 (± 1.16)	6.79 (± 1.87)		
Week 4 Sativex	6.73 (± 1.58)	6.37 (± 1.74)		
Baseline Placebo	7.4 (± 1.4)	7 (± 1.63)		
Week 4 Placebo	7.33 (± 1.84)	6.58 (± 2.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Timed 10 meters walk

End point title	Timed 10 meters walk

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: Seconds				
arithmetic mean (standard deviation)				
Baseline Sativex	39.5 (± 50.41)	20.55 (± 15.55)		
Week 4 Sativex	34.99 (± 47.09)	22.75 (± 19.36)		
Baseline Placebo	36.39 (± 47.74)	22.63 (± 20.37)		
Week 4 Placebo	34.55 (± 43.44)	22.48 (± 20.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nine Hole Peg Test (NHPT)

End point title	Nine Hole Peg Test (NHPT)

End point description:

Upper extremity function test

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: NHPT scores evolution				
arithmetic mean (standard deviation)				
Baseline DH Sativex	25.95 (± 5.54)	25.66 (± 4.19)		
Week 4 DH Sativex	27.32 (± 7.77)	24.94 (± 4.33)		
Baseline NDH Sativex	26.82 (± 3.99)	30.26 (± 8.32)		
Week 4 NDH Sativex	25.02 (± 2.71)	29.42 (± 7.99)		
Baseline DH Placebo	25.72 (± 6.51)	27.47 (± 4.95)		
Week 4 DH Placebo	25.98 (± 7.37)	26.02 (± 4.48)		
Baseline NDH Placebo	26.37 (± 4.19)	31.73 (± 8.23)		
Week 4 NDH Placebo	24.42 (± 3.75)	30.98 (± 9.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain

End point title	Pain

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: 0-10 Numeric Rating Scale				
arithmetic mean (standard deviation)				
Baseline Sativex	3.73 (± 3.22)	3.16 (± 3.17)		
Week 4 Sativex	3.33 (± 3.15)	2.63 (± 3)		
Baseline Placebo	4.4 (± 3.58)	3.84 (± 3.35)		
Week 4 Placebo	3.47 (± 2.77)	2 (± 2.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sleep Quality Numeric Rating Scale (NRS)

End point title	Sleep Quality Numeric Rating Scale (NRS)

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: 0-10 Numeric Rating Scale				
arithmetic mean (standard deviation)				
Baseline Sativex	2 (± 2.73)	2.95 (± 2.97)		
Week 4 Sativex	1.33 (± 2.89)	2.26 (± 3.19)		
Baseline Placebo	2.6 (± 3.02)	4 (± 3.53)		
Week 4 Placebo	2.33 (± 3.24)	2.37 (± 2.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Spasms

End point title	Spasms

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment

End point values	4 weeks Sativex and 4 weeks Placebo	4 weeks Placebo and 4 weeks Sativex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: Spasms Frequency Score				
arithmetic mean (standard deviation)				
Baseline Sativex	5 (± 6.49)	4.47 (± 6.5)		
Week 4 Sativex	4.28 (± 4.56)	2.58 (± 4.84)		
Baseline Placebo	4.53 (± 3.85)	5 (± 7.87)		

Week 4 Placebo	3.73 (± 4.13)	3 (± 4.85)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected and reported during two subsequent 4-weeks periods divided by a 2-week washout. The overall duration for each patient was 10 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Adverse events

Reporting group description: -

Serious adverse events	Adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 43 (51.16%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all)	10 / 43 (23.26%) 10 2 / 43 (4.65%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Respiratory, thoracic and mediastinal disorders Pharyngitis subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported