

**Clinical trial results: *Full title of Trial\******Summary**

EudraCT number*	EUDRACT 2010-022808-40
Trial protocol	Safety and Efficacy on Spasticity Symptoms of a Cannabis Sativa Extract in Motor Neuron Disease (CANALS)
Global end of trial date*	31 May 2015

**Trial information****Trial identification**

Sponsor protocol code*	Safety and Efficacy on Spasticity Symptoms of a Cannabis Sativa Extract in Motor Neuron Disease (CANALS)
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01776970
WHO universal trial number (UTN)	-

Notes:

**Sponsors details\***

Sponsor organisation name	IRCCS Ospedale San Raffaele
Sponsor organisation address	Via Olgettina, 60, Milano, Italy, 20132
Public contact	
Scientific contact	

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

**Results analysis stage**

Analysis stage*	Final
Date of interim/final analysis*	
Is this the analysis of the primary completion data?*	Yes
Global end of trial reached?*	Yes
Global end of trial date*	
Was the trial ended prematurely?	No

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## General information about the trial

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Main objective of the trial\*: *Enter a description for the main objective(s) of the trial*

The aim of our proof-of-concept study was to explore the safety and effects of a standardised oromucosal spray (nabiximols) containing a defined combination of THC and cannabidiol on spasticity related to motor neuron disease

Actual start date of recruitment*	Jan 19, 2013
Long term follow-up planned*	Yes
If Yes, rationale:	Safety X Efficacy X Ethical reason Regulatory reason Scientific research
Duration	13 Weeks
Independent data monitoring committee (IDMC) involvement?*	No
Protection of trial subjects*:	
Background therapy:	Riluzole, standard anti-spasticity drugs
Evidence for comparator:	No Clinical Trials available

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## Population of trial subjects

### Subjects enrolled per country

Country:	Italy
Planned number of subjects	60
Actual Number of subjects enrolled*	60
Worldwide total number of subjects	na
EEA total number of subjects	na

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### Subjects enrolled per age group

In utero*	
Preterm newborn - gestational age < 37wks*	
Newborns (0-27 days)*	
Infants and toddlers (28 days-23months)*	
Children (2-11 years)*	
Adolescents (12-17 years)*	
Adults (18-64 years)*	49
From 65 to 84 years*	11
85 years and over*	

## Subject disposition

**Recruitment details:** Enter key information relevant to the recruitment process for the trial (eg gates of recruitment period and territories)

The Cannabis Sativa Extract in Amyotrophic Lateral Sclerosis and other Motor Neuron Disease (CANALS) study was an investigator-initiated, randomised, doubleblind, placebo-controlled, parallel-group, phase 2 clinical trial at four tertiary centres for motor neuron disease in Italy: the Department of Neurology, Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute (Milan, Italy); Amyloid Lateral Sclerosis Centre, Istituti Clinici Scientifici Maugeri, IRCCS (Milan, Italy); Neuromuscular Centre, University of Padova (Padua, Italy); and NeuroMuscular Omnicentre (Milan, Italy). The trial was organised by the Institute of Experimental Neurology.

**Pre-assignment - Screening details:** Enter relevant information related to screening (eg screening criteria, significant events and approaches)

Eligible participants were aged 18–80 years; had possible, laboratory-supported probable, probable, or definite amyotrophic lateral sclerosis as defined by revised El Escorial criteria,<sup>4</sup> or primary lateral sclerosis according to Pringle's criteria;<sup>2</sup> had a spasticity score of 1 or greater on the five-point Modified Ashworth Scale (MAS) in two or more muscle groups; had spasticity due to motor neuron disease for at least 3 months that was incompletely controlled by therapy; were taking an antispasticity regimen that was maintained at a stable dose for 30 days before enrolment and throughout the study; and had optimised and not altered any physiotherapy regimen or medication likely to affect spasticity in the 3 weeks before start of treatment, and self-judged spasticity to be a relevant cause of movement impairment. Key exclusion criteria were any concomitant conditions that had spasticity-like symptoms or that might affect spasticity, use of cannabis or cannabinoid-based medications in the 30 days before study entry, administration of botulinum toxin during the preceding 6 months, concurrent history of significant psychiatric, renal, hepatic, cardiovascular, or convulsive disorders, cognitive impairment, fixed-tendon contractures, known or suspected history of alcohol or substance misuse, and being bedridden or tracheotomised. The full list of exclusion criteria is in the appendix. Central and local ethics committees approved the study. All participants provided written informed consent before inclusion

### Period 1

Period title*	Overall Trial
Is this the baseline period?	Yes
Allocation method*	<b>Randomised – controlled X</b> Non-randomised - controlled Not applicable
Blinding used*	<b>Double blind</b> Single blind    Not blinded

### Arms

Arm title*	Nabiximol
Arm description:	
Arm type*	Experimental X Active comparator Placebo No intervention Other
Investigational medicinal product name*	Nabiximols
Investigational medicinal product code	
Other name	Sativex

Pharmaceutical forms*	Oral Sray
Routes of administration*	Standardised pump action oromucosal spray
Dosage and administration details*	Each 100 µL actuation delivered 2.7 mg delta-9-THC and 2.5 mg cannabidiol in a 50:50 solution of ethanol and propylene glycol. Participants were instructed to self-titrate during the first 14 treatment days according to a predefined escalation scheme to their optimal dose, up to a maximum of 12 actuations in 24 h

<b>Number of subjects in period</b>	Arm Title (overall population)	Arm Title ( <i>repeat for each arms if applicable</i> )
Started*		
Completed*		
Subject non-completion reason (if applicable)		
AE, non fatal		
AE, fatal		
Consent withdrawn by subject		
Lack of efficacy		
Lost to follow up		
Physician decision		
Pregnancy		
Protocol Deviation		
Other		

## Arms

<b>Arm title*</b>	<i>Placebo</i>
Arm description:	
Arm type*	Experimental Active comparator X Placebo No intervention Other
Investigational medicinal product name*	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms*	
Routes of administration*	Standardised pump action oromucosal spray
Dosage and administration details*	Each 100 µL actuation Participants were instructed to self-titrate during the first 14 treatment days according to a predefined escalation scheme to their optimal dose, up to a maximum of 12 actuations in 24 h

<b>Number of subjects in period</b>	overall population	Sativex	Placebo
Started*	59	29	30
Completed*	59	29	30
Subject non-completion reason (if applicable)			
AE, non fatal			
AE, fatal			
Consent withdrawn by subject			
Lack of efficacy			
Lost to follow up			
Physician decision			
Pregnancy			
Protocol Deviation			
Other			

## Baseline characteristics

### Reporting groups\* Overall cohort

Reporting group title*	
Number of subjects at the baseline*	59
Reporting group description: <i>You can report per arm in the baseline period or for the overall baseline period</i>	

### Subject analysis sets

*Add a subject analysis set if you wish to report on groups different from the reporting group defined above (repeat if applicable)*

Subject analysis set title*	
Subject analysis set type*	Full Analysis X
Subject analysis set description*	<i>Enter a clear description which defines this set of subjects</i>
Number of subjects in subjects analysis set*	

### Age characteristics\*

*Complete either the age categorical, age continuous or complete both these characteristics in order to collect values for the reporting groups and optionally the subject analysis sets.*

	Characteristic title*	Units*	Age categories*
<b>Age categorical</b>			

	Characteristic title*	Units*	Central tendency*	Dispersion type*
<b>Age continuous</b>	Active Arm: 58.4 Placebo 57.2	Years		SD: Active Arm : 10.6 Placebo: 13.8

### Gender characteristics\*

	Characteristic title*	Units*	Gender categories*
<b>Gender categorical</b>	Active Arm: Male 18 (62%) Female 11 (38%)  Placebo Male: 16 (53%) Female: 14 (47%)		Female Male

### Study specific characteristics

	Characteristic title*	Units*	Categories*	Number of subject for each categories
<b>Study specific categorical</b>				
<b>Study specific categorical</b>				

<b>Study specific categorical</b>				
<b>Study specific categorical</b>				
<b>Study specific categorical</b>				

## End points

Add subject analysis set if you wish to report on groups different from reporting groups defined above

Subject analysis set title*	
Subject analysis set type*	Full Analysis Intention to treat Per protocol Safety analysis Sub-group analysis
Subject analysis set description*	
Number of subject in subject analysis set *	

## End points definitions

End point title*		
		Values
Countable or measurable?*	<i>Select countable when the end point represents data that contains distinct values.</i>	-
If countable, Countable units*:		
If measurable, Measurable units*:		
Measure type*:	Number Arithmetic Mean Median least square mean geometric mean log mean	
Precision/dyspersion type*		

End point type*	Primary Secondary Other pre-specified Post Hoc
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End point timeframe\*:

	Nabiximols group mean change from baseline (SD; n=29)	Placebo group mean change from baseline (SD; n=30)	Mean effect of treatment* (95% CI)	p value
Modified Ashworth Scale score	-0.11 (0.48)	0.16 (0.47)	-0.32 (-0.57 to -0.07)	0.013
NRS spasticity	-0.32 (2.15)	-0.12 (1.40)	-0.49 (-1.48 to 0.50)	0.324
NRS pain	-0.97 (2.12)	-0.06 (1.47)	-1.15 (-2.10 to -0.21)	0.017
NRS spasm frequency	-0.51 (1.61)	-0.13 (2.02)	-0.71 (-1.68 to 0.27)	0.153
NRS sleep disruption	-0.62 (1.99)	-0.10 (1.90)	-0.79 (-1.80 to 0.22)	0.122
10 m walk, s	-1.48 (33.09)†	-0.53 (30.54)†	0.92 (-17.39 to 19.64)	0.997
Barthel Activities of Daily Living Index	-0.34 (2.97)	-1.00 (7.47)	0.73 (-2.56 to 4.02)	0.660
Forced vital capacity, maximum % predicted	0.57 (9.21)	-6.85 (11.0)	5.38 (-1.09 to 11.85)	0.100
Body-mass index, kg/m <sup>2</sup>	-0.06 (0.42)	0.06 (0.42)	-0.12 (-0.35 to 0.11)	0.308
Amyotrophic Lateral Sclerosis Functional Rating Score—Revised	-0.10 (1.32)	-0.70 (1.82)	0.62 (-0.22 to 1.48)	0.148
Upper motor neuron score	0.46 (1.50)‡	-0.03 (1.13)	0.41 (-1.48 to 0.50)	0.227
Medical Research Council sum score	-0.79 (8.83)	0.03 (6.14)	-0.73 (-4.94 to 3.49)	0.730
Mean daily actuations§	8.03 (2.9; 1 to 12)	11.2 (1.4; 7 to 12)	..	<0.0001

NRS=numeric rating scale. \*β coefficient for mean effect of treatment from ANCOVA model adjusting for the other covariates (ie, baseline assessment for each endpoint, age, sex, disease duration, and duration of spasticity). †Test based on data for 26 participants in the placebo group and 25 in the nabiximols group. ‡Test based on data for 28 participants in the nabiximols group. §Data are mean (SD; range).

Table 2: Outcome analyses at the end of the double-blind treatment phase

Use categories only if the data for the end point can be categorized

### Category title

Specify the groups of subjects applicable to this end point

<b>Reporting groups*</b>			
Period			
Arms			
subject analysis sets			

## Adverse events

### Adverse events information

Timeframe for reporting adverse events\*: *Enter the time point(s) or time period for AE assessment*

*First patient first visit:*

*Last recruitment date:*

*Study closure:*

Adverse event reporting additional description: *Enter information about the AE collection and provide details about the method of assessment and monitoring*

	Nabiximols group (n=29)	Placebo group (n=30)
Any adverse event	22 (76%)	8 (27%)
Any possible, probable, or definite treatment-related adverse event	21 (72%)	4 (13%)
One or more definite treatment-related adverse event	0 (0%)	0 (0%)
Any moderate or severe adverse event	7 (24%)	1 (3%)
Any severe adverse event	0 (0%)	0 (0%)
Any serious adverse event	0 (0%)	0 (0%)
General disorders and administration-site conditions		
Asthenia	7 (24%)	1 (3%)
Malaise	1 (3%)	0 (0%)
Nervous system disorders		
Dizziness	2 (7%)	0 (0%)
Balance disorder	1 (3%)	0 (0%)
Memory impairment	1 (3%)	0 (0%)
Somnolence	5 (17%)	1 (3%)
Syncope	2 (7%)	0 (0%)
Tremors	1 (3%)	0 (0%)
Muscle spasticity	1 (3%)	0 (0%)
Gait disturbance	0 (0%)	0 (0%)
Psychiatric disorders		
Anxiety	1 (3%)	0 (0%)
Agitation	1 (3%)	0 (0%)
Vertigo	5 (17%)	0 (0%)
Vision blurred	1 (3%)	0 (0%)
Palpitations	1 (3%)	0 (0%)
Gastrointestinal disorders		
Dry mouth	1 (3%)	1 (3%)
Nausea	3 (10%)	0 (0%)
Oral pain	1 (3%)	0 (0%)
Oral mucosal disorder	0 (0%)	1 (3%)
Fall	1 (3%)	0 (0%)
Skin and subcutaneous tissue disorders		
Erythema	0 (0%)	1 (3%)
Skin exfoliation	0 (0%)	1 (3%)
Pruritus	0 (0%)	1 (3%)

Data are n (%). Adverse events were judged to be mild, moderate, or severe by investigators. All adverse events were codified on the basis of the Medical Dictionary for Regulatory Activities according to system organ classes. If a participant experienced more than one occurrence of a given adverse event, the participant was counted only once for that adverse event.

**Table 4: Adverse events, including most common potentially treatment-related events**

Assessment type*	Systematic or Non Systematic
Frequency threshold for reporting non-serious adverse events*	<i>Enter the frequency of non SAE that are reported in the results database for all arms or reporting groups</i>

### Dictionary used

Dictionary name*	MedDRA or CTCAE
Dictionary version*	

**Adverse events reporting group definition**

Use arms from baseline period as reporting groups

**OR**

Reporting group title\*: *Overall cohort*

For this reporting group, provide the following totals:

Subject exposed*	
Subjects affected by non -SAE*	
Total number of deaths (all causes)*	
Total number of deaths resulting from adverse event*	

**Serious adverse event details and values**

System organ class\*:

Event term\*:

**Values for serious adverse event per reporting group \***

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number	Occurrences causally related to treatment number	Fatalities number	Fatalities causally related to treatment number

**Non - Serious adverse event details and values**

System organ class\*:

Event term\*:

**Values for non-serious adverse event per reporting group\***

Threshold for non-serious adverse event reporting is:

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol\*? No

Date	Amendment

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial\*? No

If Yes, Interruption date

Interruption description

### **Limitations and caveats**

None reported

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### **Online references**

Enter PubMed identifier (PMID)

PMID: 30554828