Clinical trial results:
A double blind, randomized, placebo-controlled, parallel group study of Sativex oromucosal spray (Sativex®; Nabiximols) as adjunctive therapy in relieving uncontrolled persistent chronic pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy.

Summary

EudraCT number	2009-016064-36
Trial protocol	CZ PL BE GB DE RO HU EE LV LT BG
Global end of trial date	02 July 2015

Results information

Result version number	v1 (current)
This version publication date	30 May 2018
First version publication date	30 May 2018

Trial information

Trial identification

Sponsor protocol code	GWCA0958

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01262651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GW Pharmaceuticals Ltd.
Sponsor organisation address	Sovereign House, Vision Park, Chivers Way, Histon, Cambridge, United Kingdom, CB24 9BZ
Public contact	GW Pharmaceuticals Ltd. Switchboard, GW Pharmaceuticals Ltd., +44 1980557000, medinfo@gwpharm.com
Scientific contact	GW Pharmaceuticals Ltd. Switchboard, GW Pharmaceuticals Ltd., +44 1980557000, medinfo@gwpharm.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	27 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2015
Global end of trial reached?	Yes
Global end of trial date	02 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Sativex® (nabiximols), when used as an adjunctive (not breakthrough) measure, compared with placebo in relieving uncontrolled persistent chronic pain in participants with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy.

Protection of trial subjects:

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, and with the laws of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Romania: 48
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Czech Republic: 50
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	United States: 129
Worldwide total number of subjects	397
EEA total number of subjects	268

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)	264
From 65 to 84 years	130
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants had been clinically diagnosed with advanced cancer for which there was no known curative therapy, and had a clinical diagnosis of cancer related pain which was not wholly alleviated by their current optimized opioid treatment.

Period 1

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

Blinding implementation details:

Study drug was provided in 10 mL Type I amber glass vials labeled with the GW name, study code, participant number, visit number and the expiry date. The identity of the study drug assigned to participants was held by the interactive voice response system.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sativex

Arm description:

Sativex was self-administered by participants as a 100 microliter (µL) oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 5 weeks. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

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

Dosage and administration details:

Sativex was self-administered by participants twice daily as a 100 µL oromucosal spray, up to a maximum of 10 sprays per day for 5 weeks. Sativex oromucosal spray contained THC (27 mg/mL):CBD (25 mg/mL), in ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring. Each 100 µL actuation delivered 2.7 mg THC and 2.5 mg CBD.

Arm title	Placebo (GA-0034)

Arm description:

Placebo was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 5 weeks. Placebo oromucosal spray contained ethanol: propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings.

Arm type	Placebo
Investigational medicinal product name	Placebo (GA-0034)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

Placebo was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day for 5 weeks. Placebo oromucosal spray contained ethanol: propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings.

Number of subjects in period 1	Sativex	Placebo (GA-0034)
Started	199	198
Safety Population	199	198
Intent to Treat (ITT) Population	199	198
Received at least 1 dose of study drug	199	198
Completed	141	150
Not completed	58	48
Consent withdrawn by subject	15	11
Physician decision	2	2
Adverse Events	40	35
Met Withdrawal Criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sativex
Reporting group description:	
Sativex was self-administered by participants as a 100 microliter (µL) oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 5 weeks. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).	
Reporting group title	Placebo (GA-0034)
Reporting group description:	
Placebo was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 5 weeks. Placebo oromucosal spray contained ethanol: propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings.	

Reporting group values	Sativex	Placebo (GA-0034)	Total
Number of subjects	199	198	397
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	132	132	264
From 65-84 years	66	64	130
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	59.2	60.7	
standard deviation	± 12.0	± 11.1	-
Gender categorical Units: Subjects			
Female	88	95	183
Male	111	103	214

End points

End points reporting groups

Reporting group title	Sativex

Reporting group description:

Sativex was self-administered by participants as a 100 microliter (µL) oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 5 weeks. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

Reporting group title	Placebo (GA-0034)

Reporting group description:

Placebo was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 5 weeks. Placebo oromucosal spray contained ethanol: propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings.

Primary: Percent Improvement From Baseline In Mean Numerical Rating Scale (NRS) Average Pain At End Of Treatment

End point title	Percent Improvement From Baseline In Mean Numerical Rating Scale (NRS) Average Pain At End Of Treatment

End point description:

Participants indicated level of pain in the last 24 hours on an 11-point NRS, where a score of 0 was "no pain" and 10 was "pain as bad as you can imagine." Baseline = mean score from first day of 3-day eligibility period through to the day before first dose of study drug. End of Treatment = mean score over last (up to) 7 days to the final pain score at End of Treatment or up until Day 35, whichever is earlier, or final score available (prematurely terminated).
Percentage improvement from baseline (Imp%) was calculated as:
Imp% = (Baseline pain NRS mean - End of Treatment pain NRS mean)/Baseline pain NRS mean * 100.
For participants who died or withdrew due to disease progression, Imp% values were used. For participants who died or withdrew unrelated to disease progression before end of Week 5 (no diary data from Day 33 onwards), Imp% was zero if participant Imp% value was positive and it was Imp% for participants whose Imp% value was not positive.

End point type	Primary

End point timeframe:

Baseline, End of Treatment (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Percent Improvement				
median (inter-quartile range (Q1-Q3))	10.7 (0.0 to 30.0)	4.5 (-2.9 to 25.7)		

Statistical analyses

Statistical analysis title	Percent Improvement In Mean NRS Average Pain Score

Statistical analysis description:

Imp% = (Baseline pain NRS mean - End of Treatment pain NRS mean)/Baseline pain NRS mean * 100.
For participants who died or withdrew due to disease progression, Imp% values were used. For

participants who died or withdrew unrelated to disease progression before end of Week 5 (no diary data from Day 33 onwards), Imp% was zero if participant Imp% value was positive and it was Imp% for participants whose Imp% value was not positive.

Comparison groups	Sativex v Placebo (GA-0034)
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0854
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	8.16

Secondary: Change From Baseline In Mean NRS Average Pain At End Of Treatment

End point title	Change From Baseline In Mean NRS Average Pain At End Of Treatment

End point description:

Participants indicated the level of pain experienced in the last 24 hours on an 11-point NRS, where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine."
Change in mean NRS average pain was calculated as: End of Treatment NRS average pain score - Baseline NRS average pain score.
A negative value indicates an improvement in average pain score from Baseline.

End point type	Secondary

End point timeframe:

Baseline, End of Treatment (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Unit of a scale				
arithmetic mean (standard deviation)	-0.8 (± 1.4)	-0.6 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Mean NRS Worst Pain At End Of Treatment

End point title	Change From Baseline In Mean NRS Worst Pain At End Of Treatment

End point description:

Participants indicated the level of worst pain experienced in the last 24 hours on an 11-point NRS, where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine."
Change in mean NRS worst pain was calculated as: End of Treatment NRS worst pain score - Baseline NRS worst pain score.
A negative value indicates an improvement in worst pain score from Baseline.

End point type	Secondary

End point timeframe:

Baseline, End of Treatment (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Unit on a scale				
arithmetic mean (standard deviation)	-0.9 (± 1.4)	-0.8 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Mean Sleep Disruption NRS At End Of Treatment

End point title	Change From Baseline In Mean Sleep Disruption NRS At End Of Treatment

End point description:

Participants indicated the level of sleep disruption experienced in the last 24 hours on an 11-point NRS, where a score of 0 indicated "did not disrupt sleep" and a score of 10 indicated "completely disrupted (unable to sleep at all)."
Change in mean sleep disruption NRS was calculated as: End of Treatment sleep disruption NRS score - Baseline sleep disruption NRS score.
A negative value indicates an improvement in sleep disruption score from Baseline.

End point type	Secondary

End point timeframe:

Baseline, End of Treatment (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.8 (± 1.7)	-0.5 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Global Impression Of Change At Last Visit (Up To Day 36)

End point title	Subject Global Impression Of Change At Last Visit (Up To Day 36)

End point description:

The Subject Global Impression of Change (SGIC) was used to assess the overall status of the participant related to their cancer pain, with the markers "very much improved, much improved, slightly improved, no change, slightly worse, much worse, or very much worse". The SGIC was assessed at Day 36 or at which a participant's last evaluation is performed, such as in the case of early termination. Last visit refers to the last visit that a participant completed the assessment; this could be either Day 22 or Day 36.

End point type	Secondary

End point timeframe:

Last Visit (up to Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	179		
Units: Participants				
Very Much Improved	5	3		
Much Improved	34	26		
Slightly Improved	60	55		
No Change	56	72		
Slightly Worse	9	13		
Much Worse	6	6		
Very Much Worse	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Physician Global Impression Of Change At Last Visit (Up To Day 36)

End point title	Physician Global Impression Of Change At Last Visit (Up To Day 36)

End point description:

The Physician Global Impression of Change (PGIC) was used by the treating physician (investigator/sub-investigator) to assess if there was any change in the general functional abilities of the participant since prior to commencement of study medication, with the markers: "Very much worse, Much worse, Slightly worse, No change, Slightly improved, Much improved, Very much improved". Last visit refers to the last visit that a participant completed the assessment; this could be either Day 22 or Day 36.

End point type	Secondary

End point timeframe:

Last Visit (Up to Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	181		
Units: Participants				
Very Much Improved	6	3		
Much Improved	37	25		
Slightly Improved	56	50		
No Change	41	75		
Slightly Worse	25	19		
Much Worse	7	5		
Very Much Worse	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Satisfaction Questionnaire At Last Visit (Up To End Of Treatment)

End point title	Patient Satisfaction Questionnaire At Last Visit (Up To End Of Treatment)

End point description:

The Patient Satisfaction Questionnaire (PSQ) was used to assess level of satisfaction of the participant with the study drug, with the markers "Extremely satisfied, Very satisfied, Slightly satisfied, Neutral, Slightly dissatisfied, Very dissatisfied, Extremely dissatisfied". Last visit refers to the last visit that a participant completed the assessment; this could be either Day 22 or Day 36.

End point type	Secondary

End point timeframe:

Last Visit (Up to Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	179		
Units: Participants				
Extremely Satisfied	7	3		
Very Satisfied	42	38		
Slightly Satisfied	42	37		
Neutral	46	63		
Slightly Dissatisfied	22	20		
Very Dissatisfied	11	13		
Extremely Dissatisfied	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Daily Total Opioid Use (Morphine Equivalent) At End Of Treatment

End point title	Change From Baseline In Daily Total Opioid Use (Morphine Equivalent) At End Of Treatment

End point description:

The total daily opioid use (in morphine equivalence) was the sum of morphine equivalents of daily maintenance dose and break-through dose.
Change in daily total opioid use was calculated as: End of Treatment daily total opioid use - Baseline daily total opioid use.
A negative value indicates a decrease in use from Baseline.

End point type	Secondary

End point timeframe:

Baseline, End of Treatment (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: mg (morphine equivalent)				
arithmetic mean (standard deviation)	0.3 (± 34.7)	0.6 (± 44.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Daily Maintenance Opioid Dose (Morphine Equivalent) At End Of Treatment

End point title	Change From Baseline In Daily Maintenance Opioid Dose (Morphine Equivalent) At End Of Treatment

End point description:

The prescribed daily quantity of opioid maintenance dose was calculated as the product of dose per use and daily frequency of use. Participants were asked: "Have you used your maintenance dose painkiller today as prescribed?" If the participant answered "No" to the question, the daily opioid maintenance dose usage on that day was set to 0.
Change in daily maintenance opioid dose was calculated as: End of Treatment daily maintenance opioid dose - Baseline daily maintenance opioid dose.
A negative value indicates a decrease in dose from Baseline.

End point type	Secondary

End point timeframe:

Baseline, End of Treatment (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: mg (morphine equivalent)				
arithmetic mean (standard deviation)	0.2 (± 20.9)	-1.3 (± 38.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Daily Break-Through Opioid Dose (Morphine Equivalent) At End Of Treatment

End point title	Change From Baseline In Daily Break-Through Opioid Dose (Morphine Equivalent) At End Of Treatment

End point description:

Daily break-through opioid dose usage was calculated as the product of prescribed dose per use, and the number of uses per day. If participants took more than 1 different break-through opioid for more than 1 day, the sum of morphine equivalents dose usages for each break-through opioid was calculated for the summary.
Change in daily break-through opioid dose was calculated as: End of Treatment daily break-through opioid dose - Baseline daily maintenance opioid dose.
A negative value indicates a decrease in dose from Baseline.

End point type	Secondary

End point timeframe:

Baseline, Last Visit (Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: mg (morphine equivalent)				
arithmetic mean (standard deviation)	0.1 (± 22.2)	1.8 (± 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In NRS Constipation At Last Visit (Up To Day 36)

End point title	Change From Baseline In NRS Constipation At Last Visit (Up To

	Day 36)

End point description:

Participants indicated level of constipation on an 11-point NRS, where a score of 0 was "no constipation", and 10 was "constipation as bad as you can imagine." Last visit refers to the last visit that a participant completed the assessment; this could be either Day 22 or Day 36.
Change in NRS constipation score was calculated as: Last Visit NRS constipation score - Baseline NRS constipation score.
A negative value indicates improvement in condition from Baseline.

End point type	Secondary

End point timeframe:

Baseline, Last Visit (Up To Day 36)

End point values	Sativex	Placebo (GA-0034)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	178		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.6 (± 2.9)	-0.3 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 43 post-randomization

Adverse event reporting additional description:

The Safety Population included all participants receiving at least 1 dose of study drug. Per the Statistical Analyses Plan, if a participant randomized to placebo ever took a Sativex dose, the participant was analyzed as Sativex-treated in the Safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Sativex

Reporting group description:

The Safety Population included all participants receiving at least 1 dose of study drug.

Reporting group title	Placebo

Reporting group description:

The Safety Population included all patients receiving at least 1 dose of study drug. Per the Statistical Analyses Plan, if a participant randomized to placebo ever took a Sativex dose, the participant was analyzed as Sativex-treated in the Safety population.

Serious adverse events	Sativex	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 199 (23.62%)	43 / 198 (21.72%)	
number of deaths (all causes)	27	27	
number of deaths resulting from adverse events	27	27	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 199 (1.51%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			

subjects affected / exposed	31 / 199 (15.58%)	28 / 198 (14.14%)	
occurrences causally related to treatment / all	0 / 31	0 / 28	
deaths causally related to treatment / all	0 / 25	0 / 24	
Tumour pain			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 199 (0.50%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary toxicity			

subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disorientation			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 199 (0.50%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric perforation			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 199 (0.00%)	2 / 198 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 199 (0.50%)	2 / 198 (1.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	3 / 199 (1.51%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 199 (0.50%)	2 / 198 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 199 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 199 (0.50%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sativex	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 199 (34.67%)	53 / 198 (26.77%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 199 (8.04%)	8 / 198 (4.04%)	
occurrences (all)	16	8	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 199 (6.03%)	10 / 198 (5.05%)	
occurrences (all)	12	10	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 199 (5.53%)	13 / 198 (6.57%)	
occurrences (all)	11	14	
Nausea			
subjects affected / exposed	31 / 199 (15.58%)	20 / 198 (10.10%)	
occurrences (all)	34	21	
Vomiting			
subjects affected / exposed	15 / 199 (7.54%)	11 / 198 (5.56%)	
occurrences (all)	15	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 199 (7.04%)	12 / 198 (6.06%)	
occurrences (all)	14	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2010	• Change in the primary analysis variable from the 30% responder analysis to the continuous responder analysis with resulting increase in sample size from 370 to 380 participants. • Removal of Quality of Life assessments from the protocol as they were not sensitive enough to detect a difference between Sativex and placebo but did add excessive burden to participants. These were replaced with 2 simple questions asked to participants at each study visit about a) their level of constipation and b) their satisfaction with their medicine and recorded on a simple 0-10 NRS scale. • Reinforcing the point that the protocol included a participant population which was one of terminally ill, advanced cancer participants and that Sativex was to be dosed twice-daily, not as-needed. • The dosing paradigm was described more specifically. • The definition of optimized therapy was improved and a minimum threshold level of morphine equivalence (>90 mg transdermal drug delivery) was added for those participants where it was deemed clinically inappropriate to increase their dose because no further efficacy benefit was expected. • How rescue analgesia was addressed in the statistical analysis was clarified. • Various changes in wording to improve clarity. • Various updates to bring in line with the current protocol template, internal safety operating procedures, and any updated legislation. • The PGIC questionnaire was updated. • Safety follow-up period extended to 2 weeks.
16 July 2012	• Wording in Section 4.1.1 was amended to make it clearer for the reader with regards to the length of the eligibility period, changes to opioids during this period, and potential rescreening of participants. • The protocol was also updated to reflect an amended and expanded non-linear 'morphine equivalence' conversion scheme for methadone doses. • Wording where needed was amended to clarify that regular around-the-clock dosing with IR opioids as a maintenance dose was ideally to be every 4 hours. • Section 8.6, Access to Blinded Treatment Assignment, was updated to clarify to investigators that it was acceptable to unblind prior to contacting GW, but where possible, GW encouraged communication first. • The wording in Section 9.1.8, Clinical Laboratory Sampling, was revised to clarify how the THC test at Screening was performed and that there was a secondary test to confirm any initial positive THC tests. • Section 11.7, Follow up Procedures for Adverse Events, was updated following Food and Drug Administration guidance to clarify that GW may have needed to follow up with the center on certain adverse events of special medical interest, in particular those associated with abuse potential or addiction. • Various minor administrative changes were made throughout the protocol to aid clarity for the reader. For example, height and weight were mentioned in the synopsis but were not clear in the visit procedures. Also, the amount of blood drawn was corrected to 9 mL, and the Columbia-Suicide Severity Rating Scale assessment was corrected to show the investigator was to complete this. These were not new procedures in the protocol but merely corrections of errors to ensure the protocol accurately reflected the study procedures. References were also updated accordingly and Esoterix was renamed Labcorp Clinical Trials, which was purely to reflect a name change of the company. Additionally, wording was updated regarding additional countries where Sativex was licensed at

14 March 2013	• An annex to the protocol was issued to describe the methodology for identifying and evaluating clinical study adverse event data through systematic categorization, tabulation, and analysis that can illuminate an abuse potential signal. This impacted study procedures for United States and United Kingdom centers from the point of implementation onwards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28923526