Clinical trial results:
A multicenter, non-comparative, open-label extension study to assess the long term safety of Sativex oromucosal spray (Sativex®; Nabiximols) as adjunctive therapy in patients with uncontrolled persistent chronic cancer related pain.

Summary

EudraCT number	2009-016529-32
Trial protocol	BE GB CZ HU DE PL LT LV EE BG ES IT RO
Global end of trial date	27 January 2016

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	GWCA0999

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01337089
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	Switchboard, GW Pharmaceuticals Ltd., GW Pharmaceuticals Ltd., +44 1980557000, medinfo@gwpharm.com
Scientific contact	Switchboard, GW Pharmaceuticals Ltd., 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	20 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 January 2016
Global end of trial reached?	Yes
Global end of trial date	27 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of long-term Sativex® (nabiximols) therapy when used as an adjunctive (not breakthrough) measure in participants with advanced cancer.

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	19 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 151
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 90
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czech Republic: 51
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Romania: 85
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 172
Worldwide total number of subjects	660
EEA total number of subjects	462

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)	443
From 65 to 84 years	210
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants enrolled in this study included those who had taken part in studies NCT01262651 (GWCA0958), NCT01361607 (GWCA0962), and NCT01424566 (GWCA1103) and who chose to continue treatment by enrolling in this study, as well as new participants who met all inclusion criteria and did not meet any of the exclusion criteria.

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 Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

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 6 months. 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 as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day for 6 months. Sativex oromucosal spray contained THC (27 mg/milliliter [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.

Number of subjects in period 1	Sativex
Started	660
Received at Least 1 Dose of Study Drug	660
Safety Population	660
Efficacy Dataset	659
Completed	256
Not completed	404
Physician decision	33
Consent withdrawn by subject	129

Met withdrawal criteria	3
Adverse event	237
Lost to follow-up	2

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 6 months. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).	

Reporting group values	Sativex	Total	
Number of subjects	660	660	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	443	443	
From 65-84 years	210	210	
85 years and over	7	7	
Age continuous Units: years			
arithmetic mean	60.2		
standard deviation	± 11.1	-	
Gender categorical Units: Subjects			
Female	313	313	
Male	347	347	

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 6 months. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

Subject analysis set title	Sativex (Safety Population)
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Primary: Percent Of Participants With Treatment-emergent Adverse Events

End point title	Percent Of Participants With Treatment-emergent Adverse Events[1]

End point description:

Treatment-emergent Adverse Events (TEAEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 17.0. A TEAE is defined as an adverse event with an onset after the start of study drug treatment. The percent of participants who experienced one or more TEAEs is reported.

End point type	Primary

End point timeframe:

Baseline, Day 183

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were not performed for this open-label extension study.

End point values	Sativex (Safety Population)			
Subject group type	Subject analysis set			
Number of subjects analysed	660			
Units: percent of participants				
number (not applicable)	82.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Mean NRS Average Pain During The Last Period

End point title	Change From Baseline In Mean NRS Average Pain During The Last Period

End point description:

Participants indicated the level of pain experienced in the last 24 hours on an 11-point Numerical Rating Scale (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: Last Period 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, Last Period (Days 156-183) or last 27 days of treatment

End point values	Sativex (Safety Population)			
Subject group type	Subject analysis set			
Number of subjects analysed	634			
Units: units on a scale				
arithmetic mean (standard deviation)	0.0 (± 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Mean Sleep Disruption NRS During The Last Period

End point title	Change From Baseline In Mean Sleep Disruption NRS During The Last Period

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: Last Period 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, Last Period (Days 156-183) or last 27 days of treatment

End point values	Sativex (Safety Population)			
Subject group type	Subject analysis set			
Number of subjects analysed	634			
Units: units on a scale				
arithmetic mean (standard deviation)	0.1 (± 1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Satisfaction Questionnaire At Last Visit (Up To Day 183)

End point title	Patient Satisfaction Questionnaire At Last Visit (Up To Day 183)

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.

End point type	Secondary

End point timeframe:

Last Visit (up to Day 183)

End point values	Sativex (Safety Population)			
Subject group type	Subject analysis set			
Number of subjects analysed	618			
Units: participants				
Extremely Satisfied	56			
Very Satisfied	230			
Slightly Satisfied	185			
Neutral	82			
Slightly Dissatisfied	33			
Very Dissatisfied	22			
Extremely Dissatisfied	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In NRS Constipation At Last Visit (Up To Day 183)

End point title	Change From Baseline In NRS Constipation At Last Visit (Up To Day 183)

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.
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 183)

End point values	Sativex (Safety Population)			
Subject group type	Subject analysis set			
Number of subjects analysed	619			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1 (± 2.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Day 197 post-enrollment	
Adverse event reporting additional description:	
The Safety Population included all participants receiving at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Sativex (Safety Population)
Reporting group description:	
The Safety Population included all participants receiving at least 1 dose of study drug.	

Serious adverse events	Sativex (Safety Population)		
Total subjects affected by serious adverse events			
subjects affected / exposed	301 / 660 (45.61%)		
number of deaths (all causes)	190		
number of deaths resulting from adverse events	190		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	4 / 660 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to bone			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	3 / 660 (0.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic neoplasm			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm progression			
subjects affected / exposed	209 / 660 (31.67%)		
occurrences causally related to treatment / all	0 / 214		
deaths causally related to treatment / all	0 / 179		
Ovarian cancer			
subjects affected / exposed[1]	1 / 313 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Plasma cell myeloma			

subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	4 / 660 (0.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypertension				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inferior vena caval occlusion				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Venous thrombosis limb				

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 660 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Device occlusion			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Local swelling			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	6 / 660 (0.91%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 660 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vaginal fistula				
subjects affected / exposed[2]	1 / 313 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	3 / 660 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 660 (0.76%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	3 / 660 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Psychiatric disorders				
Agitation				

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Depression			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	4 / 660 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	2 / 660 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	5 / 660 (0.76%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Femur fracture			

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural headache			
subjects affected / exposed	2 / 660 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Radiation oesophagitis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt occlusion			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stoma complication			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Angina pectoris				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	3 / 660 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Altered state of consciousness				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Balance disorder				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebrovascular accident				

subjects affected / exposed	3 / 660 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Convulsion				
subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dementia with Lewy bodies				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Posterior reversible encephalopathy syndrome				
subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				

subjects affected / exposed	3 / 660 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	8 / 660 (1.21%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Anaemia of malignant disease				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Deafness neurosensory				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vertigo				

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 660 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis erosive			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	2 / 660 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	6 / 660 (0.91%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tongue haemorrhage				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	7 / 660 (1.06%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Acute febrile neutrophilic dermatosis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dry gangrene				

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	5 / 660 (0.76%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	2 / 660 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Osteonecrosis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	4 / 660 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 660 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	2 / 660 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	4 / 660 (0.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 660 (0.91%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 2			
Pseudomembranous colitis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 660 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subacute endocarditis				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 660 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				

subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	4 / 660 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 660 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This adverse event affects only female participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This adverse event affects only female participants.

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

Non-serious adverse events	Sativex (Safety Population)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	291 / 660 (44.09%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	41 / 660 (6.21%)		
occurrences (all)	46		
Nervous system disorders			

Dizziness			
subjects affected / exposed	51 / 660 (7.73%)		
occurrences (all)	55		
Somnolence			
subjects affected / exposed	38 / 660 (5.76%)		
occurrences (all)	43		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	39 / 660 (5.91%)		
occurrences (all)	42		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	50 / 660 (7.58%)		
occurrences (all)	51		
Fatigue			
subjects affected / exposed	35 / 660 (5.30%)		
occurrences (all)	44		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	44 / 660 (6.67%)		
occurrences (all)	44		
Diarrhoea			
subjects affected / exposed	41 / 660 (6.21%)		
occurrences (all)	46		
Nausea			
subjects affected / exposed	86 / 660 (13.03%)		
occurrences (all)	96		
Vomiting			
subjects affected / exposed	59 / 660 (8.94%)		
occurrences (all)	71		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	37 / 660 (5.61%)		
occurrences (all)	40		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	49 / 660 (7.42%) 54		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2010	Alignment with the parent study protocols following amendments in response to a United States (US) Food and Drug Administration (FDA) end of phase 2 meeting and the results of the phase 2b dose-ranging study, including changes to the target dose range, titration schedule, study questionnaires, follow-up period, terminology and general clarifications, and administrative and safety updates.
16 July 2012	* Section 11.7 was updated following FDA 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.
14 March 2013	An annex to the protocol (Annex 1) described the methodology for identifying and evaluating clinical trial adverse event data through systematic categorization, tabulation, and analysis which can illuminate an abuse potential signal. This impacted study procedures for US and United Kingdom (UK) centers from the point of implementation onwards.
09 April 2013	Two annexes to the protocol (Annex 2 [UK only] and Annex 3 [US only]) evaluated a new child-resistant, senior-friendly dispenser with integrated dose counter.
14 July 2014	An annex to the protocol (Annex 4) allowed participants in the UK to enter this study and use the dispenser with integrated dose counter without first having participated in a parent study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported