Clinical trial results:
A two-part, placebo-controlled, study of the safety and efficacy of Sativex oromucosal spray (Sativex®; Nabiximols) as adjunctive therapy in relieving uncontrolled persistent chronic pain in patients with advanced cancer, who have inadequate analgesia even with optimized chronic opioid therapy

Summary

EudraCT number	2010-022905-17
Trial protocol	ES IT GB LT PL DE HU RO BG
Global end of trial date	28 December 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	GWCA1103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01424566
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	23 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2015
Global end of trial reached?	Yes
Global end of trial date	28 December 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), compared with placebo, when used as an adjunctive measure, in relieving uncontrolled persistent chronic pain (not breakthrough pain) in participants with advanced cancer, who had inadequate analgesia even with 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	29 June 2012
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: 149
Country: Number of subjects enrolled	Romania: 66
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Lithuania: 17
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Israel: 49
Country: Number of subjects enrolled	Taiwan: 18
Worldwide total number of subjects	406
EEA total number of subjects	328

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)	259
From 65 to 84 years	141
85 years and over	6

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. Two participants entered the single-blind treatment period but did not administer any study drug.

Period 1

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

Arms

Arm title	Single-blind 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 2 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 as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day for 2 weeks. 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	Single-blind Sativex
Started	406
Received at least 1 dose of study drug	404
Single-blind Safety Population	404
Met double-blind randomization criteria	206
Completed	206
Not completed	200
Physician decision	2
Consent withdrawn by subject	16
Did not meet inclusion criteria	108
Did not administer any study drug	2

Adverse event	71
Met exclusion criteria	1

Period 2

Period 2 title	Double-blind Treatment
Is this the baseline period?	No
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 (IVRS).

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Sativex

Arm description:

Sativex was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, for 5 weeks, at the same level of dosing attained during the last 4 days of the single-blind period; however, the number of sprays could be decreased based upon tolerability throughout the study. Each 100 µL actuation delivered 2.7 mg THC and 2.5 mg CBD. To enter the double-blind treatment period (Part B), participants had to achieve at least a 15% improvement in Numerical Rating Scale (NRS) pain scores during the single-blind treatment period (Part A).

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 for 5 weeks, at the same level of dosing attained during the last 4 days of the single-blind period; however, the number of sprays could be decreased based upon tolerability throughout the study. 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	Double-blind Placebo (GA-0034)

Arm description:

Placebo was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, for 5 weeks, at the same level of dosing attained during the last 4 days of the single-blind period; however, the number of sprays could be decreased based upon tolerability throughout the study. Placebo oromucosal spray contained ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings. To enter the double-blind treatment period (Part B), participants had to achieve at least a 15% improvement in NRS pain scores during the single-blind treatment period (Part A).

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 for 5 weeks, at the same level of dosing attained during the last 4 days of the single-blind period; however, the number of sprays could be decreased based upon tolerability throughout the study. Placebo oromucosal spray contained ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings.

Number of subjects in period 2	Double-blind Sativex	Double-blind Placebo (GA-0034)
Started	103	103
Received at least 1 dose of study drug	103	103
Randomized Safety Population	103	103
Intent to Treat (ITT) Population	103	103
Completed	78	88
Not completed	25	15
Physician decision	1	1
Consent withdrawn by subject	2	-
Adverse event	21	13
Lack of efficacy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Single-blind 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 2 weeks. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).	

Reporting group values	Single-blind Sativex	Total	
Number of subjects	406	406	
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)	259	259	
From 65-84 years	141	141	
85 years and over	6	6	
Age continuous Units: years			
arithmetic mean	61.2		
standard deviation	± 11.2	-	
Gender categorical Units: Subjects			
Female	177	177	
Male	229	229	

End points

End points reporting groups

Reporting group title	Single-blind 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 2 weeks. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

Reporting group title	Double-blind Sativex

Reporting group description:

Sativex was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, for 5 weeks, at the same level of dosing attained during the last 4 days of the single-blind period; however, the number of sprays could be decreased based upon tolerability throughout the study. Each 100 µL actuation delivered 2.7 mg THC and 2.5 mg CBD. To enter the double-blind treatment period (Part B), participants had to achieve at least a 15% improvement in Numerical Rating Scale (NRS) pain scores during the single-blind treatment period (Part A).

Reporting group title	Double-blind Placebo (GA-0034)

Reporting group description:

Placebo was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, for 5 weeks, at the same level of dosing attained during the last 4 days of the single-blind period; however, the number of sprays could be decreased based upon tolerability throughout the study. Placebo oromucosal spray contained ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring and colorings. To enter the double-blind treatment period (Part B), participants had to achieve at least a 15% improvement in NRS pain scores during the single-blind treatment period (Part A).

Subject analysis set title	Single-blind Sativex (ITT Population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 efficacy endpoint. Participants were analyzed according to the treatment group they were randomized to.

Subject analysis set title	Double-blind Sativex (ITT Population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 efficacy endpoint. Participants were analyzed according to the treatment group they were randomized to.

Subject analysis set title	Double-blind Placebo (GA-0034) (ITT Population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 efficacy endpoint. Participants were analyzed according to the treatment group they were randomized to.

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

End point title	Change From Randomization 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 - Randomization (Part B) Baseline NRS average pain score.
The participant's Randomization (Part B) baseline pain 0-10 NRS value was the mean over the last 4 consecutive days of the single-blind treatment period (Part A; pre-randomization).
A negative value indicates an improvement in average pain score from Randomization (Part B) Baseline.

End point type	Primary

End point timeframe:

Randomization Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: units on a scale				
arithmetic mean (standard deviation)	0.5 (± 1.3)	0.5 (± 1.6)		

Statistical analyses

Statistical analysis title	Change From Baseline In Mean NRS Average Pain
Comparison groups	Double-blind Sativex (ITT Population) v Double-blind Placebo (GA-0034) (ITT Population)
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9173
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.38

Secondary: Percent Improvement From Eligibility Baseline In Mean NRS Average Pain At End Of Treatment

End point title	Percent Improvement From Eligibility Baseline In Mean 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". Eligibility Baseline = mean score from the 3-day eligibility period. End of Treatment = mean score over last (up to) 4 days to the final pain score at End of Treatment or up until Day 36 of the double-blind period, whichever is earlier, or final score available (prematurely terminated).
Percentage improvement from baseline (Imp%) was calculated as:
Imp% = (Eligibility Baseline pain NRS mean - End of Treatment pain NRS mean)/Eligibility 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, Imp% was zero for participants whose Imp% value was positive and it was Imp% for participants whose Imp% value was not positive.

End point type	Secondary

End point timeframe:

Eligibility Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: percent improvement				
median (inter-quartile range (Q1-Q3))	33.3 (18.2 to 51.8)	35.7 (18.8 to 51.3)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Randomization 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 - Randomization (Part B) Baseline NRS worst pain score.
The participant's Randomization (Part B) baseline worst pain 0-10 NRS value was the mean over the last 4 consecutive days of the single-blind treatment period (Part A; pre-randomization).
A negative value indicates an improvement in worst pain score from Randomization (Part B) Baseline.

End point type	Secondary

End point timeframe:

Randomization Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: units on a scale				
arithmetic mean (standard deviation)	0.2 (± 1.4)	0.5 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Randomization 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 - Randomization (Part B) Baseline sleep disruption NRS score.
The participant's Randomization (Part B) baseline sleep disruption 0-10 NRS value was the mean over the last 4 consecutive days of the single-blind treatment period (Part A; pre-randomization).
A negative value indicates an improvement in sleep disruption score from Randomization (Part B) Baseline.

End point type	Secondary

End point timeframe:

Randomization Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: units on a scale				
arithmetic mean (standard deviation)	0.2 (± 1.3)	0.5 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Global Impression Of Change At Last Visit (Up To Day 36 Of The Double-blind Period)

End point title	Subject Global Impression Of Change At Last Visit (Up To Day 36 Of The Double-blind Period)

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 of the double-blind period or the day 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 of the double-blind period.

End point type	Secondary

End point timeframe:

Last Visit (up to Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	97		
Units: participants				
Very Much Improved	6	6		
Much Improved	28	35		
Slightly Improved	35	26		
No Change	8	15		
Slightly Worse	8	8		
Much Worse	3	6		
Very Much Worse	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Physician Global Impression Of Change At Last Visit (Up To Day 36 Of The Double-blind Period)

End point title	Physician Global Impression Of Change At Last Visit (Up To Day 36 Of The Double-blind Period)

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 of the double-blind period.

End point type	Secondary

End point timeframe:

Last Visit (up to Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	97		
Units: participants				
Very Much Improved	7	7		
Much Improved	22	30		
Slightly Improved	37	25		
No Change	11	20		
Slightly Worse	4	12		
Much Worse	8	3		
Very Much Worse	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Satisfaction Questionnaire At Last Visit (Up To Day 36 Of The Double-blind Period)

End point title	Patient Satisfaction Questionnaire At Last Visit (Up To Day 36 Of The Double-blind Period)

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 of the double-blind period.

End point type	Secondary

End point timeframe:

Last Visit (up to Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	97		
Units: participants				
Extremely Satisfied	5	5		
Very Satisfied	30	38		
Slightly Satisfied	35	28		
Neutral	14	10		
Slightly Dissatisfied	2	11		
Very Dissatisfied	0	4		
Extremely Dissatisfied	3	1		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Randomization 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 equivalence of daily maintenance dose and break-through dose.

Change in daily total opioid use was calculated as: End of Treatment daily total opioid use - Randomization (Part B) Baseline daily total opioid use.
The participant's Randomization (Part B) baseline daily total opioid use value was the mean over the last 4 consecutive days of the single-blind treatment period (Part A; pre-randomization).
A negative value indicates a decrease in use from Randomization (Part B) Baseline.

End point type	Secondary

End point timeframe:

Randomization Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: mg (morphine equivalent)				
arithmetic mean (standard deviation)	9.0 (± 45.6)	15.5 (± 75.9)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Randomization 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 - Randomization (Part B) Baseline daily maintenance opioid dose.
The participant's Randomization (Part B) baseline daily maintenance opioid dose value was the mean over the last 4 consecutive days of the single-blind treatment period (Part A; pre-randomization).
A negative value indicates a decrease in dose from Randomization (Part B) Baseline.

End point type	Secondary

End point timeframe:

Randomization Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: mg (morphine equivalent)				
arithmetic mean (standard deviation)	0.0 (± 11.0)	8.5 (± 54.6)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Randomization 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 equivalence 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 - Randomization (Part B) Baseline daily maintenance opioid dose.
The participant's Randomization (Part B) baseline daily break-through opioid dose value was the mean over the last 4 consecutive days of the single-blind treatment period (Part A; pre-randomization).
A negative value indicates a decrease in dose from Randomization (Part B) Baseline.

End point type	Secondary

End point timeframe:

Randomization Baseline, End of Treatment (Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	103		
Units: mg (morphine equivalent)				
arithmetic mean (standard deviation)	9.0 (± 50.7)	7.0 (± 36.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization Baseline In NRS Constipation At Last Visit

End point title	Change From Randomization Baseline In NRS Constipation At Last Visit

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 - Randomization (Part B) Baseline NRS constipation score.
The participant's Randomization (Part B) baseline constipation NRS value was the last evaluation

(including unscheduled visits) in the single-blind treatment period (Part A) prior to the first dose of study drug in the double-blind treatment period (Part B).
A negative value indicates improvement in condition from Randomization (Part B) Baseline.

End point type	Secondary

End point timeframe:

Randomization Baseline, Last Visit (up to Day 36 of the double-blind period)

End point values	Double-blind Sativex (ITT Population)	Double-blind Placebo (GA-0034) (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	97		
Units: units on a scale				
arithmetic mean (standard deviation)	0.0 (± 1.8)	-0.2 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 43 of the double-blind period post-randomization

Adverse event reporting additional description:

The Safety Population included all participants receiving at least 1 dose of study drug. Participants were analyzed according to the treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Single-blind Sativex (Safety Population)

Reporting group description:

The Safety Population included all participants receiving at least 1 dose of study drug. Participants were analyzed according to the treatment received.

Reporting group title	Double-blind Sativex (Safety Population)

Reporting group description:

The Safety Population included all participants receiving at least 1 dose of study drug. Participants were analyzed according to the treatment received. To enter the double-blind treatment period (Part B), participants had to achieve at least a 15% improvement in NRS pain scores during the single-blind treatment period (Part A).

Reporting group title	Double-blind Placebo (GA-0034) (Safety Population)

Reporting group description:

The Safety Population included all participants receiving at least 1 dose of study drug. Participants were analyzed according to the treatment received. To enter the double-blind treatment period (Part B), participants had to achieve at least a 15% improvement in NRS pain scores during the single-blind treatment period (Part A).

Serious adverse events	Single-blind Sativex (Safety Population)	Double-blind Sativex (Safety Population)	Double-blind Placebo (GA-0034) (Safety Population)
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 404 (19.80%)	33 / 103 (32.04%)	16 / 103 (15.53%)
number of deaths (all causes)	42	23	9
number of deaths resulting from adverse events	42	23	9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	4 / 404 (0.99%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			

subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm progression			
subjects affected / exposed	41 / 404 (10.15%)	28 / 103 (27.18%)	11 / 103 (10.68%)
occurrences causally related to treatment / all	0 / 41	0 / 29	0 / 11
deaths causally related to treatment / all	0 / 35	0 / 22	0 / 9
Tumour haemorrhage			
subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 404 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral embolism			
subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Breakthrough pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pain			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ECG signs of myocardial ischaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 404 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 404 (0.25%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic coma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sedation			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 404 (0.25%)	2 / 103 (1.94%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			
subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 404 (0.25%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 404 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			

subjects affected / exposed	0 / 404 (0.00%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site cellulitis			
subjects affected / exposed	0 / 404 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 404 (0.50%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis listeria			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 404 (0.25%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 404 (0.74%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 404 (0.00%)	1 / 103 (0.97%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Single-blind Sativex (Safety Population)	Double-blind Sativex (Safety Population)	Double-blind Placebo (GA-0034) (Safety Population)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 404 (24.01%)	21 / 103 (20.39%)	17 / 103 (16.50%)
Investigations			
Weight decreased			
subjects affected / exposed	0 / 404 (0.00%)	7 / 103 (6.80%)	4 / 103 (3.88%)
occurrences (all)	0	7	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 404 (6.68%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences (all)	28	0	0
Somnolence			
subjects affected / exposed	46 / 404 (11.39%)	6 / 103 (5.83%)	1 / 103 (0.97%)
occurrences (all)	47	6	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 404 (0.00%)	5 / 103 (4.85%)	6 / 103 (5.83%)
occurrences (all)	0	5	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 404 (0.00%)	6 / 103 (5.83%)	6 / 103 (5.83%)
occurrences (all)	0	6	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	25 / 404 (6.19%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences (all)	25	0	0
Vomiting			
subjects affected / exposed	21 / 404 (5.20%)	0 / 103 (0.00%)	0 / 103 (0.00%)
occurrences (all)	21	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 404 (0.00%)	6 / 103 (5.83%)	3 / 103 (2.91%)
occurrences (all)	0	6	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2011	An administrative error led to the inclusion of blood draw volumes, in relation to laboratory samples, in the protocol synopsis and additionally, the volumes stated were inaccurate. As blood draw volumes were not mentioned anywhere else within the protocol they were removed from the synopsis.
06 December 2011	An annex to the protocol (Annex 1) was issued to allow the collection of relevant dose-concentration relationship information in participants who were representative of the target population treated with Sativex.
13 April 2012	This amendment to Protocol Annex 1 provided clarification of the participant population by detailing the different racial groups to be recruited into the pharmacokinetic (PK) annex.
15 November 2012	* Wording was amended to make it clearer for the reader with regards to the criteria for changes to opioid medications during the eligibility period. * Wording in Sections 8.2.1, 8.2.2, and where needed, was amended to clarify that regular around the clock dosing with immediate-release opioids as a maintenance dose was ideally to be every 4 hours. * Section 8.6 was updated to clarify to investigators that it was acceptable to unblind prior to contacting GW Pharmaceuticals Ltd., but where possible, GW Pharmaceuticals Ltd. encouraged communication first. * Updates were made to clarify that, for this study, the electronic data capture could not be used to amend a participant's 'status' (for example, screen fail/randomize/complete/withdrawn) within the study, or to resupply drug. These processes could only be carried out by the IVRS. * The wording in Section 9.1.8 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. However, there were no additional requirements of either the center or participant if this confirmatory test was performed. * Further text was added to both the protocol and protocol synopsis to clarify what was required of the participant, with regards to study drug dosing and continued use of the IVRS, at Day 22 of the double-blind period. * Following Food and Drug Administration guidance, the protocol was updated to clarify that GW Pharmaceuticals Ltd. may have needed to follow-up with the study center on certain adverse events of special medical interest, in particular those associated with abuse potential or addiction.
14 March 2013	An annex to the protocol (Annex 2) 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 United States (US) and United Kingdom centers from the point of implementation onwards.
16 April 2013	An annex to the protocol (Annex 3) described the methodology for the assessment of potential physical dependence and withdrawal effects by use of the Cannabis Withdrawal Scale in participants who withdrew from study drug at any point. It also allowed for the inclusion of the Health Service Utilization Questionnaire to assess participant contact with health care services.

04 July 2014	* This amendment to Protocol Annex 1 allowed Caucasian participants to be recruited from centers in the Europe and Israel as well as the US. The number of Caucasian participants to be recruited was also increased from 40 to 50 (with a related increase in overall Annex participants from 130 to 140). * Addition of PK parameters to include 6-hydroxy-(OH)-CBD and 7-OH-CBD as well as other THC and CBD minor metabolites, should validated tests have existed at the time of analysis. * There were amendments to the text to clarify that the single-blind period study drug only was to be used during Annex 1 and that its single-blind status was to be maintained.
19 January 2015	This amendment to Protocol Annex 1 included a change to the participant numbers and the countries involved as well as providing further clarification regarding the aims of the annex such as, exploring the potential PK differences between Asian and Caucasian racial groups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported