



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 |
| Consent withdrawn by subject | 16 |
| Physician decision | 2 |
| 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 |
| Consent withdrawn by subject | 2 | - |
| Physician decision | 1 | 1 |
| 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:

$$\text{Imp\%} = (\text{Eligibility Baseline pain NRS mean} - \text{End of Treatment pain NRS mean}) / \text{Eligibility Baseline pain NRS mean} * 100.$$

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 (\pm 1.4) | 0.5 (\pm 1.6) | | |

Statistical analyses

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 (\pm 1.8) | -0.2 (\pm 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 occurrences (all) | 0 / 404 (0.00%) 0 | 5 / 103 (4.85%) 5 | 6 / 103 (5.83%) 6 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 404 (0.00%) 0 | 6 / 103 (5.83%) 6 | 6 / 103 (5.83%) 6 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 25 / 404 (6.19%) 25 21 / 404 (5.20%) 21 | 0 / 103 (0.00%) 0 0 / 103 (0.00%) 0 | 0 / 103 (0.00%) 0 0 / 103 (0.00%) 0 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 0 / 404 (0.00%) 0 | 6 / 103 (5.83%) 6 | 3 / 103 (2.91%) 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 | <ul style="list-style-type: none">* 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 | <ul style="list-style-type: none"> * 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