



## Clinical trial results:

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

### Summary

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

### Results information

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

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | GWCA0958 |
|-----------------------|----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | GW Pharmaceuticals Ltd.   |
| Sponsor organisation address | Sovereign House, Vision Park, Chivers Way, Histon, Cambridge, United Kingdom, CB24 9BZ            |
| Public contact               | GW Pharmaceuticals Ltd. Switchboard, GW Pharmaceuticals Ltd., +44 1980557000, medinfo@gwpharm.com |
| Scientific contact           | GW Pharmaceuticals Ltd. Switchboard, GW Pharmaceuticals Ltd., +44 1980557000, medinfo@gwpharm.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 27 January 2016 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 02 July 2015    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 02 July 2015    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|   |     |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 264 |
| From 65 to 84 years                       | 130 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Sativex |

Arm description:

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

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

Dosage and administration details:

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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Placebo (GA-0034) |
|------------------|-------------------|

Arm description:

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

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

Dosage and administration details:

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

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

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Sativex |
|-----------------------|---------|

Reporting group description:

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

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo (GA-0034) |
|-----------------------|-------------------|

Reporting group description:

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

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

## End points

### End points reporting groups

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

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

|   |   |
|---|---|
| End point title   | Percent Improvement From Baseline In Mean Numerical Rating Scale (NRS) Average Pain At End Of Treatment |
| End point description:<br>Participants indicated level of pain in the last 24 hours on an 11-point NRS, where a score of 0 was "no pain" and 10 was "pain as bad as you can imagine." Baseline = mean score from first day of 3-day eligibility period through to the day before first dose of study drug. End of Treatment = mean score over last (up to) 7 days to the final pain score at End of Treatment or up until Day 35, whichever is earlier, or final score available (prematurely terminated).<br>Percentage improvement from baseline (Imp%) was calculated as:<br>$\text{Imp\%} = (\text{Baseline pain NRS mean} - \text{End of Treatment pain NRS mean}) / \text{Baseline pain NRS mean} * 100.$<br>For participants who died or withdrew due to disease progression, Imp% values were used. For participants who died or withdrew unrelated to disease progression before end of Week 5 (no diary data from Day 33 onwards), Imp% was zero if participant Imp% value was positive and it was Imp% for participants whose Imp% value was not positive. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline, End of Treatment (Day 36)   |   |

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

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Percent Improvement In Mean NRS Average Pain Score |
| Statistical analysis description:<br>$\text{Imp\%} = (\text{Baseline pain NRS mean} - \text{End of Treatment pain NRS mean}) / \text{Baseline pain NRS mean} * 100.$<br>For participants who died or withdrew due to disease progression, Imp% values were used. For |  |

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

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

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

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

End point description:

Participants indicated the level of pain experienced in the last 24 hours on an 11-point NRS, where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine."

Change in mean NRS average pain was calculated as: End of Treatment NRS average pain score - Baseline NRS average pain score.

A negative value indicates an improvement in average pain score from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (Day 36)

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

### Statistical analyses

No statistical analyses for this end point

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

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



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**End point description:**

Participants indicated the level of worst pain experienced in the last 24 hours on an 11-point NRS, where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine."

Change in mean NRS worst pain was calculated as: End of Treatment NRS worst pain score - Baseline NRS worst pain score.

A negative value indicates an improvement in worst pain score from Baseline.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

Baseline, End of Treatment (Day 36)

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

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**Statistical analyses**

No statistical analyses for this end point

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

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

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End point description:

Participants indicated the level of sleep disruption experienced in the last 24 hours on an 11-point NRS, where a score of 0 indicated "did not disrupt sleep" and a score of 10 indicated "completely disrupted (unable to sleep at all)."

Change in mean sleep disruption NRS was calculated as: End of Treatment sleep disruption NRS score - Baseline sleep disruption NRS score.

A negative value indicates an improvement in sleep disruption score from Baseline.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

Baseline, End of Treatment (Day 36)

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Last Visit (up to Day 36)

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Last Visit (Up to Day 36)

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

### Statistical analyses

No statistical analyses for this end point

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

|                           |  |
|---------------------------|--|
| End point title           | Patient Satisfaction Questionnaire At Last Visit (Up To End Of Treatment)  |
| End point description:    | The Patient Satisfaction Questionnaire (PSQ) was used to assess level of satisfaction of the participant with the study drug, with the markers "Extremely satisfied, Very satisfied, Slightly satisfied, Neutral, Slightly dissatisfied, Very dissatisfied, Extremely dissatisfied". Last visit refers to the last visit that a participant completed the assessment; this could be either Day 22 or Day 36. |
| End point type            | Secondary  |
| End point timeframe:      |  |
| Last Visit (Up to Day 36) |  |

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The total daily opioid use (in morphine equivalence) was the sum of morphine equivalents of daily maintenance dose and break-through dose.

Change in daily total opioid use was calculated as: End of Treatment daily total opioid use - Baseline daily total opioid use.

A negative value indicates a decrease in use from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (Day 36)

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The prescribed daily quantity of opioid maintenance dose was calculated as the product of dose per use and daily frequency of use. Participants were asked: "Have you used your maintenance dose painkiller today as prescribed?" If the participant answered "No" to the question, the daily opioid maintenance dose usage on that day was set to 0.

Change in daily maintenance opioid dose was calculated as: End of Treatment daily maintenance opioid dose - Baseline daily maintenance opioid dose.

A negative value indicates a decrease in dose from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (Day 36)

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Daily break-through opioid dose usage was calculated as the product of prescribed dose per use, and the number of uses per day. If participants took more than 1 different break-through opioid for more than 1 day, the sum of morphine equivalents dose usages for each break-through opioid was calculated for the summary.

Change in daily break-through opioid dose was calculated as: End of Treatment daily break-through opioid dose - Baseline daily maintenance opioid dose.

A negative value indicates a decrease in dose from Baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Last Visit (Day 36)

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

### Statistical analyses

No statistical analyses for this end point

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

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

**End point description:**

Participants indicated level of constipation on an 11-point NRS, where a score of 0 was "no constipation", and 10 was "constipation as bad as you can imagine." Last visit refers to the last visit that a participant completed the assessment; this could be either Day 22 or Day 36.

Change in NRS constipation score was calculated as: Last Visit NRS constipation score - Baseline NRS constipation score.

A negative value indicates improvement in condition from Baseline.

**End point type**

Secondary

**End point timeframe:**

Baseline, Last Visit (Up To Day 36)

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

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Day 43 post-randomization

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Sativex |
|-----------------------|---------|

Reporting group description:

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

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

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

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



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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 04 October 2010 | <ul style="list-style-type: none"><li>• Change in the primary analysis variable from the 30% responder analysis to the continuous responder analysis with resulting increase in sample size from 370 to 380 participants.</li><li>• Removal of Quality of Life assessments from the protocol as they were not sensitive enough to detect a difference between Sativex and placebo but did add excessive burden to participants. These were replaced with 2 simple questions asked to participants at each study visit about a) their level of constipation and b) their satisfaction with their medicine and recorded on a simple 0-10 NRS scale.</li><li>• Reinforcing the point that the protocol included a participant population which was one of terminally ill, advanced cancer participants and that Sativex was to be dosed twice-daily, not as-needed.</li><li>• The dosing paradigm was described more specifically.</li><li>• The definition of optimized therapy was improved and a minimum threshold level of morphine equivalence (&gt;90 mg transdermal drug delivery) was added for those participants where it was deemed clinically inappropriate to increase their dose because no further efficacy benefit was expected.</li><li>• How rescue analgesia was addressed in the statistical analysis was clarified.</li><li>• Various changes in wording to improve clarity.</li><li>• Various updates to bring in line with the current protocol template, internal safety operating procedures, and any updated legislation.</li><li>• The PGIC questionnaire was updated.</li><li>• Safety follow-up period extended to 2 weeks.</li></ul>   |
| 16 July 2012    | <ul style="list-style-type: none"><li>• Wording in Section 4.1.1 was amended to make it clearer for the reader with regards to the length of the eligibility period, changes to opioids during this period, and potential rescreening of participants.</li><li>• The protocol was also updated to reflect an amended and expanded non-linear 'morphine equivalence' conversion scheme for methadone doses.</li><li>• Wording where needed was amended to clarify that regular around-the-clock dosing with IR opioids as a maintenance dose was ideally to be every 4 hours.</li><li>• Section 8.6, Access to Blinded Treatment Assignment, was updated to clarify to investigators that it was acceptable to unblind prior to contacting GW, but where possible, GW encouraged communication first.</li><li>• The wording in Section 9.1.8, Clinical Laboratory Sampling, was revised to clarify how the THC test at Screening was performed and that there was a secondary test to confirm any initial positive THC tests.</li><li>• Section 11.7, Follow up Procedures for Adverse Events, was updated following Food and Drug Administration guidance to clarify that GW may have needed to follow up with the center on certain adverse events of special medical interest, in particular those associated with abuse potential or addiction.</li><li>• Various minor administrative changes were made throughout the protocol to aid clarity for the reader. For example, height and weight were mentioned in the synopsis but were not clear in the visit procedures. Also, the amount of blood drawn was corrected to 9 mL, and the Columbia-Suicide Severity Rating Scale assessment was corrected to show the investigator was to complete this. These were not new procedures in the protocol but merely corrections of errors to ensure the protocol accurately reflected the study procedures. References were also updated accordingly and Esoterix was renamed Labcorp Clinical Trials, which was purely to reflect a name change of the company. Additionally, wording was updated regarding additional countries where Sativex was licensed at</li></ul> |

|               |   |
|---------------|---|
| 14 March 2013 | <ul style="list-style-type: none"> <li>An annex to the protocol was issued to describe the methodology for identifying and evaluating clinical study adverse event data through systematic categorization, tabulation, and analysis that can illuminate an abuse potential signal. This impacted study procedures for United States and United Kingdom centers from the point of implementation onwards.</li> </ul> |
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

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## Online references

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