



## Clinical trial results:

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

### Summary

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

### Results information

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

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | GWCA0999 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01337089 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 20 September 2016 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 27 January 2016   |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 27 January 2016   |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 19 January 2011 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 443 |
| From 65 to 84 years                       | 210 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|           |         |
|-----------|---------|
| Arm title | Sativex |
|-----------|---------|

Arm description:

Sativex was self-administered by participants as a 100 microliter (µL) oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 6 months. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

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

Dosage and administration details:

Sativex was self-administered by participants as a 100 µL oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day for 6 months. Sativex oromucosal spray contained THC (27 mg/milliliter [mL]):CBD (25 mg/mL), in ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring. Each 100 µL actuation delivered 2.7 mg THC and 2.5 mg CBD.

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

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

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Sativex was self-administered by participants as a 100 microliter (µL) oromucosal spray in the morning and evening, up to a maximum of 10 sprays per day, for 6 months. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

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

## End points

### End points reporting groups

|  |                             |
|--|-----------------------------|
| Reporting group title  | Sativex                     |
| Reporting group description:<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 6 months. Each 100 µL actuation delivered 2.7 milligrams (mg) delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD). |                             |
| Subject analysis set title   | Sativex (Safety Population) |
| Subject analysis set type  | Safety analysis             |
| Subject analysis set description:<br>The Safety Population included all participants receiving at least 1 dose of study drug.  |                             |

### Primary: Percent Of Participants With Treatment-emergent Adverse Events

|  |   |
|--|---|
| End point title  | Percent Of Participants With Treatment-emergent Adverse Events <sup>[1]</sup> |
| End point description:<br>Treatment-emergent Adverse Events (TEAEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 17.0. A TEAE is defined as an adverse event with an onset after the start of study drug treatment. The percent of participants who experienced one or more TEAEs is reported. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline, Day 183  |   |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Statistical analyses were not performed for this open-label extension study.   |   |

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

### Statistical analyses

No statistical analyses for this end point

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

|   |  |
|---|--|
| End point title   | Change From Baseline In Mean NRS Average Pain During The Last Period |
| End point description:<br>Participants indicated the level of pain experienced in the last 24 hours on an 11-point Numerical Rating Scale (NRS), where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine."<br>Change in mean NRS average pain was calculated as: Last Period NRS average pain score - Baseline NRS average pain score.<br>A negative value indicates an improvement in average pain score from Baseline. |  |
| End point type  | Secondary  |

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

Change in mean sleep disruption NRS was calculated as: Last Period sleep disruption NRS score - Baseline sleep disruption NRS score.

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

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

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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



End point description:

The Patient Satisfaction Questionnaire (PSQ) was used to assess level of satisfaction of the participant with the study drug, with the markers "extremely satisfied, very satisfied, slightly satisfied, neutral, slightly dissatisfied, very dissatisfied, extremely dissatisfied". Last visit refers to the last visit that a participant completed the assessment.

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

End point timeframe:

Last Visit (up to Day 183)

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

A negative value indicates improvement in condition from Baseline.

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

End point timeframe:

Baseline, Last Visit (up to Day 183)

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Sativex (Safety Population) |  |  |  |
| Subject group type                   | Subject analysis set        |  |  |  |
| Number of subjects analysed          | 619                         |  |  |  |
| Units: units on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) | -0.1 ( $\pm$ 2.5)           |  |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Day 197 post-enrollment

Adverse event reporting additional description:

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

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

### Dictionary used

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

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

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Sativex (Safety Population) |
|-----------------------|-----------------------------|

Reporting group description:

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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



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

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

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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This adverse event affects only female participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This adverse event affects only female participants.

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

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

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

|  |                        |  |  |
|--|------------------------|--|--|
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 49 / 660 (7.42%)<br>54 |  |  |
|--|------------------------|--|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported