



## Clinical trial results:

### A Multicentre, Single-Arm, Open-Label Study of the Repeated Administration of Qutenza<sup>TM</sup> (Capsaicin (8%) high-concentration patch) for the Treatment of Peripheral Neuropathic Pain (PNP)

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2009-016457-18                               |
| Trial protocol           | IE FR BE GB CZ FI ES AT IT HU NL SK PL SI GR |
| Global end of trial date | 26 September 2013                            |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 04 June 2016  |
| First version publication date | 23 May 2015   |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Updates required due to non-substantial reasons |

#### Trial information

##### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | E05-CL-3001/STRIDE |
|-----------------------|--------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01252160 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Astellas Pharma Europe Ltd   |
| Sponsor organisation address | 2000 Hillswood Drive, Chertsey, United Kingdom, KT16 0RS   |
| Public contact               | Associate Medical Director - Pain Therapeutic Area, Astellas Pharma Europe Ltd, <a href="mailto:Astellas.resultsdisclosure@astellas.com">Astellas.resultsdisclosure@astellas.com</a> |
| Scientific contact           | Associate Medical Director - Pain Therapeutic Area, Astellas Pharma Europe Ltd, <a href="mailto:Astellas.resultsdisclosure@astellas.com">Astellas.resultsdisclosure@astellas.com</a> |

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                       | 26 September 2013 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 26 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 26 September 2013 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the safety and efficacy of repeat applications of Qutenza TM (Capsaicin (8%) high-concentration patch) over 52 weeks in participants with Peripheral Neuropathic Pain (PNP).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information. Approval for the study protocol, dated 30 Apr 2010, was obtained from the relevant competent authorities prior to study initiation.

Background therapy:

Participants receiving first patch application could receive oral and transdermal opioid medication if it did not exceed a total oral daily dose of morphine of 80 mg or the equivalent, which was to be calculated using the Opioid Equivalence Guidance. Any changes, additions or discontinuations to medications were assessed and recorded at every study visit. A short acting opioid could be administered to relieve treatment-associated discomfort during and/or after treatment procedures, while the patient was in the clinic. Participants could receive concomitant systemic non-opioid pain medications for the treatment of Peripheral Neuropathic Pain (PNP).

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 28 October 2010 |
| 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 | Netherlands: 11    |
| Country: Number of subjects enrolled | Poland: 8          |
| Country: Number of subjects enrolled | Romania: 12        |
| Country: Number of subjects enrolled | Slovakia: 5        |
| Country: Number of subjects enrolled | Slovenia: 3        |
| Country: Number of subjects enrolled | Spain: 33          |
| Country: Number of subjects enrolled | United Kingdom: 73 |
| Country: Number of subjects enrolled | Austria: 15        |
| Country: Number of subjects enrolled | Belgium: 22        |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | Finland: 13        |
| Country: Number of subjects enrolled | France: 40         |
| Country: Number of subjects enrolled | Greece: 9          |

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | Ireland: 7 |
| Country: Number of subjects enrolled | Italy: 34  |
| Worldwide total number of subjects   | 306        |
| EEA total number of subjects         | 306        |

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)                      | 197 |
| From 65 to 84 years                       | 102 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

This open-label, single-arm, multicenter study was conducted at 63 sites in Europe: 3 in Austria, 5 in Belgium, 4 in Czech Republic, 2 in Finland, 6 in France, 2 in Greece, 1 in Hungary, 2 in Ireland, 9 in Italy, 2 in Netherlands, 3 in Poland, 2 in Romania, 1 in Slovakia, 2 in Slovenia, 10 in Spain, and 9 in the UK.

### Pre-assignment

Screening details:

Study population consisted of 306 enrolled non-diabetic adult participants (18-90 years) with moderate to severe pain due to Peripheral Neuropathic Pain (PNP) with Postherpetic Neuralgia (PHN), HIV-associated Neuropathy (HIV-AN), Post-traumatic Nerve Injury (PNI) and Idiopathic Small Nerve Neuropathy (ISNN).

### Period 1

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

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | PHN [Post-herpetic Neuralgia] |

Arm description:

Participants with identified postherpetic neuralgia.

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Qutenza [Capsaicin (8%) high-concentration patch] |
| Investigational medicinal product code | ASP0805   |
| Other name                             |   |
| Pharmaceutical forms                   | Transdermal patch                                 |
| Routes of administration               | Topical use                                       |

Dosage and administration details:

Qutenza is a high-concentration (8%) capsaicin patch which was applied to intact, non-irritated, dry skin. Each patch contained a total of 179 mg of capsaicin or 640 µg of capsaicin per cm<sup>2</sup> of patch (8%). Up to 4 patches (1120 cm<sup>2</sup>) could be applied at any 1 application. The patches were applied for 30 min (feet) or 60 min (other body locations). Patients were pre-treated with a local topical anesthetic (for a period as determined by the prescribing information of the product used) prior to the patch application. The choice of topical anesthetic was at the investigator's discretion. After topical anesthetic was removed Qutenza was applied to painful area(s). Following removal of the patch treated area was cleaned with the gel provided.

|                  |   |
|------------------|---|
| <b>Arm title</b> | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] |
|------------------|---|

Arm description:

Participants with identified human immunodeficiency virus-associated neuropathy.

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Qutenza [Capsaicin (8%) high-concentration patch] |
| Investigational medicinal product code | ASP0805   |
| Other name                             |   |
| Pharmaceutical forms                   | Transdermal patch                                 |
| Routes of administration               | Topical use                                       |

Dosage and administration details:

Qutenza is a high-concentration (8%) capsaicin patch which was applied to intact, non-irritated, dry skin. Each patch contained a total of 179 mg of capsaicin or 640 µg of capsaicin per cm<sup>2</sup> of patch (8%). Up to 4 patches (1120 cm<sup>2</sup>) could be applied at any 1 application. The patches were applied for 30 min (feet) or 60 min (other body locations). Patients were pre-treated with a local topical anesthetic (for a period as determined by the prescribing information of the product used) prior to the patch

application. The choice of topical anesthetic was at the investigator's discretion. After topical anesthetic was removed Qutenza was applied to painful area(s). Following removal of the patch treated area was cleaned with the gel provided.

|   |   |
|---|---|
| <b>Arm title</b>  | PNI [Post-traumatic Nerve Injury]                 |
| Arm description:<br>Participants with identified post-traumatic nerve injury. |   |
| Arm type  | Experimental                                      |
| Investigational medicinal product name  | Qutenza [Capsaicin (8%) high-concentration patch] |
| Investigational medicinal product code  | ASP0805   |
| Other name  |   |
| Pharmaceutical forms  | Transdermal patch                                 |
| Routes of administration  | Topical use                                       |

Dosage and administration details:

Qutenza is a high-concentration (8%) capsaicin patch which was applied to intact, non-irritated, dry skin. Each patch contained a total of 179 mg of capsaicin or 640 µg of capsaicin per cm<sup>2</sup> of patch (8%). Up to 4 patches (1120 cm<sup>2</sup>) could be applied at any 1 application. The patches were applied for 30 min (feet) or 60 min (other body locations). Patients were pre-treated with a local topical anesthetic (for a period as determined by the prescribing information of the product used) prior to the patch application. The choice of topical anesthetic was at the investigator's discretion. After topical anesthetic was removed Qutenza was applied to painful area(s). Following removal of the patch treated area was cleaned with the gel provided.

|   |   |
|---|---|
| <b>Arm title</b>  | Other type of Peripheral Neuropathic Pain [PNP]   |
| Arm description:<br>Participants with identified peripheral neuropathic pain. |   |
| Arm type  | Experimental                                      |
| Investigational medicinal product name  | Qutenza [Capsaicin (8%) high-concentration patch] |
| Investigational medicinal product code  | ASP0805   |
| Other name  |   |
| Pharmaceutical forms  | Transdermal patch                                 |
| Routes of administration  | Topical use                                       |

Dosage and administration details:

Qutenza is a high-concentration (8%) capsaicin patch which was applied to intact, non-irritated, dry skin. Each patch contained a total of 179 mg of capsaicin or 640 µg of capsaicin per cm<sup>2</sup> of patch (8%). Up to 4 patches (1120 cm<sup>2</sup>) could be applied at any 1 application. The patches were applied for 30 min (feet) or 60 min (other body locations). Patients were pre-treated with a local topical anesthetic (for a period as determined by the prescribing information of the product used) prior to the patch application. The choice of topical anesthetic was at the investigator's discretion. After topical anesthetic was removed Qutenza was applied to painful area(s). Following removal of the patch treated area was cleaned with the gel provided.

| Number of subjects in period 1 | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] |
|--------------------------------|-------------------------------|---|-----------------------------------|
|                                |                               |   |                                   |
| Started                        | 107                           | 80  | 99                                |
| Completed                      | 66                            | 45  | 54                                |
| Not completed                  | 41                            | 35  | 45                                |
| Other                          | 1                             | 5   | 2                                 |
| Lack of efficacy               | 16                            | 8   | 24                                |

|                              |    |    |   |
|------------------------------|----|----|---|
| Protocol Violation           | 3  | 2  | 1 |
| Consent withdrawn by subject | 11 | 13 | 8 |
| Adverse Event                | 5  | 1  | 4 |
| Lost to follow-up            | 5  | 6  | 6 |

| <b>Number of subjects in period 1</b> | Other type of<br>Peripheral<br>Neuropathic Pain<br>[PNP] |
|---------------------------------------|--|
| Started                               | 20   |
| Completed                             | 11   |
| Not completed                         | 9  |
| Other                                 | 1  |
| Lack of efficacy                      | 6  |
| Protocol Violation                    | -  |
| Consent withdrawn by subject          | 1  |
| Adverse Event                         | 1  |
| Lost to follow-up                     | -  |

## Baseline characteristics

### Reporting groups

|  |   |
|--|---|
| Reporting group title  | PHN [Post-herpetic Neuralgia]                               |
| Reporting group description:<br>Participants with identified postherpetic neuralgia.                             |   |
| Reporting group title  | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] |
| Reporting group description:<br>Participants with identified human immunodeficiency virus-associated neuropathy. |   |
| Reporting group title  | PNI [Post-traumatic Nerve Injury]                           |
| Reporting group description:<br>Participants with identified post-traumatic nerve injury.                        |   |
| Reporting group title  | Other type of Peripheral Neuropathic Pain [PNP]             |
| Reporting group description:<br>Participants with identified peripheral neuropathic pain.                        |   |

| Reporting group values  | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] |
|---|-------------------------------|---|-----------------------------------|
| Number of subjects  | 107                           | 80  | 99                                |
| Age categorical   |                               |   |                                   |
| The mean age of patients enrolled in the study was 57.9 years in the range from 20 to 90 years. The oldest patients were in the Postherpetic neuralgia (PHN) group with mean age 70.5 years and the range from 36 to 90 years. The youngest patients were in the Human immunodeficiency virus-associated neuropathy (HIV-AN) group with mean age of 51.5 years and the range of 22 to 76 years. The Post traumatic nerve injury (PNI) group had a mean age of 49.7 years and the age range from 20 to 81 years. |                               |   |                                   |
| 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)  | 27                            | 71  | 83                                |
| From 65-84 years  | 36                            | 8   | 11                                |
| 85 years and over   | 44                            | 1   | 5                                 |
| Age continuous  |                               |   |                                   |
| Units: years  |                               |   |                                   |
| arithmetic mean   | 70.5                          | 51.5  | 49.7                              |
| standard deviation  | ± 10.85                       | ± 10.97   | ± 13.48                           |
| Gender categorical  |                               |   |                                   |
| Units: Subjects   |                               |   |                                   |
| Female  | 50                            | 15  | 55                                |
| Male  | 57                            | 65  | 44                                |
| Brief Pain Inventory (BPI-DN Question 5) baseline average pain  |                               |   |                                   |
| Brief Pain Inventory (BPI) questions are based on a scale of 1 (no pain) to 10 (pain as bad as can be imagined). BPI-DN Question 5 was used to assess participants baseline average pain.   |                               |   |                                   |

|  |        |        |        |
|--|--------|--------|--------|
| Units: Number  |        |        |        |
| arithmetic mean  | 6.2    | 6.1    | 6.6    |
| standard deviation   | ± 1.55 | ± 1.75 | ± 1.68 |
| Time Since Diagnosis of Neuropathic Pain (Years)   |        |        |        |
| Time since diagnosis is defined as the date of baseline visit minus the date when diagnosis was made plus 1 day divided by 365.25. Time since diagnosis is presented for all groups, Human immunodeficiency virus-associated neuropathy (HIV-AN; N=79), Postherpetic neuralgia (PHN; N=107) and Post-traumatic nerve injury (PNI; N=99). |        |        |        |
| Units: Years   |        |        |        |
| arithmetic mean  | 3.9    | 7.4    | 4      |
| standard deviation   | ± 4.97 | ± 5.78 | ± 4.34 |

| Reporting group values  | Other type of Peripheral Neuropathic Pain [PNP] | Total |  |
|---|---|-------|--|
| Number of subjects  | 20  | 306   |  |
| Age categorical   |   |       |  |
| The mean age of patients enrolled in the study was 57.9 years in the range from 20 to 90 years. The oldest patients were in the Postherpetic neuralgia (PHN) group with mean age 70.5 years and the range from 36 to 90 years. The youngest patients were in the Human immunodeficiency virus-associated neuropathy (HIV-AN) group with mean age of 51.5 years and the range of 22 to 76 years. The Post traumatic nerve injury (PNI) group had a mean age of 49.7 years and the age range from 20 to 81 years. |   |       |  |
| Units: Subjects   |   |       |  |
| In utero  | 0   | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)  | 0   | 0     |  |
| Newborns (0-27 days)  | 0   | 0     |  |
| Infants and toddlers (28 days-23 months)  | 0   | 0     |  |
| Children (2-11 years)   | 0   | 0     |  |
| Adolescents (12-17 years)   | 0   | 0     |  |
| Adults (18-64 years)  | 16  | 197   |  |
| From 65-84 years  | 3   | 58    |  |
| 85 years and over   | 1   | 51    |  |
| Age continuous  |   |       |  |
| Units: years  |   |       |  |
| arithmetic mean   | 56.5  | -     |  |
| standard deviation  | ± 10.84   | -     |  |
| Gender categorical  |   |       |  |
| Units: Subjects   |   |       |  |
| Female  | 12  | 132   |  |
| Male  | 8   | 174   |  |
| Brief Pain Inventory (BPI-DN Question 5) baseline average pain  |   |       |  |
| Brief Pain Inventory (BPI) questions are based on a scale of 1 (no pain) to 10 (pain as bad as can be imagined). BPI-DN Question 5 was used to assess participants baseline average pain.   |   |       |  |
| Units: Number   |   |       |  |
| arithmetic mean   | 6.4   | -     |  |
| standard deviation  | ± 1.38  | -     |  |
| Time Since Diagnosis of Neuropathic Pain (Years)  |   |       |  |
| Time since diagnosis is defined as the date of baseline visit minus the date when diagnosis was made plus 1 day divided by 365.25. Time since diagnosis is presented for all groups, Human immunodeficiency virus-associated neuropathy (HIV-AN; N=79), Postherpetic neuralgia (PHN; N=107) and Post-traumatic nerve injury (PNI; N=99).  |   |       |  |



|                    |        |   |  |
|--------------------|--------|---|--|
| Units: Years       |        |   |  |
| arithmetic mean    | 7.7    |   |  |
| standard deviation | ± 7.98 | - |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | PHN [Post-herpetic Neuralgia]                               |
| Reporting group description:  |   |
| Participants with identified postherpetic neuralgia.  |   |
| Reporting group title   | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] |
| Reporting group description:  |   |
| Participants with identified human immunodeficiency virus-associated neuropathy.  |   |
| Reporting group title   | PNI [Post-traumatic Nerve Injury]                           |
| Reporting group description:  |   |
| Participants with identified post-traumatic nerve injury.   |   |
| Reporting group title   | Other type of Peripheral Neuropathic Pain [PNP]             |
| Reporting group description:  |   |
| Participants with identified peripheral neuropathic pain.   |   |
| Subject analysis set title  | Safety Analysis Set (SAF)                                   |
| Subject analysis set type   | Safety analysis   |
| Subject analysis set description:   |   |
| Safety Analysis Set (SAF) was defined and used for all analyses (both safety and efficacy) and it included all patients who received study patch application. |   |

### Primary: Safety (Adverse Events[AE], Serious AEs [SAEs] and Treatment-Emergent AEs [TEAEs]) (SAF)

|  |   |
|--|---|
| End point title  | Safety (Adverse Events[AE], Serious AEs [SAEs] and Treatment-Emergent AEs [TEAEs]) (SAF) <sup>[1]</sup> |
| End point description:   |   |
| This endpoint evaluated safety of repeated Qutenza (Capsaicin (8%) high-concentration patch) applications, including the effect in participants diagnosed with different types of PNP. There were 3 deaths reported in the study due to the events of cerebral hemorrhage, pneumonia and squamous cell carcinoma; all events leading to death were not related to Qutenza. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Baseline to End of Treatment (EOT)   |   |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Adverse events (AEs) are summarized as counts over the entire study. Statistical analyses was not completed for this endpoint.

| End point values                         | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                       | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed              | 107                           | 80  | 99                                | 20  |
| Units: Number of participants            |                               |   |                                   |   |
| number (not applicable)                  |                               |   |                                   |   |
| TEAE (Treatment Emergent Adverse Events) | 87                            | 62  | 86                                | 17  |
| Drug-related TEAEs                       | 78                            | 42  | 73                                | 14  |
| Deaths                                   | 2                             | 1   | 0                                 | 0   |
| Serious TEAEs                            | 14                            | 8   | 13                                | 2   |

|   |    |    |    |    |
|---|----|----|----|----|
| Drug-related serious TEAEs                    | 0  | 0  | 0  | 0  |
| TEAEs leading to discontinuation              | 5  | 1  | 4  | 1  |
| Drug related TEAEs leading to discontinuation | 1  | 0  | 1  | 1  |
| Application site reactions                    | 74 | 30 | 68 | 13 |

## Statistical analyses

No statistical analyses for this end point

### Primary: Sensory Testing of most Sensitive Area(s) (Mean value, Area Size per Patch Application) (SAF)

|                 |  |
|-----------------|--|
| End point title | Sensory Testing of most Sensitive Area(s) (Mean value, Area Size per Patch Application) (SAF) <sup>[2]</sup> |
|-----------------|--|

End point description:

This endpoint was used to complete sensory testing of most sensitive areas to which patches are applied. During this exam participants were assessed on change from the sensory assessments performed at the screening visit. Participants response to warm, cold, sharp (pinprick), vibration sensations, light brush, deep tendon reflexes, most sensitive areas, and allodynia were assessed at each patch application visit. Assessment was performed at week 26 (if applicable), End of Treatment (EOT) and planned or early termination visits. Data was reported for the Week 26, EOT and as a patient mean of all applications.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Timeframe for this endpoint was by patch application (including last application) from Baseline to End of Treatment (EOT) at each patch application.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Sensory testing of the most sensitive area(s) and the corresponding areas of allodynia was assessed by location counts and absolute value of area size. Statistical analyses was not completed for this endpoint.

| End point values                     | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--------------------------------------|-------------------------------|---|-----------------------------------|---|
| Subject group type                   | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed          | 107                           | 80  | 99                                | 20  |
| Units: Number of participants        |                               |   |                                   |   |
| arithmetic mean (standard deviation) |                               |   |                                   |   |
| Screening [N=107;79;98;19]           | 325.8 (± 239.55)              | 615.8 (± 395.43)  | 182.3 (± 180.31)                  | 411.6 (± 324.92)                                |
| 1st Application [N=107;80;99;20]     | 327.2 (± 235.22)              | 606.2 (± 371.64)  | 192.6 (± 191.65)                  | 456.3 (± 303.77)                                |
| 2nd Application [N=85;51;76;18]      | 290.6 (± 206.64)              | 567.1 (± 344.79)  | 179.9 (± 208.69)                  | 494.2 (± 327.82)                                |
| 3rd Application [N=59;29;58;13]      | 273.1 (± 225.55)              | 537.7 (± 360.03)  | 168.8 (± 193.42)                  | 399.2 (± 301.67)                                |
| 4th Application [N=35;16;39;10]      | 281.5 (± 190.58)              | 488.9 (± 330.04)  | 149 (± 174.56)                    | 335.8 (± 332.57)                                |
| 5th Application [N=21;8;16;7]        | 271.7 (± 221.54)              | 462.4 (± 290.25)  | 133.2 (± 151.15)                  | 407.1 (± 368.18)                                |

|                                   |                  |                  |                  |                  |
|-----------------------------------|------------------|------------------|------------------|------------------|
| 6th Application [N=6;1;6;3]       | 270.7 (± 286.42) | 1626 (± 0)       | 238.5 (± 254.25) | 145.3 (± 59.97)  |
| Last Application [N=107;80;99;20] | 307 (± 242.73)   | 604.6 (± 408.68) | 193.9 (± 205.31) | 446.6 (± 335.38) |
| Week 26 [N=107;80;99;20]          | 288 (± 227.23)   | 587.6 (± 402.12) | 189.9 (± 206.99) | 446.6 (± 335.38) |
| EOT [N=106;80;99;20]              | 254 (± 225.58)   | 558.6 (± 406.7)  | 183.9 (± 198.63) | 430.8 (± 368.98) |
| Patient Mean (All Applications)   | 294.4 (± 211.97) | 586 (± 367.48)   | 184.5 (± 176.05) | 460.9 (± 327.33) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Neurological Assessment (SAF)

|                 |                               |
|-----------------|-------------------------------|
| End point title | Neurological Assessment (SAF) |
|-----------------|-------------------------------|

End point description:

An abbreviated neurological examination was performed at the screening visit, at all patch application visits, at week 26 visit (if applicable), and at the planned or early termination visit. It included assessments of gait, muscle strength, and reflexes. The assessments were classified as normal, abnormal-not clinically significant and abnormal-clinically significant. Endpoint of interest was the number and percentage of participants with each neurological assessment score at the different study time points.

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

End point timeframe:

Baseline (Screening, All Patch application visits, Week 26) to End of Treatment (EOT)

| End point values                                   | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                                 | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                        | 107                           | 80  | 99                                | 20  |
| Units: Number of Participants                      |                               |   |                                   |   |
| number (not applicable)                            |                               |   |                                   |   |
| Scr Gait Normal [N=106;N=80;N=98;N=20]             | 100                           | 53  | 84                                | 17  |
| Scr Gait Abnormal NCS [N=106;N=80;N=98;N=20]       | 6                             | 16  | 10                                | 2   |
| Scr Gait Abnormal CS [N=106;N=80;N=98;N=20]        | 0                             | 11  | 4                                 | 1   |
| Scr Muscle Strength Normal [N=106;N=79;N=99;N=20]  | 104                           | 66  | 91                                | 18  |
| Scr Muscle Strength Abn NCS [N=106;N=79;N=99;N=20] | 2                             | 9   | 3                                 | 2   |
| Scr Muscle Strength Abn CS [N=106;N=79;N=99;N=20]  | 0                             | 4   | 5                                 | 0   |
| Scr Reflexes Normal [N=106;N=80;N=99;N=20]         | 94                            | 32  | 85                                | 13  |

|  |     |    |    |    |
|--|-----|----|----|----|
| Scr Reflexes Abnormal<br>NCS[N=106;N=80;N=99;N=20]     | 9   | 26 | 9  | 5  |
| Scr Reflexes Abnormal<br>CS[N=106;N=80;N=99;N=20]      | 3   | 22 | 5  | 2  |
| W26 Gait<br>Normal[N=107;N=80;N=99;N=20]               | 7   | 5  | 4  | 0  |
| W26 Gait Abnormal<br>NCS[N=107;N=80;N=99;N=20]         | 0   | 3  | 0  | 0  |
| W26 Gait Abnormal<br>CS[N=107;N=80;N=99;N=20]          | 0   | 0  | 0  | 0  |
| W26 Muscle Strength<br>Normal[N=107;N=80;N=99;N=20]    | 7   | 6  | 3  | 0  |
| W26 Muscle Strength Abnor<br>NCS[N=107;N=80;N=99;N=20] | 0   | 2  | 0  | 0  |
| W26 Muscle Strength Abnor<br>CS[N=107;N=80;N=99;N=20]  | 0   | 0  | 1  | 0  |
| W26 Reflexes<br>Normal[N=107;N=80;N=99;N=20]           | 6   | 4  | 4  | 0  |
| W26 Reflexes Abnormal<br>NCS[N=107;N=80;N=99;N=20]     | 0   | 4  | 0  | 0  |
| W26 Reflexes Abnormal<br>CS[N=107;N=80;N=99;N=20]      | 1   | 0  | 0  | 0  |
| EOT Gait<br>Normal[N=106;N=80;N=98;N=20]               | 99  | 60 | 88 | 18 |
| EOT Gait Abnormal<br>NCS[N=106;N=80;N=98;N=20]         | 7   | 16 | 3  | 2  |
| EOT Gait Abnormal<br>CS[N=106;N=80;N=98;N=20]          | 0   | 4  | 7  | 0  |
| EOT Muscle Strength<br>Normal[N=106;N=80;N=98;N=20]    | 104 | 72 | 90 | 19 |
| EOT Muscle Strength Abn<br>NCS[N=106;N=80;N=98;N=20]   | 2   | 6  | 2  | 1  |
| EOT Muscle Strength Abn<br>CS[N=106;N=80;N=98;N=20]    | 0   | 2  | 7  | 0  |
| EOT Reflexes<br>Normal[N=106;N=80;N=99;N=20]           | 95  | 29 | 89 | 14 |
| EOT Reflexes Abn NCS<br>[N=106;N=80;N=99;N=20]         | 9   | 38 | 6  | 3  |
| EOT Reflexes Abn CS<br>[N=106;N=80;N=99;N=20]          | 2   | 13 | 4  | 3  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline Vital Signs (SAF)

| End point title | Change from Baseline Vital Signs (SAF) |
|-----------------|--|
|-----------------|--|

End point description:

Before All Applications (Before App) is assessed within 15 minutes prior to application of topical anesthetic and After All Applications (After App) within 5 minutes after patch removal. Sys Blood pressure=Systolic Blood Pressure. Dia Blood Press=Diastolic Blood Pressure. Participants for PHN group Before Subject Mean (all applications) N=106; After Subject Mean (all applications) N=107; Week 26; N=7 and EOT N=107. Participants for HIV-AN group for Before Subject Mean (all applications) N=79; After Subject Mean (all applications) N=79; Week 26; N=9 and EOT N=79. For PNI group Before Subject Mean (all applications) N=99; After Subject Mean (all applications) N=99; Week 26; N=4 and EOT N=99. For "Other" number of participants is as follows Before Subject Mean (all applications) N=20; After Subject Mean (all applications) N=20; Week 26; N=0 and EOT N=20. For group Other (describing other neuropathic pain) Week 26 values are not available for Systolic, Diastolic and Pulse rate.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Baseline to End of Treatment (EOT). Vital signs, including BP and PR were measured at screening, at all patch application visits (within 15 min prior to application of topical anesthetic and within 5 min after patch removal) and week 26 visit and EOT. |           |

| End point values                          | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|---|-------------------------------|---|-----------------------------------|---|
| Subject group type                        | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed               | 107                           | 80  | 99                                | 20  |
| Units: Number                             |                               |   |                                   |   |
| arithmetic mean (standard deviation)      |                               |   |                                   |   |
| Sys Blood Press [Before App Subject Mean] | -1.9 (± 14.3)                 | -1.1 (± 14.67)  | 0.6 (± 11.57)                     | 2.3 (± 16.09)                                   |
| Sys Blood Press [After App Subject Mean]  | 6.2 (± 16.54)                 | -0.3 (± 15.3)   | 2.2 (± 13.7)                      | 4.4 (± 13.67)                                   |
| Sys Blood Press Week 26                   | 10.1 (± 10.73)                | -9.2 (± 19.41)  | 0.5 (± 3.32)                      | 0 (± 0)   |
| Sys Blood Press EOT                       | -1.5 (± 16.89)                | -2.2 (± 17.05)  | 1.4 (± 15.96)                     | -1.9 (± 18.92)                                  |
| Dia Blood Press [Before App Subject Mean] | -2.1 (± 9.48)                 | -1.2 (± 9.24)   | 0 (± 9.69)                        | -0.2 (± 9.35)                                   |
| Dia Blood Press [After App Subject Mean]  | 1.3 (± 11.06)                 | 0.1 (± 9.1)   | 0.6 (± 10.36)                     | 2.8 (± 9.43)                                    |
| Dia Blood Press Week 26                   | 0.9 (± 5.67)                  | -3.6 (± 15.49)  | -1.3 (± 6.75)                     | 0 (± 0)   |
| Dia Blood Press EOT                       | -1.7 (± 11.35)                | -1.9 (± 11.02)  | 0.4 (± 11.77)                     | -2.6 (± 10.19)                                  |
| Pulse Rate [Before App Subject Mean]      | -0.3 (± 10.03)                | 0.1 (± 10.88)   | -0.6 (± 8.99)                     | -1.6 (± 8.17)                                   |
| Pulse Rate [After App Subject Mean]       | -1.6 (± 10.58)                | -1.4 (± 9.54)   | -0.8 (± 9.8)                      | -1.8 (± 8.27)                                   |
| Pulse Rate Week 26                        | -9.1 (± 10.73)                | 2.9 (± 11.65)   | -5.5 (± 6.66)                     | 0 (± 0)   |
| Pulse Rate EOT                            | 0.1 (± 12.6)                  | 0.6 (± 13.36)   | 1.9 (± 11.18)                     | -1.7 (± 10.59)                                  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Dermal Assessment at Patch Applications (SAF)

|  |   |
|--|---|
| End point title  | Dermal Assessment at Patch Applications (SAF) |
| End point description:   |   |
| Dermal assessment was done at patch applications to determine if there were any signs of irritation. It was completed at all patch application visits (prior to application of topical anesthetic, within 5 min and 60 min after patch removal), at week 26 visit (if applicable), and at the EOT or early termination visits. Scale for assessment was based on a 0 to 7 point severity score. The endpoints of interest were counts by category as listed; [No evidence of irritation], [Minimal erythema barely perceptible], [Definite erythema, readily visible; minimal and edema or minimal popular response], [Erythema and papules], [Definite edema], [Erythema, edema, and papules], [Vesicular eruption], [Strong reaction spreading beyond test site] and [Combined category ≥ 4 (definite edema or higher)]. |   |
| End point type   | Secondary                                     |
| End point timeframe:   |   |
| Baseline to End of Treatment (EOT).  |   |

| <b>End point values</b>                                | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                                     | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                            | 107                           | 80  | 99                                | 20  |
| Units: Number of Participants                          |                               |   |                                   |   |
| number (not applicable)                                |                               |   |                                   |   |
| 1st App Before anesthetic[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 1st App 5min after patch[Combined category $\geq 4$ ]  | 6                             | 2   | 5                                 | 0   |
| 1st App 60min after patch[Combined category $\geq 4$ ] | 5                             | 1   | 4                                 | 0   |
| 2nd App Before anesthetic[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 2nd App 5min after patch[Combined category $\geq 4$ ]  | 6                             | 0   | 3                                 | 0   |
| 2nd App 60min after patch[Combined category $\geq 4$ ] | 3                             | 1   | 4                                 | 0   |
| 3rd App Before anesthetic[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 3rd App 5min after patch[Combined category $\geq 4$ ]  | 1                             | 0   | 2                                 | 0   |
| 3rd App 60min after patch[Combined category $\geq 4$ ] | 1                             | 0   | 1                                 | 0   |
| 4th App Before anesthetic[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 4th App 5min after patch[Combined category $\geq 4$ ]  | 0                             | 0   | 1                                 | 0   |
| 4th App 60min after patch[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 5th App Before anesthetic[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 5th App 5min after patch[Combined category $\geq 4$ ]  | 0                             | 0   | 0                                 | 0   |
| 5th App 60min after patch[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 6th App Before anesthetic[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |
| 6th App 5min after patch[Combined category $\geq 4$ ]  | 0                             | 0   | 0                                 | 0   |
| 6th App 60min after patch[Combined category $\geq 4$ ] | 0                             | 0   | 0                                 | 0   |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline Brief Pain Inventory Question 5 (average pain)(SAF)

|  |  |
|--|--|
| End point title  | Change from Baseline Brief Pain Inventory Question 5 (average pain)(SAF) |
| End point description:   |  |
| Responses to BPI Question 5 (average pain) were recorded daily and weekly ( $\pm 2$ days) from the 1st patch application until the planned or early termination visit. Weekly response was recorded on the day chosen by patient during the 1st patch application visit ( $\pm 2$ days). Each BPI item uses a 0 to 10 rating scale anchored at zero for "no pain" and 10 for "pain as bad as you can imagine" for severity and "does not interfere" to "completely interferes" for interference. Number of participants for each month was as follows; Month 1[N=106;79;99;20]; Month 2[N=102;69;95;19];Month 3[N=97;65;89;18];Month 4[N=91;64;89;18];Month 5[N=90;58;79;18];Month 6[N=81;59;77;16];Month 7[N=79;58;72;15];Month 8[N=75;56;69;15]; Month 9[N=70;49;69;14]; Month 10[N=70;47;64;12]; Month 11[N=68;43;60;11]; Month 12[N=63;42;58;11];Month 13[N=54;41;49;9];Month 14[N=42;29;44;5];Month 15[N=23;21;25;3]; Month 16[N=8;6;3;2]; Month 17[N=2;2;1;1]; Month 18[N=1;0;1;1]; Month 19[N=1;0;1;0];Month 20[N=1;0;0;0]. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline to End of Treatment (EOT).  |  |

| End point values                     | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--------------------------------------|-------------------------------|---|-----------------------------------|---|
| Subject group type                   | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed          | 107                           | 80  | 99                                | 20  |
| Units: Number of Participants        |                               |   |                                   |   |
| arithmetic mean (standard deviation) |                               |   |                                   |   |
| Month 1 Post-baseline                | -0.9 ( $\pm 1.25$ )           | -0.7 ( $\pm 1.3$ )  | -1.1 ( $\pm 1.49$ )               | -0.6 ( $\pm 1.07$ )                             |
| Month 2 Post-baseline                | -1 ( $\pm 1.41$ )             | -1.1 ( $\pm 1.52$ )   | -1.3 ( $\pm 1.89$ )               | -0.7 ( $\pm 0.96$ )                             |
| Month 3 Post-baseline                | -1 ( $\pm 1.35$ )             | -1 ( $\pm 1.57$ )   | -1.3 ( $\pm 1.69$ )               | -0.7 ( $\pm 1.06$ )                             |
| Month 4 Post-baseline                | -1.3 ( $\pm 1.54$ )           | -1.3 ( $\pm 1.96$ )   | -1.6 ( $\pm 1.71$ )               | -0.9 ( $\pm 1.12$ )                             |
| Month 5 Post-baseline                | -1.4 ( $\pm 1.51$ )           | -1.3 ( $\pm 1.81$ )   | -1.6 ( $\pm 1.93$ )               | -1 ( $\pm 1.36$ )                               |
| Month 6 Post-baseline                | -1.4 ( $\pm 1.61$ )           | -1.1 ( $\pm 1.83$ )   | -1.9 ( $\pm 1.89$ )               | -0.8 ( $\pm 1.05$ )                             |
| Month 7 Post-baseline                | -1.5 ( $\pm 1.76$ )           | -1.2 ( $\pm 1.86$ )   | -2 ( $\pm 1.89$ )                 | -0.9 ( $\pm 1.32$ )                             |
| Month 8 Post-baseline                | -1.6 ( $\pm 1.75$ )           | -1.2 ( $\pm 1.74$ )   | -2.2 ( $\pm 2.04$ )               | -1.3 ( $\pm 1.46$ )                             |
| Month 9 Post-baseline                | -1.5 ( $\pm 1.99$ )           | -1.2 ( $\pm 1.75$ )   | -2 ( $\pm 2.12$ )                 | -1.5 ( $\pm 1.34$ )                             |
| Month 10 Post-baseline               | -1.6 ( $\pm 1.96$ )           | -1.3 ( $\pm 1.58$ )   | -1.9 ( $\pm 2.06$ )               | -1.7 ( $\pm 1.71$ )                             |
| Month 11 Post-baseline               | -1.7 ( $\pm 2.01$ )           | -1.5 ( $\pm 1.62$ )   | -2 ( $\pm 2.21$ )                 | -1.4 ( $\pm 1.67$ )                             |
| Month 12 Post-baseline               | -1.7 ( $\pm 1.92$ )           | -1.5 ( $\pm 1.83$ )   | -2.3 ( $\pm 2.19$ )               | -2.1 ( $\pm 1.56$ )                             |
| Month 13 Post-baseline               | -1.8 ( $\pm 1.87$ )           | -1.8 ( $\pm 2.09$ )   | -2.3 ( $\pm 2.23$ )               | -2.2 ( $\pm 1.85$ )                             |
| Month 14 Post-baseline               | -1.6 ( $\pm 1.96$ )           | -1.5 ( $\pm 1.72$ )   | -2.1 ( $\pm 2.47$ )               | -2.5 ( $\pm 2.17$ )                             |
| Month 15 Post-baseline               | -1.6 ( $\pm 2.32$ )           | -1.9 ( $\pm 1.66$ )   | -1.7 ( $\pm 2.09$ )               | -0.8 ( $\pm 1.45$ )                             |
| Month 16 Post-baseline               | -2.6 ( $\pm 2.04$ )           | -2.3 ( $\pm 2.69$ )   | 0.6 ( $\pm 0.93$ )                | -1.8 ( $\pm 0.71$ )                             |
| Month 17 Post-baseline               | -1.8 ( $\pm 2.21$ )           | -0.9 ( $\pm 0.09$ )   | -0.3 ( $\pm 99999$ )              | -2.9 ( $\pm 99999$ )                            |
| Month 18 Post-baseline               | -2.8 ( $\pm 99999$ )          | 0 ( $\pm 0$ )   | 0.2 ( $\pm 99999$ )               | -2.9 ( $\pm 99999$ )                            |
| Month 19 Post-baseline               | -3.6 ( $\pm 99999$ )          | 0 ( $\pm 0$ )   | 0.2 ( $\pm 99999$ )               | 0 ( $\pm 99999$ )                               |
| Month 20 Post-baseline               | -3 ( $\pm 99999$ )            | 0 ( $\pm 0$ )   | 0 ( $\pm 0$ )                     | 0 ( $\pm 0$ )                                   |

## Statistical analyses



No statistical analyses for this end point

### Secondary: Tolerability of patch application (SAF)

|   |   |
|---|---|
| End point title   | Tolerability of patch application (SAF) |
| End point description:<br>Analyses of tolerability include summaries of the percent of intended patch application time overall and by patients' individual neuropathic diagnosis. Duration of patch application was the difference between the stop and start times, and it was presented as a percentage of intended patch application duration. The proportion of patients completing at least 90% of the intended patch application were reported at each patch application. Additionally, a patient was deemed to have had an early patch removal if they had an AE with study drug action of temporary discontinuation, if the patch application duration was less than 100%, or if the patient went on to receive additional subsequent patch applications. |   |
| End point type  | Secondary                               |
| End point timeframe:<br>Duration of patch application was the difference between the stop and start times.  |   |

| End point values                                   | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                                 | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                        | 107                           | 80  | 99                                | 20  |
| Units: Number                                      |                               |   |                                   |   |
| arithmetic mean (standard deviation)               |                               |   |                                   |   |
| Time to 2nd patch application(days)[N=85;51;76;18] | 98.3 (± 49.79)                | 111.1 (± 43.57)   | 94.8 (± 47.02)                    | 84.3 (± 24.62)                                  |
| Time to 3rd patch application(days)[N=59;29;58;13] | 103.3 (± 40.94)               | 127.3 (± 55.56)   | 107.9 (± 44.87)                   | 104.8 (± 28.7)                                  |
| Time to 4th patch application(days)[N=35;16;39;10] | 94.7 (± 29.08)                | 110.1 (± 35.61)   | 103.8 (± 28.19)                   | 80 (± 12.78)                                    |
| Time to 5th patch application(days)[N=21;8;16;7]   | 89.8 (± 22.06)                | 79.4 (± 7.91)   | 83.3 (± 19.38)                    | 74.4 (± 12.42)                                  |
| Time to 6th patch application(days)[N=6;1;6;3]     | 85 (± 32.54)                  | 91 (± 0)  | 74.8 (± 10.98)                    | 70 (± 10.39)                                    |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline Brief Pain Inventory (BPI) Question 6 (pain now)(SAF)

|  |  |
|--|--|
| End point title  | Change from Baseline Brief Pain Inventory (BPI) Question 6 (pain now)(SAF) |
| End point description:<br>Brief Pain Inventory (BPI) Question 6 (pain now) was used to assess participants pain now. Participants completed questionnaire with numeric rating scale measuring severity of pain and its interference with daily function on a 0-10 rating scale,using 0 to identify "no pain" and 10 "pain as bad as you can imagine". Data reported is subject mean of all applications before each patch application and to within 5 min and after 1 hour after each patch application. |  |
| End point type   | Secondary  |

End point timeframe:

Response to BPI Question 6 (pain now) was recorded before topical anesthetic application, within 5 min following patch removal, and after 1 hour following patch removal.

| End point values                                   | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                                 | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                        | 107                           | 80  | 99                                | 20  |
| Units: Number                                      |                               |   |                                   |   |
| arithmetic mean (standard deviation)               |                               |   |                                   |   |
| Subject Mean All Applications [Prior to patch]     | -0.5 (± 1.15)                 | -0.2 (± 0.83)   | -0.4 (± 0.85)                     | -0.2 (± 1.18)                                   |
| Subject Mean All Applications [5 min after patch]  | 0.6 (± 2.28)                  | -0.7 (± 2.35)   | -0.3 (± 2.32)                     | -0.6 (± 1.54)                                   |
| Subject Mean All Applications [1 hour after patch] | -0.7 (± 2.2)                  | -1 (± 2.3)  | -1 (± 2.22)                       | -1 (± 1.57)                                     |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Patient Global Impression of Change (PGIC) for combined category of very much improved + much improved + minimally improved (SAF)

|                 |   |
|-----------------|---|
| End point title | Patient Global Impression of Change (PGIC) for combined category of very much improved + much improved + minimally improved (SAF) |
|-----------------|---|

End point description:

The Patient Global Impression of Change (PGIC) is a patient-rated instrument that measures change in participants overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Data reported is the percentage of participants who reported improvement in their overall status (combined category of very much improved + much improved + minimally improved) for each application. Participants answered a PGIC questionnaire at patch application visits (except 1st patch application visit) and 4 weeks after each patch application visit, at week 26 visit (if applicable), and at the planned or early termination visit.

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

End point timeframe:

Baseline to End of Treatment (EOT). Safety Analysis Set (SAF).

| End point values            | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|-----------------------------|-------------------------------|---|-----------------------------------|---|
| Subject group type          | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed | 107                           | 80  | 99                                | 20  |

|  |      |      |      |      |
|--|------|------|------|------|
| Units: percent                         |      |      |      |      |
| number (not applicable)                |      |      |      |      |
| 1st App [4 weeks after]                | 61.5 | 54.5 | 67.4 | 47.1 |
| 2nd App [Prior to patch application]   | 47.9 | 55.3 | 68.3 | 50   |
| 2nd App [4 weeks after]                | 67.7 | 76.9 | 81.5 | 69.2 |
| 3rd App [Prior to patch application]   | 80.9 | 70.8 | 73.5 | 75   |
| 3rd App [4 weeks after]                | 69   | 75   | 73.3 | 72.7 |
| 4th App [Prior to patch application]   | 66.7 | 100  | 83.3 | 88.9 |
| 4th App [4 weeks after]                | 80   | 91.7 | 71.9 | 87.5 |
| 5th App [Prior to patch application]   | 94.7 | 88.9 | 80   | 83.3 |
| 5th App [4 weeks after]                | 87.5 | 85.7 | 66.7 | 83.3 |
| 6th App [Prior to patch application]   | 80   | 0    | 66.7 | 66.7 |
| 6th App [4 weeks after]                | 100  | 0    | 60   | 66.7 |
| Last App [Prior to patch application]] | 57.9 | 65.1 | 70.8 | 71.4 |
| Last App [4 weeks after]               | 57.7 | 53.8 | 65.4 | 52.9 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline EQ-5D VAS Questionnaire (SAF)

|   |  |
|---|--|
| End point title   | Change from Baseline EQ-5D VAS Questionnaire (SAF) |
| End point description:  |  |
| <p>The EQ-5D is used as a measure of participants health-related quality of life (HRQoL) on a visual analog scale (VAS) on a graduated (0 to 100) scale, with higher scores for higher HRQoL. The EQ-5D self-reported questionnaire includes a VAS, which records the respondent's self-rated health status on a graduated (0 to 100) scale, with higher scores for higher HRQoL. It also includes the EQ-5D descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions is assessed in 3 levels: "no problems", "some problems", or "extreme problems/unable to perform activity". Data represented is the subject mean of all applications from Baseline to EOT.</p> |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline to End of Treatment [EOT]  |  |

| End point values                                | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|---|-------------------------------|---|-----------------------------------|---|
| Subject group type                              | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                     | 107                           | 80  | 99                                | 20  |
| Units: Number                                   |                               |   |                                   |   |
| arithmetic mean (standard deviation)            |                               |   |                                   |   |
| All App[Prior to Patch App N=74 N=39 N=66 N=14] | 0.3 (± 18.2)                  | 3.4 (± 16.16)   | -1.8 (± 15.2)                     | 0.1 (± 10.82)                                   |
| All App[4 Weeks After N=86 N=55 N=86 N=16]      | 1.9 (± 24.71)                 | 3 (± 31.75)   | 1.9 (± 24.02)                     | -2.2 (± 14.75)                                  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline HADS (Hospital Anxiety and Depression Scale)(SAF)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline HADS (Hospital Anxiety and Depression Scale)(SAF) |
|-----------------|--|

End point description:

The HADS is a self-report scale developed for the assessment of anxiety and depression in non-psychiatric populations. In this study it was used to screen for the presence of moderate to severe depressive symptomatology and to assess co-morbid depression during the course of the study. It contains 14 items rated on a 4-point Likert-type scale. There are 2 sub-scales, one assessing depression and the other anxiety. The 7-item depression and anxiety subscales yield scores of 0 to 21 that are interpreted with the following cut-off points: 0 to 7, normal; 8 to 10, mild mood disturbance; 11 to 14, moderate mood disturbance; and 15 to 21, severe mood disturbance. Full Analysis Set (FAS) was used for analysis and data presented represents change from baseline.

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

End point timeframe:

Baseline to End of Treatment [EOT}.

| End point values                       | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                     | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed            | 107                           | 80  | 99                                | 20  |
| Units: Number                          |                               |   |                                   |   |
| arithmetic mean (standard deviation)   |                               |   |                                   |   |
| 1st App 4 weeks after[N=82;51;84;15]   | -0.5 (± 3.28)                 | 0.6 (± 3.57)  | -0.5 (± 2.97)                     | -0.7 (± 2.94)                                   |
| 2nd App Prior to patch[N=72;34;60;14]  | -1.1 (± 2.82)                 | -0.7 (± 3.01)   | -0.6 (± 3.07)                     | -2.1 (± 2.4)                                    |
| 2nd App 4 weeks after[N=60;24;54;13]   | -0.8 (± 3.16)                 | -0.3 (± 3.43)   | -1.3 (± 3.13)                     | -1.8 (± 2.62)                                   |
| 3rd App Prior to patch[N=46;21;49;11]  | -0.7 (± 2.99)                 | -0.2 (± 2.68)   | -1 (± 3.11)                       | -1.5 (± 2.77)                                   |
| 3rd App 4 weeks after[N=43;13;44;11]   | -0.6 (± 2.95)                 | -0.9 (± 3.8)  | -0.9 (± 3.37)                     | -1 (± 3.1)                                      |
| 4th App Prior to patch[N=30;11;36;8]   | -1.1 (± 3.03)                 | -2.3 (± 3.2)  | -1.6 (± 3.21)                     | -1.1 (± 2.1)                                    |
| 4th App 4 weeks after[N=24;12;33;8]    | -0.3 (± 3.03)                 | -0.3 (± 3.98)   | -0.7 (± 2.8)                      | -0.5 (± 1.6)                                    |
| 5th App Prior to patch[N=19;8;16;5]    | -1.3 (± 3.07)                 | 0.5 (± 4.21)  | -1.6 (± 3.61)                     | -0.6 (± 1.67)                                   |
| 5th App 4 weeks after[N=16;7;12;6]     | -1.3 (± 2.89)                 | 0.7 (± 4.5)   | -0.7 (± 4.01)                     | -1.7 (± 3.39)                                   |
| 6th App Prior to patch[N=5;0;6;3]      | -0.4 (± 4.56)                 | 0 (± 0)   | 2.5 (± 3.02)                      | -1.3 (± 2.89)                                   |
| 6th App 4 weeks after[N=4;0;5;3]       | -1.8 (± 3.86)                 | 0 (± 0)   | 1.2 (± 4.02)                      | -1.3 (± 0.58)                                   |
| Last App Prior to patch[N=73;38;64;13] | -0.6 (± 2.91)                 | -0.7 (± 2.78)   | -1 (± 3.45)                       | -1.5 (± 2.4)                                    |
| Last App 4 weeks after[N=74;47;78;16]  | -0.5 (± 3.27)                 | -0.1 (± 3.5)  | -0.8 (± 3.54)                     | -1 (± 3.16)                                     |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline WPAI:NP (Work Productivity and Activity Impairment Questionnaire )Items 2-6 Scores(SAF)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline WPAI:NP (Work Productivity and Activity Impairment Questionnaire )Items 2-6 Scores(SAF) |
|-----------------|--|

End point description:

The WPAI:NP is a self-report scale developed for the assessment of work productivity and activity impairment related to neuropathic pain. It contains 6 items. The 1st item asks if the patient is currently working. Items 2 to 4 ask for responses in terms of the number of hours during the past 7 days associated with various activities. Items 5 and 6 are rated on a 10-point Likert-type scale ranging from "problem had no effect on my work/daily activities" to "problem completely prevented me from doing my work/daily activities". Safety Analysis Set (SAF) was used for analysis and data represented shows change from baseline represented as subject mean of all applications to questions 2-6.

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

End point timeframe:

Baseline to End of Treatment [EOT].

| End point values                              | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|---|-------------------------------|---|-----------------------------------|---|
| Subject group type                            | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                   | 107                           | 80  | 99                                | 20  |
| Units: Number                                 |                               |   |                                   |   |
| arithmetic mean (standard deviation)          |                               |   |                                   |   |
| Q2 Mean All App Prior to patch[N=6;11;27;5]   | -5 (± 10.61)                  | -4 (± 9.66)   | -1.4 (± 8.69)                     | 6.5 (± 6.59)                                    |
| Q2 Mean All App 4 weeks after [N=8;15;34;5]   | -1.4 (± 12.56)                | 4.6 (± 37.99)   | -1.2 (± 14.21)                    | 5.7 (± 8.69)                                    |
| Q3 Mean All App Prior to patch[N=6;11;27;5]   | -2 (± 15.27)                  | -0.5 (± 1.98)   | -1.2 (± 6.6)                      | 3 (± 6.71)                                      |
| Q3 Mean All App 4 weeks after[N=8;15;34;5]    | -0.9 (± 17.32)                | 3.9 (± 14.59)   | 4.6 (± 16.8)                      | 5.8 (± 6.52)                                    |
| Q4 Mean All App Prior to patch[N=6;11;27;5]   | -1.8 (± 17.15)                | -3.7 (± 14.92)  | 1.9 (± 9.79)                      | 2.3 (± 3.72)                                    |
| Q4 Mean All App 4 weeks after[N=8;15;34;5]    | 4.1 (± 12.76)                 | -6.9 (± 24.01)  | -2.2 (± 20.98)                    | 4 (± 14.25)                                     |
| Q5 Mean All App Prior to patch[N=6;8;23;4]    | -0.9 (± 0.82)                 | -0.4 (± 0.65)   | -0.7 (± 1.26)                     | -1.3 (± 1.7)                                    |
| Q5 Mean all App 4 weeks after[N=8;12;27;4]    | -0.6 (± 0.71)                 | -0.9 (± 1.29)   | -0.8 (± 1.74)                     | -1.8 (± 3.25)                                   |
| Q6 Mean All App Prior to patch[N=74;39;66;14] | -0.6 (± 1.59)                 | -0.6 (± 1.1)  | -0.8 (± 1.41)                     | -0.6 (± 0.97)                                   |

|  |               |               |               |               |
|--|---------------|---------------|---------------|---------------|
| Q6 Mean All App 4 weeks after[N=86;55;86;16] | -0.5 (± 2.44) | -0.9 (± 1.76) | -1.2 (± 2.27) | -0.8 (± 1.33) |
|--|---------------|---------------|---------------|---------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Self-assessment of Treatment (SAT) (SAF)

|  |  |
|--|--|
| End point title  | Self-assessment of Treatment (SAT) (SAF) |
| End point description:   |  |
| Participants answered a SAT questionnaire at week 26 (if applicable) and the planned or early termination visit. The SAT assesses treatment satisfaction by using a 5-point Likert-type scale ranging from -2 (a strong negative response) to 2 (a strong positive response); zero indicates a neutral response. The questionnaire contains each of the following questions: 1. How do you assess your pain level after treatment in this study? 2. How do you assess your activity level after treatment in this study? 3. How has your quality of life changed after treatment in this study? 4. Would you undergo this treatment again? 5. How do you compare the treatment you received in this study to previous medication or therapies for your pain?. Data was represented by counts in combined categories [Worse: (-2) + (-1)] [Not Better or Worse: (-2) + (-1) + (0)] and [Better: (1) + (2)]. |  |
| End point type   | Secondary                                |
| End point timeframe:   |  |
| Baseline to End of Treatment (EOT)   |  |

| End point values                                   | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|--|-------------------------------|---|-----------------------------------|---|
| Subject group type                                 | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                        | 107                           | 80  | 99                                | 20  |
| Units: Number of participants                      |                               |   |                                   |   |
| number (not applicable)                            |                               |   |                                   |   |
| Pain Level [Worse] [N=71;48;65;17]                 | 7                             | 6   | 10                                | 2   |
| Pain Level [Not Better or Worse] [N=71;48;65;17]   | 26                            | 20  | 23                                | 8   |
| Pain Level [Better] [N=71;48;65;17]                | 38                            | 22  | 32                                | 7   |
| Activity Level [Worse] [N=71;48;65;17]             | 13                            | 10  | 12                                | 2   |
| Activity Level[Not Better or Worse][N=71;48;65;17] | 38                            | 23  | 34                                | 10  |
| Activity Level [Better] [N=71;48;65;17]            | 20                            | 15  | 19                                | 5   |
| Quality of Life[Worse][N=71;48;65;17]              | 6                             | 5   | 6                                 | 0   |
| Quality of Life[Not Better orWorse][N=71;48;65;17] | 40                            | 27  | 28                                | 11  |
| Quality of Life[Better][N=71;48;65;17]             | 25                            | 16  | 31                                | 6   |
| Treatment again[Worse][N=71;48;65;17]              | 22                            | 16  | 22                                | 9   |
| Treatment again[Not Better orWorse][N=71;48;65;17] | 14                            | 7   | 10                                | 0   |
| Treatment again[Better][N=71;48;65;17]             | 35                            | 25  | 33                                | 8   |

|  |    |    |    |   |
|--|----|----|----|---|
| Compare treatment[Worse][N=71;48;65;17]            | 15 | 8  | 15 | 4 |
| Compare treatment[Not Better Worse][N=71;48;65;17] | 24 | 20 | 14 | 7 |
| Compare treatment[Better][N=71;48;65;17]           | 32 | 20 | 36 | 6 |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Use of Concomitant Pain Medication following Patch Application(SAF)

|                 |   |
|-----------------|---|
| End point title | Use of Concomitant Pain Medication following Patch Application(SAF) |
|-----------------|---|

End point description:

Concomitant medication use was assessed throughout the study, from Baseline to End of Treatment or early termination visit. Classes of interest were: chronic medication for neuropathic pain, antidepressants, antiepileptic drugs, and opioids. Data presented reflects concomitant medication post-application used on days 1 through 5 after patch application.

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

End point timeframe:

Baseline to End of Treatment[EOT]

| End point values                                | PHN [Post-herpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-traumatic Nerve Injury] | Other type of Peripheral Neuropathic Pain [PNP] |
|---|-------------------------------|---|-----------------------------------|---|
| Subject group type                              | Reporting group               | Reporting group   | Reporting group                   | Reporting group                                 |
| Number of subjects analysed                     | 107                           | 80  | 99                                | 20  |
| Units: Number of Participants                   |                               |   |                                   |   |
| number (not applicable)                         |                               |   |                                   |   |
| ANALGESICS                                      | 42                            | 23  | 36                                | 5   |
| ANESTHETICS                                     | 4                             | 1   | 5                                 | 0   |
| ANTIEPILEPTICS                                  | 1                             | 1   | 0                                 | 0   |
| ANTIHISTAMINES FOR SYSTEMIC USE                 | 1                             | 1   | 0                                 | 0   |
| ANTIINFLAMMATORY AND ANTIRHEUMATIC              | 11                            | 2   | 8                                 | 0   |
| ANTIPRURITICS, INCL ANTIHISTAMINES, ANESTHETICS | 0                             | 1   | 0                                 | 0   |
| CARDIAC THERAPY                                 | 3                             | 3   | 2                                 | 0   |
| COUGH AND COLD PREPARATIONS                     | 0                             | 4   | 1                                 | 0   |
| DRUGS FOR CONSTIPATION                          | 3                             | 1   | 0                                 | 0   |
| EMOLLIENTS AND PROTECTIVES                      | 3                             | 1   | 0                                 | 0   |
| OPHTHALMOLOGICALS                               | 8                             | 1   | 6                                 | 0   |
| OTHER DERMATOLOGICAL PREPARATIONS               | 7                             | 1   | 6                                 | 0   |
| OTHER GYNECOLOGICALS                            | 3                             | 2   | 2                                 | 0   |
| OTOLOGICALS                                     | 0                             | 1   | 0                                 | 0   |
| STOMATOLOGICAL PREPARATIONS                     | 10                            | 1   | 6                                 | 0   |

|   |    |   |   |   |
|---|----|---|---|---|
| THROAT PREPARATIONS                             | 0  | 1 | 0 | 0 |
| TOPICAL PRODUCTS FOR JOINT AND<br>MUSCULAR PAIN | 10 | 2 | 8 | 0 |
| UNSPECIFIED HERBAL AND<br>TRADITIONAL MEDICINE  | 3  | 1 | 0 | 0 |
| UROLOGICALS                                     | 0  | 1 | 0 | 0 |
| VASOPROTECTIVES                                 | 0  | 1 | 0 | 0 |

## Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are summarized as counts over the entire study and by patch application. Within each of these time periods AEs are summarized overall and by individual neuropathic diagnosis. Only TEAEs were analyzed in this study.

Adverse event reporting additional description:

Each AE was categorized based on which patch applications it occurred between (i.e., between 1st and 2nd, between 2nd and 3rd, etc., or after last). Each AE was additionally categorized based on whether it occurred within 7 days after a patch application, and also based on whether it occurred more than 7 days after a patch application.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 13.1.  |

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | PHN [Postherpetic Neuralgia] |
|-----------------------|------------------------------|

Reporting group description: -

|                       |   |
|-----------------------|---|
| Reporting group title | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] |
|-----------------------|---|

Reporting group description: -

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | PNI [Post-Traumatic Nerve Injury] |
|-----------------------|-----------------------------------|

Reporting group description: -

|                       |   |
|-----------------------|---|
| Reporting group title | Other type of Peripheral Neuropathic Pain [PNP] |
|-----------------------|---|

Reporting group description: -

| <b>Serious adverse events</b>                     | PHN [Postherpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-Traumatic Nerve Injury] |
|---|------------------------------|---|-----------------------------------|
| Total subjects affected by serious adverse events |                              |   |                                   |
| subjects affected / exposed                       | 14 / 107 (13.08%)            | 8 / 80 (10.00%)   | 13 / 99 (13.13%)                  |
| number of deaths (all causes)                     | 2                            | 1   | 0                                 |
| number of deaths resulting from adverse events    |                              |   |                                   |
| Vascular disorders                                |                              |   |                                   |
| Aortic dissection                                 |                              |   |                                   |
| subjects affected / exposed                       | 0 / 107 (0.00%)              | 1 / 80 (1.25%)  | 0 / 99 (0.00%)                    |
| occurrences causally related to treatment / all   | 0 / 0                        | 0 / 1   | 0 / 0                             |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0   | 0 / 0                             |
| Deep vein thrombosis                              |                              |   |                                   |
| subjects affected / exposed                       | 0 / 107 (0.00%)              | 0 / 80 (0.00%)  | 1 / 99 (1.01%)                    |
| occurrences causally related to treatment / all   | 0 / 0                        | 0 / 0   | 0 / 1                             |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0   | 0 / 0                             |
| Peripheral ischaemia                              |                              |   |                                   |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed   | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Surgical and medical procedures                                     |                 |                |                |
| Chemotherapy  |                 |                |                |
| subjects affected / exposed   | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Hip arthroplasty  |                 |                |                |
| subjects affected / exposed   | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Hip surgery   |                 |                |                |
| subjects affected / exposed   | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Knee arthroplasty   |                 |                |                |
| subjects affected / exposed   | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Spinal laminectomy  |                 |                |                |
| subjects affected / exposed   | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                |                |
| B-cell unclassifiable lymphoma high grade                           |                 |                |                |
| subjects affected / exposed   | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Basal cell carcinoma  |                 |                |                |
| subjects affected / exposed   | 2 / 107 (1.87%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| Squamous cell carcinoma<br>subjects affected / exposed  | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all           | 0 / 1           | 0 / 0          | 0 / 0          |
| General disorders and administration<br>site conditions |                 |                |                |
| Chest pain  |                 |                |                |
| subjects affected / exposed                             | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Malaise   |                 |                |                |
| subjects affected / exposed                             | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Pyrexia   |                 |                |                |
| subjects affected / exposed                             | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Psychiatric disorders                                   |                 |                |                |
| Suicidal ideation                                       |                 |                |                |
| subjects affected / exposed                             | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural<br>complications       |                 |                |                |
| Hip fracture  |                 |                |                |
| subjects affected / exposed                             | 2 / 107 (1.87%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Lumbar vertebral fracture                               |                 |                |                |
| subjects affected / exposed                             | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0          | 0 / 0          |
| Investigations  |                 |                |                |
| Biopsy  |                 |                |                |
| subjects affected / exposed                             | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Biopsy bone                                     |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                 |                |                |
| Bradycardia                                     |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Cardiac failure                                 |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Ventricular tachycardia                         |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                 |                |                |
| Chronic obstructive pulmonary disease           |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Haemoptysis                                     |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                 |                |                |
| Cerebral haemorrhage                            |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| Complex regional pain syndrome                  |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Dizziness                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Neuralgia                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Partial seizures                                |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                 |                |                |
| Abdominal pain upper                            |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Ascites   |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastrointestinal ulcer haemorrhage              |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Nausea  |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Subileus  |                 |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                 |                |                |
| Bladder disorder                                |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Haematuria                                      |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Nephrolithiasis                                 |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Renal colic                                     |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                 |                |                |
| Arthralgia                                      |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Fistula   |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Mobility decreased                              |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| Muskuloskeletal chest pain                      |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Osteoarthritis                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                 |                |                |
| Hypothyroidism                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                 |                |                |
| Bronchitis                                      |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 0 / 80 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 0 / 80 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| HIV peripheral neuropathy                       |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Influenza                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection               |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| Pneumonia                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 2 / 80 (2.50%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 0          |
| Pyelonephritis                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Sepsis  |                 |                |                |
| subjects affected / exposed                     | 1 / 107 (0.93%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Urosepsis                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Viral pericarditis                              |                 |                |                |
| subjects affected / exposed                     | 0 / 107 (0.00%) | 1 / 80 (1.25%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |

|   |   |  |  |
|---|---|--|--|
| <b>Serious adverse events</b>                     | Other type of Peripheral Neuropathic Pain [PNP] |  |  |
| Total subjects affected by serious adverse events |   |  |  |
| subjects affected / exposed                       | 2 / 20 (10.00%)                                 |  |  |
| number of deaths (all causes)                     | 0   |  |  |



|   |                |  |  |
|---|----------------|--|--|
| number of deaths resulting from adverse events  |                |  |  |
| <b>Vascular disorders</b>                       |                |  |  |
| Aortic dissection                               |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Deep vein thrombosis                            |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Peripheral ischaemia                            |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Surgical and medical procedures</b>          |                |  |  |
| Chemotherapy                                    |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hip arthroplasty                                |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hip surgery                                     |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Knee arthroplasty                               |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Spinal laminectomy                              |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |  |  |
| B-cell unclassifiable lymphoma high grade                           |                |  |  |
| subjects affected / exposed   | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Basal cell carcinoma  |                |  |  |
| subjects affected / exposed   | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Squamous cell carcinoma   |                |  |  |
| subjects affected / exposed   | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| General disorders and administration site conditions                |                |  |  |
| Chest pain  |                |  |  |
| subjects affected / exposed   | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Malaise   |                |  |  |
| subjects affected / exposed   | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Pyrexia   |                |  |  |
| subjects affected / exposed   | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Psychiatric disorders   |                |  |  |
| Suicidal ideation   |                |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Injury, poisoning and procedural                                    |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| complications                                   |                |  |  |
| Hip fracture                                    |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lumbar vertebral fracture                       |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Biopsy  |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Biopsy bone                                     |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Bradycardia                                     |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac failure                                 |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ventricular tachycardia                         |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Chronic obstructive pulmonary disease           |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |

|   |                |  |  |
|---|----------------|--|--|
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haemoptysis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Cerebral haemorrhage                            |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Complex regional pain syndrome                  |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dizziness                                       |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neuralgia                                       |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Partial seizures                                |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain upper                            |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites   |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |

|   |                |  |  |
|---|----------------|--|--|
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal ulcer haemorrhage              |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Subileus  |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Bladder disorder                                |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haematuria                                      |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nephrolithiasis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal colic                                     |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Fistula   |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Mobility decreased                              |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Muskuloskeletal chest pain                      |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Osteoarthritis                                  |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Endocrine disorders                             |                |  |  |
| Hypothyroidism                                  |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bronchitis                                      |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| HIV peripheral neuropathy                       |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Influenza                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pyelonephritis                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis  |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Upper respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Urinary tract infection                         |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Urosepsis                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Viral pericarditis                              |                |  |  |
| subjects affected / exposed                     | 0 / 20 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | PHN [Postherpetic Neuralgia] | HIV-AN [Human Immunodeficiency Virus-associated Neuropathy] | PNI [Post-Traumatic Nerve Injury] |
|---|------------------------------|---|-----------------------------------|
| Total subjects affected by non-serious adverse events |                              |   |                                   |
| subjects affected / exposed                           | 77 / 107 (71.96%)            | 44 / 80 (55.00%)  | 76 / 99 (76.77%)                  |
| Vascular disorders                                    |                              |   |                                   |
| Hypertension  |                              |   |                                   |
| subjects affected / exposed                           | 6 / 107 (5.61%)              | 1 / 80 (1.25%)  | 3 / 99 (3.03%)                    |
| occurrences (all)                                     | 8                            | 1   | 3                                 |
| Surgical and medical procedures                       |                              |   |                                   |
| Haemangioma removal                                   |                              |   |                                   |
| subjects affected / exposed                           | 0 / 107 (0.00%)              | 0 / 80 (0.00%)  | 0 / 99 (0.00%)                    |
| occurrences (all)                                     | 0                            | 0   | 0                                 |
| General disorders and administration site conditions  |                              |   |                                   |
| Application site erythema                             |                              |   |                                   |
| subjects affected / exposed                           | 24 / 107 (22.43%)            | 2 / 80 (2.50%)  | 19 / 99 (19.19%)                  |
| occurrences (all)                                     | 42                           | 3   | 42                                |
| Application site pain                                 |                              |   |                                   |
| subjects affected / exposed                           | 46 / 107 (42.99%)            | 21 / 80 (26.25%)  | 40 / 99 (40.40%)                  |
| occurrences (all)                                     | 110                          | 34  | 92                                |
| Influenza like illness                                |                              |   |                                   |
| subjects affected / exposed                           | 1 / 107 (0.93%)              | 1 / 80 (1.25%)  | 0 / 99 (0.00%)                    |
| occurrences (all)                                     | 1                            | 1   | 0                                 |
| Pain  |                              |   |                                   |
| subjects affected / exposed                           | 13 / 107 (12.15%)            | 6 / 80 (7.50%)  | 16 / 99 (16.16%)                  |
| occurrences (all)                                     | 29                           | 6   | 35                                |
| Psychiatric disorders                                 |                              |   |                                   |



|   |  |  |   |
|---|--|--|---|
| Middle insomnia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 107 (0.00%)<br>0   | 0 / 80 (0.00%)<br>0  | 0 / 99 (0.00%)<br>0   |
| Injury, poisoning and procedural complications<br>Muscle strain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 107 (0.00%)<br>0   | 0 / 80 (0.00%)<br>0  | 0 / 99 (0.00%)<br>0   |
| Investigations<br>Biopsy skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Blood iron decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 107 (0.00%)<br>0<br><br>0 / 107 (0.00%)<br>0<br><br>1 / 107 (0.93%)<br>1   | 1 / 80 (1.25%)<br>1<br><br>0 / 80 (0.00%)<br>0<br><br>0 / 80 (0.00%)<br>0  | 0 / 99 (0.00%)<br>0<br><br>0 / 99 (0.00%)<br>0<br><br>0 / 99 (0.00%)<br>0   |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 1 / 107 (0.93%)<br>1   | 4 / 80 (5.00%)<br>4  | 2 / 99 (2.02%)<br>2   |
| Nervous system disorders<br>Allodynia<br>subjects affected / exposed<br>occurrences (all)<br><br>Burning sensation<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed | 1 / 107 (0.93%)<br>1<br><br>11 / 107 (10.28%)<br>29<br><br>1 / 107 (0.93%)<br>1<br><br>4 / 107 (3.74%)<br>5<br><br>0 / 107 (0.00%) | 0 / 80 (0.00%)<br>0<br><br>8 / 80 (10.00%)<br>13<br><br>0 / 80 (0.00%)<br>0<br><br>1 / 80 (1.25%)<br>1<br><br>2 / 80 (2.50%) | 0 / 99 (0.00%)<br>0<br><br>20 / 99 (20.20%)<br>51<br><br>0 / 99 (0.00%)<br>0<br><br>6 / 99 (6.06%)<br>7<br><br>1 / 99 (1.01%) |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| occurrences (all)                               | 0                 | 2                | 2                |
| Gastrointestinal disorders                      |                   |                  |                  |
| Abdominal pain                                  |                   |                  |                  |
| subjects affected / exposed                     | 0 / 107 (0.00%)   | 0 / 80 (0.00%)   | 3 / 99 (3.03%)   |
| occurrences (all)                               | 0                 | 0                | 3                |
| Abdominal pain upper                            |                   |                  |                  |
| subjects affected / exposed                     | 0 / 107 (0.00%)   | 1 / 80 (1.25%)   | 0 / 99 (0.00%)   |
| occurrences (all)                               | 0                 | 1                | 0                |
| Gastrointestinal disorder                       |                   |                  |                  |
| subjects affected / exposed                     | 0 / 107 (0.00%)   | 0 / 80 (0.00%)   | 0 / 99 (0.00%)   |
| occurrences (all)                               | 0                 | 0                | 0                |
| Gastrooesophageal reflux disease                |                   |                  |                  |
| subjects affected / exposed                     | 0 / 107 (0.00%)   | 0 / 80 (0.00%)   | 0 / 99 (0.00%)   |
| occurrences (all)                               | 0                 | 0                | 0                |
| Nausea  |                   |                  |                  |
| subjects affected / exposed                     | 4 / 107 (3.74%)   | 1 / 80 (1.25%)   | 8 / 99 (8.08%)   |
| occurrences (all)                               | 5                 | 1                | 8                |
| Vomiting  |                   |                  |                  |
| subjects affected / exposed                     | 2 / 107 (1.87%)   | 1 / 80 (1.25%)   | 2 / 99 (2.02%)   |
| occurrences (all)                               | 3                 | 1                | 2                |
| Skin and subcutaneous tissue disorders          |                   |                  |                  |
| Erythema  |                   |                  |                  |
| subjects affected / exposed                     | 29 / 107 (27.10%) | 1 / 80 (1.25%)   | 29 / 99 (29.29%) |
| occurrences (all)                               | 79                | 1                | 77               |
| Musculoskeletal and connective tissue disorders |                   |                  |                  |
| Arthralgia                                      |                   |                  |                  |
| subjects affected / exposed                     | 3 / 107 (2.80%)   | 0 / 80 (0.00%)   | 3 / 99 (3.03%)   |
| occurrences (all)                               | 3                 | 0                | 4                |
| Back pain                                       |                   |                  |                  |
| subjects affected / exposed                     | 3 / 107 (2.80%)   | 4 / 80 (5.00%)   | 2 / 99 (2.02%)   |
| occurrences (all)                               | 3                 | 4                | 2                |
| Pain in extremity                               |                   |                  |                  |
| subjects affected / exposed                     | 2 / 107 (1.87%)   | 11 / 80 (13.75%) | 5 / 99 (5.05%)   |
| occurrences (all)                               | 2                 | 19               | 7                |
| Metabolism and nutrition disorders              |                   |                  |                  |

|  |                      |                     |                     |
|--|----------------------|---------------------|---------------------|
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)      | 1 / 107 (0.93%)<br>1 | 0 / 80 (0.00%)<br>0 | 1 / 99 (1.01%)<br>1 |
| Vitamin B12 deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 107 (0.00%)<br>0 | 0 / 80 (0.00%)<br>0 | 0 / 99 (0.00%)<br>0 |
| Infections and infestations  |                      |                     |                     |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)             | 2 / 107 (1.87%)<br>2 | 0 / 80 (0.00%)<br>0 | 2 / 99 (2.02%)<br>2 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)              | 2 / 107 (1.87%)<br>2 | 0 / 80 (0.00%)<br>0 | 7 / 99 (7.07%)<br>8 |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 107 (0.93%)<br>1 | 0 / 80 (0.00%)<br>0 | 0 / 99 (0.00%)<br>0 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)        | 2 / 107 (1.87%)<br>2 | 0 / 80 (0.00%)<br>0 | 4 / 99 (4.04%)<br>5 |

|   |  |  |  |
|---|--|--|--|
| <b>Non-serious adverse events</b>   | Other type of<br>Peripheral<br>Neuropathic Pain<br>[PNP] |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 17 / 20 (85.00%)   |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0                                      |  |  |
| Surgical and medical procedures<br>Haemangioma removal<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1                                      |  |  |
| General disorders and administration<br>site conditions<br>Application site erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Application site pain | 6 / 20 (30.00%)<br>10                                    |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza like illness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>5 / 20 (25.00%)</p> <p>15</p> <p>1 / 20 (5.00%)</p> <p>1</p> <p>8 / 20 (40.00%)</p> <p>16</p> |  |  |
| <p>Psychiatric disorders</p> <p>Middle insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 20 (5.00%)</p> <p>1</p>   |  |  |
| <p>Injury, poisoning and procedural complications</p> <p>Muscle strain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 20 (5.00%)</p> <p>1</p>   |  |  |
| <p>Investigations</p> <p>Biopsy skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood iron decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p> <p>1 / 20 (5.00%)</p> <p>1</p>     |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>0 / 20 (0.00%)</p> <p>0</p>   |  |  |
| <p>Nervous system disorders</p> <p>Allodynia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Burning sensation</p> <p>subjects affected / exposed</p>   | <p>1 / 20 (5.00%)</p> <p>1</p> <p>6 / 20 (30.00%)</p>  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| occurrences (all)                               | 12              |  |  |
| Dizziness                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Neuralgia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Paraesthesia                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Abdominal pain upper                            |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Gastrointestinal disorder                       |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Gastrooesophageal reflux disease                |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 3 / 20 (15.00%) |  |  |
| occurrences (all)                               | 6               |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 2 / 20 (10.00%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Erythema  |                 |  |  |
| subjects affected / exposed                     | 3 / 20 (15.00%) |  |  |
| occurrences (all)                               | 10              |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 20 (5.00%)<br>2 |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)      | 1 / 20 (5.00%)<br>1 |  |  |
| Metabolism and nutrition disorders   |                     |  |  |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)      | 1 / 20 (5.00%)<br>1 |  |  |
| Vitamin B12 deficiency<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1 |  |  |
| Infections and infestations  |                     |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1 |  |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)              | 0 / 20 (0.00%)<br>0 |  |  |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| The original study protocol for this study was dated 30 Apr 2010. There were 4 non-substantial amendments to the study protocol, dated 22 Oct 2010, 01 Mar 2011, 02 Dec 2011, and 28 May 2013. |
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Notes: