



## Clinical trial results:

### A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of the Safety and Efficacy of a Single Treatment of AGN-214868 in Patients With Postherpetic Neuralgia

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-002240-24    |
| Trial protocol           | DE AT PL          |
| Global end of trial date | 30 September 2015 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 10 November 2016 |
| First version publication date | 10 November 2016 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 214868-007 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01678924 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Allergan plc  |
| Sponsor organisation address | 2525 Dupont Drive, Irvine, United States, 92623-9534  |
| Public contact               | Therapeutic Area Head, Allergan plc, +1 714-246-4500, clinicaltrials@allergan.com                   |
| Scientific contact           | Allergan Ltd. EU Regulatory Affairs, Allergan Ltd., +44 1628494 444, ml-eu_reg_affairs@allergan.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 22 December 2015  |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 30 September 2015 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and efficacy of AGN-214868 compared with placebo in the treatment of postherpetic neuralgia (PHN).

Protection of trial subjects:

This trial had investigator meetings at the outset to review all protocol procedures and investigator responsibilities under Good Clinical Practice (GCP). At the meeting, the conduct of the trial was explained and instructions were provided to ensure accuracy and consistency in data collection. This trial was conducted in conformance with GCP standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 16 January 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 75        |
| Country: Number of subjects enrolled | Austria: 7        |
| Country: Number of subjects enrolled | Germany: 141      |
| Country: Number of subjects enrolled | United States: 57 |
| Worldwide total number of subjects   | 280               |
| EEA total number of subjects         | 223               |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |     |
|----------------------|-----|
| Adults (18-64 years) | 102 |
| From 65 to 84 years  | 178 |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2 sequential dose cohort study. Patients in cohort 1 were randomized (1:2:2 ratio) to receive a two treatment sessions of AGN 214868 (total dose of either 32.5 or 65 µg) or placebo. Cohort 2 patients randomized (1:1 ratio) to receive a single treatment session

### Pre-assignment

Screening details:

Patients had to be male or female, 18 to 80 years of age at screening with persistent Postherpetic Neuralgia (PHN) with pain present for  $\geq 9$  months (36 weeks) after the onset of a herpes zoster skin rash affecting the cervical, thoracic, lumbar, or sacral dermatomes.

### Period 1

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

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | AGN 214868 130µg |

Arm description:

Single treatment session; total dose given as 65 injections into the area of pain on Day 1

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | AGN 214868      |
| Investigational medicinal product code |                 |
| Other name                             | Senrebotase     |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intradermal use |

Dosage and administration details:

65 injections of 2.0 micrograms/0.1ml into the area of pain on Day 1, for a total dose of 130 micrograms.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | AGN 214868 65µg |
|------------------|-----------------|

Arm description:

Single treatment session; total dose given as 65 injections into the area of pain on Day 1

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | AGN 214868      |
| Investigational medicinal product code |                 |
| Other name                             | Senrebotase     |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intradermal use |

Dosage and administration details:

65 injections of 1.0 micrograms/0.1ml into the area of pain on Day 1 for a total dose of 65 micrograms

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | AGN 214868 32.5µg |
|------------------|-------------------|

Arm description:

Single treatment session; total dose given as 65 injections into the area of pain on Day 1

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                 |
|--|-----------------|
| Investigational medicinal product name | AGN 214868      |
| Investigational medicinal product code |                 |
| Other name                             | Senrebotase     |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intradermal use |

Dosage and administration details:

65 injections of 0.5 micrograms/0.1ml into the area of pain on Day 1 for a total dose of 32.5 micrograms

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Single treatment session; placebo given as 65 injections into the area of pain on Day 1

|  |                 |
|--|-----------------|
| Arm type                               | Placebo         |
| Investigational medicinal product name | Placebo         |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intradermal use |

Dosage and administration details:

65 injections of placebo/0.1ml into the area of pain on Day 1.

| <b>Number of subjects in period 1</b> | AGN 214868 130µg | AGN 214868 65µg | AGN 214868 32.5µg |
|---------------------------------------|------------------|-----------------|-------------------|
| Started                               | 64               | 63              | 30                |
| Completed                             | 54               | 51              | 28                |
| Not completed                         | 10               | 12              | 2                 |
| Consent withdrawn by subject          | -                | 3               | -                 |
| Adverse event, non-fatal              | 1                | 1               | -                 |
| Unable to attend scheduled visits     | -                | -               | -                 |
| Personal Reasons                      | 2                | 2               | 2                 |
| Lost to follow-up                     | -                | 4               | -                 |
| Lack of efficacy                      | 7                | 2               | -                 |

| <b>Number of subjects in period 1</b> | Placebo |
|---------------------------------------|---------|
| Started                               | 123     |
| Completed                             | 105     |
| Not completed                         | 18      |
| Consent withdrawn by subject          | 2       |
| Adverse event, non-fatal              | 1       |
| Unable to attend scheduled visits     | 1       |
| Personal Reasons                      | 7       |
| Lost to follow-up                     | 2       |
| Lack of efficacy                      | 5       |



## Baseline characteristics

### Reporting groups

|  |                   |
|--|-------------------|
| Reporting group title  | AGN 214868 130µg  |
| Reporting group description:   |                   |
| Single treatment session; total dose given as 65 injections into the area of pain on Day 1 |                   |
| Reporting group title  | AGN 214868 65µg   |
| Reporting group description:   |                   |
| Single treatment session; total dose given as 65 injections into the area of pain on Day 1 |                   |
| Reporting group title  | AGN 214868 32.5µg |
| Reporting group description:   |                   |
| Single treatment session; total dose given as 65 injections into the area of pain on Day 1 |                   |
| Reporting group title  | Placebo           |
| Reporting group description:   |                   |
| Single treatment session; placebo given as 65 injections into the area of pain on Day 1    |                   |

| Reporting group values            | AGN 214868 130µg | AGN 214868 65µg | AGN 214868 32.5µg |
|-----------------------------------|------------------|-----------------|-------------------|
| Number of subjects                | 64               | 63              | 30                |
| Age categorical                   |                  |                 |                   |
| Units: Subjects                   |                  |                 |                   |
| Adults (18 to less than 40 years) | 1                | 3               | 1                 |
| Adults (40 to less than 65 years) | 20               | 19              | 12                |
| Adults (65 years and over)        | 43               | 41              | 17                |
| Age continuous                    |                  |                 |                   |
| Units: years                      |                  |                 |                   |
| arithmetic mean                   | 66.6             | 65.3            | 65                |
| standard deviation                | ± 10.47          | ± 12.82         | ± 11.99           |
| Gender categorical                |                  |                 |                   |
| Units: Subjects                   |                  |                 |                   |
| Male                              | 37               | 34              | 13                |
| Female                            | 27               | 29              | 17                |
| Race and Ethnicity                |                  |                 |                   |
| Units: Subjects                   |                  |                 |                   |
| Caucasian                         | 56               | 52              | 26                |
| Black                             | 3                | 4               | 1                 |
| Asian                             | 0                | 2               | 2                 |
| Hispanic                          | 5                | 4               | 1                 |
| Other                             | 0                | 1               | 0                 |
| Weight                            |                  |                 |                   |
| Units: Kilograms                  |                  |                 |                   |
| arithmetic mean                   | 84.9             | 82.3            | 80                |
| standard deviation                | ± 19.15          | ± 17.67         | ± 14.48           |
| Height                            |                  |                 |                   |
| Units: Centimeters                |                  |                 |                   |
| arithmetic mean                   | 169.8            | 167.7           | 169.1             |
| standard deviation                | ± 10.22          | ± 10.98         | ± 8.91            |

| Reporting group values | Placebo | Total |  |
|------------------------|---------|-------|--|
| Number of subjects     | 123     | 280   |  |

|                                       |             |     |  |
|---------------------------------------|-------------|-----|--|
| Age categorical<br>Units: Subjects    |             |     |  |
| Adults (18 to less than 40 years)     | 0           | 5   |  |
| Adults (40 to less than 65 years)     | 46          | 97  |  |
| Adults (65 years and over)            | 77          | 178 |  |
| Age continuous<br>Units: years        |             |     |  |
| arithmetic mean                       | 67          |     |  |
| standard deviation                    | $\pm 8.13$  | -   |  |
| Gender categorical<br>Units: Subjects |             |     |  |
| Male                                  | 50          | 134 |  |
| Female                                | 73          | 146 |  |
| Race and Ethnicity<br>Units: Subjects |             |     |  |
| Caucasian                             | 112         | 246 |  |
| Black                                 | 7           | 15  |  |
| Asian                                 | 1           | 5   |  |
| Hispanic                              | 2           | 12  |  |
| Other                                 | 1           | 2   |  |
| Weight<br>Units: Kilograms            |             |     |  |
| arithmetic mean                       | 78.8        |     |  |
| standard deviation                    | $\pm 17.83$ | -   |  |
| Height<br>Units: Centimeters          |             |     |  |
| arithmetic mean                       | 166.4       |     |  |
| standard deviation                    | $\pm 9.07$  | -   |  |



## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | AGN 214868 130µg                      |
| Reporting group description:  |                                       |
| Single treatment session; total dose given as 65 injections into the area of pain on Day 1  |                                       |
| Reporting group title   | AGN 214868 65µg                       |
| Reporting group description:  |                                       |
| Single treatment session; total dose given as 65 injections into the area of pain on Day 1  |                                       |
| Reporting group title   | AGN 214868 32.5µg                     |
| Reporting group description:  |                                       |
| Single treatment session; total dose given as 65 injections into the area of pain on Day 1  |                                       |
| Reporting group title   | Placebo                               |
| Reporting group description:  |                                       |
| Single treatment session; placebo given as 65 injections into the area of pain on Day 1   |                                       |
| Subject analysis set title  | Intent to Treat population - Cohort 1 |
| Subject analysis set type   | Intention-to-treat                    |
| Subject analysis set description:   |                                       |
| The total modified intent to treat (mITT) population of 279 patients, consists of all randomized patients who received treatment and at least 1 postbaseline weekly average pain intensity score. Cohort 1 includes 154 patients from the mITT population |                                       |
| Subject analysis set title  | Intent to Treat population - Cohort 2 |
| Subject analysis set type   | Intention-to-treat                    |
| Subject analysis set description:   |                                       |
| The total modified intent to treat (mITT) population of 279 patients, consists of all randomized patients who received treatment and at least 1 postbaseline weekly average pain intensity score. Cohort 2 includes 125 patients from the mITT population |                                       |

### Primary: Change from Baseline in Average Pain Intensity Score - Cohort 1

|  |  |
|--|--|
| End point title  | Change from Baseline in Average Pain Intensity Score - Cohort 1 <sup>[1]</sup> |
| End point description:   |  |
| The average pain intensity score at each week was the mean of the daily average pain intensity scores reported in the patient's eDiary during each 7-day period, starting with the day of study treatment injection. patients used the 11-point Likert scale, with anchors at 0 = "no pain" and 10 = "pain as bad as you can imagine" Baseline was defined as the mean of the daily average pain intensity scores reported during the baseline period for the 7 days immediately prior to the treatment. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Baseline to Week 12  |  |

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868 65µg          | AGN 214868 32.5µg       | Placebo                  |  |
|--|--------------------------|-------------------------|--------------------------|--|
| Subject group type                           | Reporting group          | Reporting group         | Reporting group          |  |
| Number of subjects analysed                  | 63                       | 30                      | 123                      |  |
| Units: units on a scale                      |                          |                         |                          |  |
| least squares mean (confidence interval 95%) |                          |                         |                          |  |
| Week 1                                       | -0.88 (-1.249 to -0.538) | -1.02 (-1.38 to -0.587) | -1.11 (-1.425 to -0.808) |  |

|         |                          |                          |                          |  |
|---------|--------------------------|--------------------------|--------------------------|--|
| Week 2  | -1.33 (-1.746 to -0.968) | -1.56 (-1.963 to -1.017) | -1.57 (-1.97 to -1.174)  |  |
| Week 3  | -1.66 (-2.143 to -1.203) | -1.93 (-2.426 to -1.227) | -1.84 (-2.248 to -1.388) |  |
| Week 4  | -1.78 (-2.277 to -1.31)  | -2.2 (-2.721 to -1.432)  | -1.98 (-2.423 to -1.482) |  |
| Week 5  | -1.83 (-2.321 to -1.384) | -2.19 (-2.675 to -1.379) | -2.1 (-2.557 to -1.554)  |  |
| Week 6  | -1.97 (-2.442 to -1.495) | -2.07 (-2.597 to -1.297) | -2.34 (-2.755 to -1.697) |  |
| Week 7  | -2 (-2.481 to -1.506)    | -2.08 (-2.572 to -1.328) | -2.32 (-2.746 to -1.673) |  |
| Week 8  | -2.11 (-2.591 to -1.618) | -2.02 (-2.53 to -1.263)  | -2.4 (-2.825 to -1.745)  |  |
| Week 9  | -2.21 (-2.66 to -1.701)  | -2.15 (-2.682 to -1.352) | -2.52 (-2.805 to -1.733) |  |
| Week 10 | -2.28 (-2.679 to -1.674) | -2.29 (-2.812 to -1.481) | -2.48 (-2.743 to -1.634) |  |
| Week 11 | -2.27 (-2.684 to -1.672) | -2.46 (-2.996 to -1.57)  | -2.56 (-2.807 to -1.724) |  |
| Week 12 | -2.2 (-2.626 to -1.6)    | -2.53 (-3.061 to -1.605) | -2.65 (-2.886 to -1.783) |  |

## Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | 65ug vs. 32.5ug - Week 1            |
| Comparison groups                       | AGN 214868 65µg v AGN 214868 32.5µg |
| Number of subjects included in analysis | 93                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.633 <sup>[2]</sup>              |
| Method                                  | Type 3 sum of squares               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | 0.14                                |
| Confidence interval                     |                                     |
| level                                   | 90 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.343                              |
| upper limit                             | 0.623                               |

Notes:

[2] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | 65ug vs. Placebo - Week 1      |
| Comparison groups                       | AGN 214868 65µg v Placebo      |
| Number of subjects included in analysis | 186                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.307 <sup>[3]</sup>         |
| Method                                  | Type 3 sum of squares          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.23                           |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | -0.144  |
| upper limit         | 0.613   |

Notes:

[3] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | 32.5ug vs. Placebo - Week 1    |
| Comparison groups                       | AGN 214868 32.5µg v Placebo    |
| Number of subjects included in analysis | 153                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.744 <sup>[4]</sup>         |
| Method                                  | Type 3 sum of squares          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.09                           |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.384                         |
| upper limit                             | 0.574                          |

Notes:

[4] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | 65ug vs. 32.5ug - week 12           |
| Comparison groups                       | AGN 214868 65µg v AGN 214868 32.5µg |
| Number of subjects included in analysis | 93                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.495 <sup>[5]</sup>              |
| Method                                  | Type 3 sum of squares               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | 0.33                                |
| Confidence interval                     |                                     |
| level                                   | 90 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.473                              |
| upper limit                             | 1.139                               |

Notes:

[5] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | 65ug vs. Placebo - week 12 |
| Comparison groups                 | AGN 214868 65µg v Placebo  |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 186                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.25 <sup>[6]</sup>          |
| Method                                  | Type 3 sum of squares          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.45                           |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.196                         |
| upper limit                             | 1.101                          |

Notes:

[6] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | 32.5ug vs. Placebo - week 12   |
| Comparison groups                       | AGN 214868 32.5µg v Placebo    |
| Number of subjects included in analysis | 153                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.806 <sup>[7]</sup>         |
| Method                                  | Type 3 sum of squares          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.12                           |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.684                         |
| upper limit                             | 0.922                          |

Notes:

[7] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

### **Primary: Change From Baseline in Average Pain Intensity Score - Cohort 2**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Average Pain Intensity Score - Cohort 2 <sup>[8]</sup> |
|-----------------|--|

End point description:

The average pain intensity score at each week was the mean of the daily average pain intensity scores reported in the patient's eDiary during each 7-day period, starting with the day of study treatment injection. patients used the 11-point Likert scale, with anchors at 0 = "no pain" and 10 = "pain as bad as you can imagine" Baseline was defined as the mean of the daily average pain intensity scores reported during the baseline period for the 7 days immediately prior to the treatment.

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

End point timeframe:

Baseline to Week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>130µg      | Placebo                  |  |  |
|--|--------------------------|--------------------------|--|--|
| Subject group type                           | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed                  | 64                       | 61                       |  |  |
| Units: units on a scale                      |                          |                          |  |  |
| least squares mean (confidence interval 95%) |                          |                          |  |  |
| Week 1                                       | -0.78 (-1.093 to -0.451) | -0.88 (-1.19 to -0.492)  |  |  |
| Week 2                                       | -1.12 (-1.508 to -0.701) | -1.37 (-1.791 to -0.799) |  |  |
| Week 3                                       | -1.45 (-1.788 to -0.952) | -1.65 (-2.064 to -1.057) |  |  |
| Week 4                                       | -1.62 (-1.934 to -1.072) | -1.9 (-2.344 to -1.269)  |  |  |
| Week 5                                       | -1.88 (-2.202 to -1.301) | -1.88 (-2.366 to -1.257) |  |  |
| Week 6                                       | -2.04 (-2.226 to -1.305) | -1.9 (-2.339 to -1.235)  |  |  |
| Week 7                                       | -2.14 (-2.345 to -1.352) | -1.9 (-2.352 to -1.225)  |  |  |
| Week 8                                       | -2.29 (-2.405 to -1.404) | -1.96 (-2.412 to -1.27)  |  |  |
| Week 9                                       | -2.35 (-2.493 to -1.497) | -2 (-2.457 to -1.293)    |  |  |
| Week 10                                      | -2.44 (-2.584 to -1.557) | -2.04 (-2.515 to -1.311) |  |  |
| Week 11                                      | -2.49 (-2.647 to -1.581) | -2.03 (-2.489 to -1.314) |  |  |
| Week 12                                      | -2.49 (-2.659 to -1.632) | -2.03 (-2.538 to -1.354) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | 130ug vs. Placebo - Week 1     |
| Comparison groups                       | AGN 214868 130µg v Placebo     |
| Number of subjects included in analysis | 125                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.683 <sup>[9]</sup>         |
| Method                                  | Type 3 sum of squares          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.1                            |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.293                         |
| upper limit                             | 0.485                          |

Notes:

[9] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | 130ug vs. Placebo - Week 12 |
| Comparison groups                 | AGN 214868 130µg v Placebo  |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 125                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.271 <sup>[10]</sup>        |
| Method                                  | Type 3 sum of squares          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.47                          |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.166                         |
| upper limit                             | 0.233                          |

Notes:

[10] - Obtained from analysis of covariance model including treatment as fixed effect, and baseline maximal area of spontaneous pain and corresponding baseline average pain intensity score as covariates, with the type 3 sum of squares.

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 1

|                        |   |
|------------------------|---|
| End point title        | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 1 <sup>[11]</sup>   |
| End point description: | The total modified intent to treat (mITT) population of 279 patients, consists of all randomized patients who received treatment and at least 1 postbaseline weekly average pain intensity score. Cohort 1 includes 154 patients from the mITT population |
| End point type         | Secondary   |
| End point timeframe:   | Baseline to Week 1  |

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 61                 | 30                   | 61              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 18                 | 33.3                 | 21.3            |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 2

|                        |  |
|------------------------|--|
| End point title        | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 2 <sup>[12]</sup>  |
| End point description: | Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline |
| End point type         | Secondary  |

End point timeframe:

The total modified intent to treat (mITT) population of 279 patients, consists of all randomized patients who received treatment and at least 1 postbaseline weekly average pain intensity score. Cohort 1 includes 154 patients from the mITT population

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 63                 | 30                   | 60              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 27                 | 40                   | 36.7            |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 3

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 3 <sup>[13]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 3

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 60                 | 30                   | 60              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 35                 | 50                   | 50              |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 4

|   |   |
|---|---|
| End point title   | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 4 <sup>[14]</sup> |
| End point description:<br>Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease), and in 10% increments, up to 100% improvement, in average pain intensity score at each week compared with baseline  |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline to Week 4  |   |
| Notes:<br>[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: No Statistical Analysis is reported for this outcome measure |   |

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 61                 | 30                   | 57              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 40                 | 53.3                 | 52.6            |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 5

|   |   |
|---|---|
| End point title   | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 5 <sup>[15]</sup> |
| End point description:<br>Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline  |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline to Week 5  |   |
| Notes:<br>[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: No Statistical Analysis is reported for this outcome measure |   |

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 59                 | 30                   | 57              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 40.7               | 53.3                 | 52.6            |  |

### Statistical analyses



No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 6

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 6 <sup>[16]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 6

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 58                 | 30                   | 55              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 41.4               | 50                   | 54.5            |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 7

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 7 <sup>[17]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 7

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 60                 | 30                   | 57              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 43.3               | 56.7                 | 50.9            |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 8

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 8 <sup>[18]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 8

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 58                 | 30                   | 56              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 43.1               | 50                   | 55.4            |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 9

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 9 <sup>[19]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 9

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 55                 | 27                   | 52              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 43.6               | 51.9                 | 51.9            |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 10

|                 |  |
|-----------------|--|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 10 <sup>[20]</sup> |
|-----------------|--|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 10

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 56                 | 28                   | 52              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 46.4               | 53.6                 | 55.8            |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 11

|                 |  |
|-----------------|--|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 11 <sup>[21]</sup> |
|-----------------|--|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 11

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 53                 | 28                   | 52              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 47.2               | 53.6                 | 59.6            |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 1 - Week 12 <sup>[22]</sup> |
|-----------------|--|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 12

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values              | AGN 214868<br>65µg | AGN 214868<br>32.5µg | Placebo         |  |
|-------------------------------|--------------------|----------------------|-----------------|--|
| Subject group type            | Reporting group    | Reporting group      | Reporting group |  |
| Number of subjects analysed   | 50                 | 27                   | 49              |  |
| Units: percentage of patients |                    |                      |                 |  |
| number (not applicable)       | 48                 | 63                   | 63.3            |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 1

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 1 <sup>[23]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement

(decrease) in average pain intensity score at each week compared with baseline

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline to Week 1   |           |

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 63                  | 59              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 14.3                | 20.3            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 2

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 2 <sup>[24]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 2

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 62                  | 58              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 25.8                | 27.6            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 -

### Week 3

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 3 <sup>[25]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 3

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 59                  | 58              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 30.5                | 39.7            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 4

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 4 <sup>[26]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 4

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 60                  | 58              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 35                  | 43.1            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 5

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 5 <sup>[27]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 5

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values            | AGN 214868<br>130µg | Placebo         |  |  |
|-----------------------------|---------------------|-----------------|--|--|
| Subject group type          | Reporting group     | Reporting group |  |  |
| Number of subjects analysed | 57                  | 57              |  |  |
| Units: Baseline to Week 5   |                     |                 |  |  |
| number (not applicable)     | 42.1                | 45.6            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 6

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 6 <sup>[28]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 6

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 53                  | 57              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 45.3                | 45.6            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 7

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 7 <sup>[29]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 7

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 50                  | 56              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 50                  | 48.2            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 8

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 8 <sup>[30]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 8



Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 51                  | 55              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 54.9                | 49.1            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 9

|                 |   |
|-----------------|---|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 9 <sup>[31]</sup> |
|-----------------|---|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 9

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 51                  | 55              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 58.8                | 45.5            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 10

|                 |  |
|-----------------|--|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 10 <sup>[32]</sup> |
|-----------------|--|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement

(decrease) in average pain intensity score at each week compared with baseline

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline to Week 10  |           |

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 51                  | 55              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 64.7                | 47.3            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 11

|                 |  |
|-----------------|--|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 11 <sup>[33]</sup> |
|-----------------|--|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 11

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 50                  | 54              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 64                  | 42.6            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Average Pain Intensity Score Responders - Cohort 2 -

## Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Average Pain Intensity Score Responders - Cohort 2 - Week 12 <sup>[34]</sup> |
|-----------------|--|

End point description:

Average Pain Intensity Score Responder is defined as a patient who had at least a 30% improvement (decrease) in average pain intensity score at each week compared with baseline

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

End point timeframe:

Baseline to Week 12

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|                               |                     |                 |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>       | AGN 214868<br>130µg | Placebo         |  |  |
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 44                  | 50              |  |  |
| Units: percentage of patients |                     |                 |  |  |
| number (not applicable)       | 61.4                | 40              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 2

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 2 <sup>[35]</sup> |
|-----------------|--|

End point description:

The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 2

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                                     |                                    |                              |  |
|--|-------------------------------------|------------------------------------|------------------------------|--|
| <b>End point values</b>                      | AGN 214868<br>65µg                  | AGN 214868<br>32.5µg               | Placebo                      |  |
| Subject group type                           | Reporting group                     | Reporting group                    | Reporting group              |  |
| Number of subjects analysed                  | 61                                  | 27                                 | 60                           |  |
| Units: Square Centimeters (cm2)              |                                     |                                    |                              |  |
| least squares mean (confidence interval 95%) | -25.07 (-<br>37.544 to -<br>13.564) | -34.07 (-<br>60.871 to -<br>4.114) | -26.1 (-38.58<br>to -14.053) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 4

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 4 <sup>[36]</sup> |
|-----------------|--|

End point description:

The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 4

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg                  | AGN 214868<br>32.5µg             | Placebo                             |  |
|--|-------------------------------------|----------------------------------|-------------------------------------|--|
| Subject group type                           | Reporting group                     | Reporting group                  | Reporting group                     |  |
| Number of subjects analysed                  | 62                                  | 29                               | 60                                  |  |
| Units: Square Centimeters (cm2)              |                                     |                                  |                                     |  |
| least squares mean (confidence interval 95%) | -27.65 (-<br>40.978 to -<br>15.412) | -25.96 (-<br>49.316 to<br>0.309) | -32.23 (-<br>48.543 to -<br>16.214) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 8

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 8 <sup>[37]</sup> |
|-----------------|--|

End point description:

The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 8

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg                  | AGN 214868<br>32.5µg               | Placebo                             |  |
|--|-------------------------------------|------------------------------------|-------------------------------------|--|
| Subject group type                           | Reporting group                     | Reporting group                    | Reporting group                     |  |
| Number of subjects analysed                  | 56                                  | 28                                 | 55                                  |  |
| Units: Square Centimeters (cm2)              |                                     |                                    |                                     |  |
| least squares mean (confidence interval 95%) | -29.86 (-<br>45.876 to -<br>15.566) | -37.18 (-<br>64.825 to -<br>1.989) | -34.04 (-<br>48.026 to -<br>22.134) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 1 - Week 12 <sup>[38]</sup> |
|-----------------|---|

End point description:

The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 12

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg                  | AGN 214868<br>32.5µg        | Placebo                             |  |
|--|-------------------------------------|-----------------------------|-------------------------------------|--|
| Subject group type                           | Reporting group                     | Reporting group             | Reporting group                     |  |
| Number of subjects analysed                  | 57                                  | 29                          | 54                                  |  |
| Units: Square Centimeters (cm2)              |                                     |                             |                                     |  |
| least squares mean (confidence interval 95%) | -30.99 (-<br>46.118 to -<br>17.138) | -31.4 (-61.185<br>to 3.853) | -35.03 (-<br>53.242 to -<br>18.425) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 2

|   |  |
|---|--|
| End point title   | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 2 <sup>[39]</sup> |
| End point description:<br>The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.                                  |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline to Week 2  |  |
| Notes:<br>[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: No Statistical Analysis is reported for this outcome measure |  |

|  |                          |                             |  |  |
|--|--------------------------|-----------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg      | Placebo                     |  |  |
| Subject group type                           | Reporting group          | Reporting group             |  |  |
| Number of subjects analysed                  | 57                       | 57                          |  |  |
| Units: Square Centimeters (cm2)              |                          |                             |  |  |
| least squares mean (confidence interval 95%) | -9.86 (-38.087 to 18.02) | -27.52 (-43.841 to -10.854) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 4

|   |  |
|---|--|
| End point title   | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 4 <sup>[40]</sup> |
| End point description:<br>The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.                                  |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline to Week 4  |  |
| Notes:<br>[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: No Statistical Analysis is reported for this outcome measure |  |

|  |                           |                            |  |  |
|--|---------------------------|----------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg       | Placebo                    |  |  |
| Subject group type                           | Reporting group           | Reporting group            |  |  |
| Number of subjects analysed                  | 58                        | 59                         |  |  |
| Units: Square Centimeters (cm2)              |                           |                            |  |  |
| least squares mean (confidence interval 95%) | -22.23 (-48.893 to 3.903) | -25.67 (-42.901 to -7.909) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 8

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 8 <sup>[41]</sup> |
|-----------------|--|

End point description:

The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 8

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                           |                             |  |  |
|--|---------------------------|-----------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg       | Placebo                     |  |  |
| Subject group type                           | Reporting group           | Reporting group             |  |  |
| Number of subjects analysed                  | 53                        | 57                          |  |  |
| Units: Square Centimeters (cm2)              |                           |                             |  |  |
| least squares mean (confidence interval 95%) | -42.92 (-65.58 to -23.08) | -31.95 (-47.299 to -13.978) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Maximal Area of Spontaneous Pain - Cohort 2 - Week 12 <sup>[42]</sup> |
|-----------------|---|

End point description:

The assessment of maximal area of spontaneous pain was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of pain were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 12

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>130µg        | Placebo                    |  |  |
|--|----------------------------|----------------------------|--|--|
| Subject group type                           | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed                  | 54                         | 57                         |  |  |
| Units: Square Centimeters (cm2)              |                            |                            |  |  |
| least squares mean (confidence interval 95%) | -36.73 (-67.719 to -8.696) | -32.6 (-49.823 to -12.574) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area of Allodynia - Cohort 1 - Week 2

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area of Allodynia - Cohort 1 - Week |
|-----------------|---|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 2

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg         | AGN 214868<br>32.5µg       | Placebo                     |  |
|--|----------------------------|----------------------------|-----------------------------|--|
| Subject group type                           | Reporting group            | Reporting group            | Reporting group             |  |
| Number of subjects analysed                  | 61                         | 27                         | 60                          |  |
| Units: Square Centimeters (cm2)              |                            |                            |                             |  |
| least squares mean (confidence interval 95%) | -40.06 (-89.75 to -12.158) | -14.42 (-34.431 to 23.824) | -52.73 (-67.258 to -24.248) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area of Allodynia - Cohort 1 - Week 4

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area of Allodynia - Cohort 1 - Week |
|-----------------|---|



End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 4

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg                   | AGN 214868<br>32.5µg                | Placebo                             |  |
|--|--------------------------------------|-------------------------------------|-------------------------------------|--|
| Subject group type                           | Reporting group                      | Reporting group                     | Reporting group                     |  |
| Number of subjects analysed                  | 62                                   | 29                                  | 60                                  |  |
| Units: Square Centimeters (cm2)              |                                      |                                     |                                     |  |
| least squares mean (confidence interval 95%) | -54.12 (-<br>118.867 to -<br>19.566) | -23.07 (-<br>41.985 to -<br>19.468) | -58.14 (-<br>70.452 to -<br>26.048) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Area of Allodynia - Cohort 1 - Week 8

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area of Allodynia - Cohort 1 - Week |
|-----------------|---|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 8

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg                   | AGN 214868<br>32.5µg               | Placebo                             |  |
|--|--------------------------------------|------------------------------------|-------------------------------------|--|
| Subject group type                           | Reporting group                      | Reporting group                    | Reporting group                     |  |
| Number of subjects analysed                  | 56                                   | 28                                 | 55                                  |  |
| Units: Square Centimeters (cm2)              |                                      |                                    |                                     |  |
| least squares mean (confidence interval 95%) | -74.46 (-<br>136.541 to -<br>43.526) | -50.47 (-<br>75.433 to -<br>4.124) | -71.54 (-<br>85.155 to -<br>37.104) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area of Allodynia - Cohort 1 - Week 12

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Area of Allodynia - Cohort 1 - Week 12 <sup>[46]</sup> |
|-----------------|--|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 12

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg                   | AGN 214868<br>32.5µg             | Placebo                            |  |
|--|--------------------------------------|----------------------------------|------------------------------------|--|
| Subject group type                           | Reporting group                      | Reporting group                  | Reporting group                    |  |
| Number of subjects analysed                  | 57                                   | 29                               | 54                                 |  |
| Units: Square Centimeters (cm2)              |                                      |                                  |                                    |  |
| least squares mean (confidence interval 95%) | -67.71 (-<br>130.695 to -<br>35.611) | -39.96 (-<br>62.646 to<br>8.446) | -70.46 (-<br>92.167 to -<br>29.97) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area of Allodynia - Cohort 2 - Week 2

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area of Allodynia - Cohort 2 - Week |
|-----------------|---|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 2

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                                    |                                     |  |  |
|--|------------------------------------|-------------------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg                | Placebo                             |  |  |
| Subject group type                           | Reporting group                    | Reporting group                     |  |  |
| Number of subjects analysed                  | 57                                 | 57                                  |  |  |
| Units: Square Centimeters (cm2)              |                                    |                                     |  |  |
| least squares mean (confidence interval 95%) | -36.66 (-<br>59.461 to -<br>0.328) | -60.71 (-<br>98.564 to -<br>36.369) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area of Allodynia - Cohort 2 - Week 4

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area of Allodynia - Cohort 2 - Week |
|-----------------|---|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 4

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                                     |                                      |  |  |
|--|-------------------------------------|--------------------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg                 | Placebo                              |  |  |
| Subject group type                           | Reporting group                     | Reporting group                      |  |  |
| Number of subjects analysed                  | 58                                  | 59                                   |  |  |
| Units: Square Centimeters (cm2)              |                                     |                                      |  |  |
| least squares mean (confidence interval 95%) | -54.33 (-<br>72.041 to -<br>13.677) | -69.39 (-<br>116.234 to -<br>45.112) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area of Allodynia - Cohort 2 - Week 8

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area of Allodynia - Cohort 2 - Week |
|-----------------|---|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 8

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                                     |                                      |  |  |
|--|-------------------------------------|--------------------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg                 | Placebo                              |  |  |
| Subject group type                           | Reporting group                     | Reporting group                      |  |  |
| Number of subjects analysed                  | 53                                  | 57                                   |  |  |
| Units: Square Centimeters (cm2)              |                                     |                                      |  |  |
| least squares mean (confidence interval 95%) | -78.78 (-<br>99.958 to -<br>43.748) | -75.58 (-<br>113.401 to -<br>50.634) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Area of Allodynia - Cohort 2 - Week 12

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Area of Allodynia - Cohort 2 - Week 12 <sup>[50]</sup> |
|-----------------|--|

End point description:

The assessment of maximal area of allodynia was conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Areas of allodynia were quantified at a central reading center.

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

End point timeframe:

Baseline to Week 12

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                                     |                                      |  |  |
|--|-------------------------------------|--------------------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg                 | Placebo                              |  |  |
| Subject group type                           | Reporting group                     | Reporting group                      |  |  |
| Number of subjects analysed                  | 54                                  | 57                                   |  |  |
| Units: Square Centimeters (cm2)              |                                     |                                      |  |  |
| least squares mean (confidence interval 95%) | -77.98 (-<br>99.148 to -<br>36.515) | -79.99 (-<br>129.775 to -<br>49.428) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia

## Cohort 1 - Week 2

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 2 <sup>[51]</sup> |
|-----------------|--|

End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

End point timeframe:

Baseline to Week 2

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                          |                          |                         |  |
|--|--------------------------|--------------------------|-------------------------|--|
| <b>End point values</b>                      | AGN 214868<br>65µg       | AGN 214868<br>32.5µg     | Placebo                 |  |
| Subject group type                           | Reporting group          | Reporting group          | Reporting group         |  |
| Number of subjects analysed                  | 48                       | 21                       | 50                      |  |
| Units: units on a scale                      |                          |                          |                         |  |
| least squares mean (confidence interval 95%) | -17.4 (-25.67 to -10.68) | -21.2 (-30.01 to -10.09) | -15.3 (-22.76 to -7.32) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 4

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 4 <sup>[52]</sup> |
|-----------------|--|

End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

End point timeframe:

Baseline to Week 4

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg       | AGN 214868<br>32.5µg     | Placebo                 |  |
|--|--------------------------|--------------------------|-------------------------|--|
| Subject group type                           | Reporting group          | Reporting group          | Reporting group         |  |
| Number of subjects analysed                  | 50                       | 25                       | 51                      |  |
| Units: units on a scale                      |                          |                          |                         |  |
| least squares mean (confidence interval 95%) | -21.9 (-29.67 to -15.57) | -20.5 (-28.34 to -11.34) | -12.3 (-19.02 to -5.01) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 8

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 8 <sup>[53]</sup> |
|-----------------|--|

End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to 100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

End point timeframe:

Baseline to Week 8

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg      | AGN 214868<br>32.5µg     | Placebo                  |  |
|--|-------------------------|--------------------------|--------------------------|--|
| Subject group type                           | Reporting group         | Reporting group          | Reporting group          |  |
| Number of subjects analysed                  | 51                      | 22                       | 49                       |  |
| Units: units on a scale                      |                         |                          |                          |  |
| least squares mean (confidence interval 95%) | -22.7 (-31.18 to -15.8) | -24.8 (-34.73 to -14.45) | -19.4 (-27.27 to -10.15) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia Cohort 1 - Week 12 <sup>[54]</sup> |
|-----------------|---|

End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to 100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of

the area of allodynia and pain.

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

End point timeframe:

Baseline to Week 12

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>65µg       | AGN 214868<br>32.5µg    | Placebo                  |  |
|--|--------------------------|-------------------------|--------------------------|--|
| Subject group type                           | Reporting group          | Reporting group         | Reporting group          |  |
| Number of subjects analysed                  | 51                       | 23                      | 46                       |  |
| Units: units on a scale                      |                          |                         |                          |  |
| least squares mean (confidence interval 95%) | -19.2 (-27.51 to -12.14) | -21.6 (-33.46 to -9.41) | -21.5 (-28.99 to -12.79) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 2

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 2 <sup>[55]</sup> |
|-----------------|--|

End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to 100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

End point timeframe:

Baseline to Week 2

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

| End point values                             | AGN 214868<br>130µg     | Placebo                 |  |  |
|--|-------------------------|-------------------------|--|--|
| Subject group type                           | Reporting group         | Reporting group         |  |  |
| Number of subjects analysed                  | 53                      | 55                      |  |  |
| Units: units on a scale                      |                         |                         |  |  |
| least squares mean (confidence interval 95%) | -19 (-26.102 to -11.03) | -16.2 (-23.4 to -9.691) |  |  |

## Statistical analyses

**Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 4**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 4 <sup>[56]</sup> |
|-----------------|--|

## End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to 100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

## End point timeframe:

Baseline to Week 4

## Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                            |                           |  |  |
|--|----------------------------|---------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg        | Placebo                   |  |  |
| Subject group type                           | Reporting group            | Reporting group           |  |  |
| Number of subjects analysed                  | 52                         | 55                        |  |  |
| Units: units on a scale                      |                            |                           |  |  |
| least squares mean (confidence interval 95%) | -20.6 (-27.941 to -10.867) | -20.5 (-29.487 to -13.64) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 8**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 8 <sup>[57]</sup> |
|-----------------|--|

## End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to 100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

## End point timeframe:

Baseline to Week 8

## Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure



|  |                            |                            |  |  |
|--|----------------------------|----------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg        | Placebo                    |  |  |
| Subject group type                           | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed                  | 48                         | 52                         |  |  |
| Units: units on a scale                      |                            |                            |  |  |
| least squares mean (confidence interval 95%) | -28.7 (-35.924 to -21.285) | -19.7 (-27.721 to -11.895) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Evoked Pain Score in the Area of Allodynia - Cohort 2 - Week 12 <sup>[58]</sup> |
|-----------------|---|

End point description:

Assessment of evoked pain were conducted by a qualified and trained investigator or designee (eg, physician, physician's assistant, nurse practitioner, and nurse). Evoked pain was scored using a visual analog scale (VAS; 0 to 100 mm scale with anchors of 0 = No pain and 100 = Worst pain imaginable). The patient was asked to use the VAS to rate the unpleasantness of 3 brush strokes within the center of the area of allodynia and pain.

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

End point timeframe:

Baseline to Week 12

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No Statistical Analysis is reported for this outcome measure

|  |                           |                            |  |  |
|--|---------------------------|----------------------------|--|--|
| <b>End point values</b>                      | AGN 214868<br>130µg       | Placebo                    |  |  |
| Subject group type                           | Reporting group           | Reporting group            |  |  |
| Number of subjects analysed                  | 47                        | 51                         |  |  |
| Units: units on a scale                      |                           |                            |  |  |
| least squares mean (confidence interval 95%) | -26.9 (-37.75 to -16.548) | -19.1 (-26.996 to -10.612) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Event reporting occurred over a 6 month period from May to October of 2015

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | AGN 214868 130µg |
|-----------------------|------------------|

Reporting group description:

Single treatment session of AGN-214868, total dose given as injections into the area of pain on Day 1

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | AGN 214868 65µg |
|-----------------------|-----------------|

Reporting group description:

Single treatment session of AGN-214868, total dose given as injections into the area of pain on Day 1

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | AGN 214868 32.5µg |
|-----------------------|-------------------|

Reporting group description:

Single treatment session of AGN-214868, total dose given as injections into the area of pain on Day 1

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

Reporting group description:

Single treatment session of AGN-214868 placebo, given as injections into the area of pain on Day 1

| Serious adverse events  | AGN 214868 130µg | AGN 214868 65µg | AGN 214868 32.5µg |
|---|------------------|-----------------|-------------------|
| Total subjects affected by serious adverse events                   |                  |                 |                   |
| subjects affected / exposed   | 2 / 64 (3.13%)   | 8 / 63 (12.70%) | 2 / 30 (6.67%)    |
| number of deaths (all causes)                                       | 0                | 0               | 0                 |
| number of deaths resulting from adverse events                      | 0                | 0               | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                 |                   |
| Basal cell carcinoma  |                  |                 |                   |
| subjects affected / exposed   | 0 / 64 (0.00%)   | 1 / 63 (1.59%)  | 1 / 30 (3.33%)    |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1           | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |
| Breast cancer   |                  |                 |                   |
| subjects affected / exposed   | 0 / 64 (0.00%)   | 1 / 63 (1.59%)  | 0 / 30 (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             |
| Squamous cell carcinoma   |                  |                 |                   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 30 (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          |
| Adenocarcinoma of colon                         |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Malignant melanoma                              |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Fractured sacrum                                |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Pubis fracture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Rib fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Urethral injury                                 |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Vascular disorders                              |                |                |                |
| Aortic aneurysm                                 |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 30 (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          |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Cardiac disorders                                    |                |                |                |
| Atrial fibrillation                                  |                |                |                |
| subjects affected / exposed                          | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Myocardial infarction                                |                |                |                |
| subjects affected / exposed                          | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Angina unstable                                      |                |                |                |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                             |                |                |                |
| Thalamic infarction                                  |                |                |                |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 30 (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          |
| Blood and lymphatic system disorders                 |                |                |                |
| Anaemia  |                |                |                |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| General disorders and administration site conditions |                |                |                |
| Oedema peripheral                                    |                |                |                |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Gastrointestinal disorders                           |                |                |                |
| Gastrooesophageal reflux disease                     |                |                |                |
| subjects affected / exposed                          | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Hepatobiliary disorders                              |                |                |                |
| Cholecystitis  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 64 (0.00%) | 2 / 63 (3.17%) | 0 / 30 (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          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Haemothorax                                     |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Joint crepitation                               |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| Infections and infestations                     |                |                |                |
| Pyelonephritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 30 (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          |
| Erysipelas                                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| <b>Furuncle</b>                                 |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |
| <b>Labyrinthitis</b>                            |                |                |                |
| subjects affected / exposed                     | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 30 (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          |

| <b>Serious adverse events</b>  | Placebo          |  |  |
|--|------------------|--|--|
| <b>Total subjects affected by serious adverse events</b>                   |                  |  |  |
| subjects affected / exposed  | 10 / 123 (8.13%) |  |  |
| number of deaths (all causes)  | 1                |  |  |
| number of deaths resulting from adverse events                             | 0                |  |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                  |  |  |
| <b>Basal cell carcinoma</b>  |                  |  |  |
| subjects affected / exposed  | 0 / 123 (0.00%)  |  |  |
| occurrences causally related to treatment / all                            | 0 / 0            |  |  |
| deaths causally related to treatment / all                                 | 0 / 0            |  |  |
| <b>Breast cancer</b>   |                  |  |  |
| subjects affected / exposed  | 1 / 123 (0.81%)  |  |  |
| occurrences causally related to treatment / all                            | 0 / 1            |  |  |
| deaths causally related to treatment / all                                 | 0 / 0            |  |  |
| <b>Squamous cell carcinoma</b>   |                  |  |  |
| subjects affected / exposed  | 0 / 123 (0.00%)  |  |  |
| occurrences causally related to treatment / all                            | 0 / 0            |  |  |
| deaths causally related to treatment / all                                 | 0 / 0            |  |  |
| <b>Adenocarcinoma of colon</b>   |                  |  |  |
| subjects affected / exposed  | 0 / 123 (0.00%)  |  |  |
| occurrences causally related to treatment / all                            | 0 / 0            |  |  |
| deaths causally related to treatment / all                                 | 0 / 0            |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Malignant melanoma                              |                 |  |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fractured sacrum                                |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pubis fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rib fracture                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urethral injury                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic aneurysm                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial infarction                           |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Angina unstable                                      |                 |  |  |
| subjects affected / exposed                          | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Nervous system disorders                             |                 |  |  |
| Thalamic infarction                                  |                 |  |  |
| subjects affected / exposed                          | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Blood and lymphatic system disorders                 |                 |  |  |
| Anaemia  |                 |  |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Oedema peripheral                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Gastrointestinal disorders                           |                 |  |  |
| Gastrooesophageal reflux disease                     |                 |  |  |
| subjects affected / exposed                          | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hepatobiliary disorders                              |                 |  |  |
| Cholecystitis  |                 |  |  |
| subjects affected / exposed                          | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| Haemothorax  |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Joint crepitation                               |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteoarthritis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Pyelonephritis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 123 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Erysipelas                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Furuncle  |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Labyrinthitis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 123 (0.81%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | AGN 214868 130µg | AGN 214868 65µg  | AGN 214868 32.5µg |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                   |
| subjects affected / exposed                           | 38 / 64 (59.38%) | 39 / 63 (61.90%) | 20 / 30 (66.67%)  |
| Nervous system disorders                              |                  |                  |                   |
| Dizziness   |                  |                  |                   |
| subjects affected / exposed                           | 1 / 64 (1.56%)   | 2 / 63 (3.17%)   | 3 / 30 (10.00%)   |
| occurrences (all)                                     | 1                | 2                | 3                 |
| General disorders and administration site conditions  |                  |                  |                   |
| Injection site pain                                   |                  |                  |                   |
| subjects affected / exposed                           | 6 / 64 (9.38%)   | 1 / 63 (1.59%)   | 0 / 30 (0.00%)    |
| occurrences (all)                                     | 6                | 1                | 0                 |
| Infections and infestations                           |                  |                  |                   |
| Upper respiratory tract infection                     |                  |                  |                   |
| subjects affected / exposed                           | 4 / 64 (6.25%)   | 5 / 63 (7.94%)   | 1 / 30 (3.33%)    |
| occurrences (all)                                     | 4                | 5                | 1                 |
| Nasopharyngitis                                       |                  |                  |                   |
| subjects affected / exposed                           | 3 / 64 (4.69%)   | 5 / 63 (7.94%)   | 2 / 30 (6.67%)    |
| occurrences (all)                                     | 3                | 5                | 2                 |
| Urinary tract infection                               |                  |                  |                   |
| subjects affected / exposed                           | 1 / 64 (1.56%)   | 2 / 63 (3.17%)   | 2 / 30 (6.67%)    |
| occurrences (all)                                     | 1                | 2                | 2                 |

| <b>Non-serious adverse events</b>                     | Placebo           |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 70 / 123 (56.91%) |  |  |
| Nervous system disorders                              |                   |  |  |
| Dizziness   |                   |  |  |
| subjects affected / exposed                           | 2 / 123 (1.63%)   |  |  |
| occurrences (all)                                     | 2                 |  |  |
| General disorders and administration site conditions  |                   |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Injection site pain<br>subjects affected / exposed<br>occurrences (all)               | 6 / 123 (4.88%)<br>6 |  |  |
| Infections and infestations   |                      |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 8 / 123 (6.50%)<br>8 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 9 / 123 (7.32%)<br>9 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 7 / 123 (5.69%)<br>7 |  |  |

## **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**

None reported