



Clinical trial results:

A Randomized, Double-Blind, Placebo- and Active-Controlled Study of DS-5565 in Subjects with Pain Associated with Fibromyalgia

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-005162-20 |
| Trial protocol | AT BE ES PT SI PL |
| Global end of trial date | 12 January 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 08 December 2017 |
| First version publication date | 08 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | DS5565-A-E310 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02187471 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Daiichi Sankyo, Inc. |
| Sponsor organisation address | 211 Mt. Airy Road, Basking Ridge, United States, 07920 |
| Public contact | Clinical Trial Information Contact, Daiichi Sankyo, Inc., +1 7325905000, eu_cta@dsi.com |
| Scientific contact | Clinical Trial Information Contact, Daiichi Sankyo, Inc., +1 7325905000, eu_cta@dsi.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 | 09 May 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare change in weekly average daily pain score (ADPS) from baseline to Week 13 in subjects receiving either dose of DS-5565 versus placebo.
Weekly ADPS is based on daily pain scores reported by the subject that best describes his or her worst pain over the previous 24 hours.

Protection of trial subjects:

This trial was conducted under ICH E6 Good Clinical Practice, which has its foundation in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 15 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects**Subjects enrolled per country**

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 86 |
| Country: Number of subjects enrolled | Portugal: 22 |
| Country: Number of subjects enrolled | Slovenia: 11 |
| Country: Number of subjects enrolled | Spain: 101 |
| Country: Number of subjects enrolled | Austria: 29 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Argentina: 88 |
| Country: Number of subjects enrolled | Belarus: 12 |
| Country: Number of subjects enrolled | Chile: 45 |
| Country: Number of subjects enrolled | Colombia: 1 |
| Country: Number of subjects enrolled | Mexico: 29 |
| Country: Number of subjects enrolled | Russian Federation: 27 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Ukraine: 74 |
| Country: Number of subjects enrolled | United States: 760 |
| Worldwide total number of subjects | 1301 |
| EEA total number of subjects | 264 |

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) | 1174 |
| From 65 to 84 years | 127 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 2526 patients screened, 1301 from 15 countries were randomized into study groups.

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 | Subject, Investigator |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Patients take one each of placebo tablet and capsule, twice daily (BID)

| | |
|--|----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo tablet matching DS-5565 tablet

| | |
|--|-----------------|
| Investigational medicinal product name | Placebo capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo capsule matching pregabalin capsule

| | |
|------------------|------------|
| Arm title | Pregabalin |
|------------------|------------|

Arm description:

Patients take one pregabalin capsule and one placebo tablet BID

| | |
|--|--------------------------------|
| Arm type | Other product - not comparator |
| Investigational medicinal product name | Pregabalin capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

75 mg capsule for one week, then 150 mg capsule

| | |
|--|----------------|
| Investigational medicinal product name | Placebo tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Placebo tablet matching DS-5565 tablet

| | |
|------------------|-----------------|
| Arm title | DS5565 15 mg QD |
|------------------|-----------------|

Arm description:

Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD)

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo tablet matching DS-5565 tablet

| | |
|--|-----------------|
| Investigational medicinal product name | Placebo capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo capsule matching pregabalin capsule

| | |
|--|----------------|
| Investigational medicinal product name | DS-5565 tablet |
| Investigational medicinal product code | |
| Other name | mirogabalin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

DS-5565 (mirogabalin) 15 mg tablet

| | |
|------------------|------------------|
| Arm title | DS5565 15 mg BID |
|------------------|------------------|

Arm description:

Patients take one DS-5565 tablet and one placebo capsule BID

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | DS-5565 tablet |
| Investigational medicinal product code | |
| Other name | mirogabalin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

DS-5565 (mirogabalin) 15 mg tablet

| | |
|--|-----------------|
| Investigational medicinal product name | Placebo capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo capsule matching pregabalin capsule

| Number of subjects in period 1 | Placebo | Pregabalin | DS5565 15 mg QD |
|---|--------------------|--------------------|--------------------|
| Started | 325 | 324 | 326 |
| Completed Double-Blind Treatment Period | 249 | 242 | 240 |
| Completed Tapering Period | 278 | 269 | 263 |
| Completed Follow-up | 194 ^[1] | 193 ^[2] | 199 ^[3] |
| Entered Open-label Extension Study | 99 ^[4] | 88 ^[5] | 84 ^[6] |
| Safety Analysis Set | 324 | 319 | 324 |
| mITT Analysis Set | 324 | 319 | 324 |
| Completed | 249 | 242 | 240 |
| Not completed | 76 | 82 | 86 |
| Consent withdrawn by subject | 23 | 29 | 22 |
| Adverse event, non-fatal | 24 | 34 | 44 |
| Missing | - | - | - |
| Lack of efficacy | 18 | 9 | 13 |
| Protocol deviation | 4 | 5 | 4 |
| No reason provided | 7 | 5 | 3 |

| Number of subjects in period 1 | DS5565 15 mg BID |
|---|--------------------|
| Started | 326 |
| Completed Double-Blind Treatment Period | 246 |
| Completed Tapering Period | 273 |
| Completed Follow-up | 194 ^[7] |
| Entered Open-label Extension Study | 100 ^[8] |
| Safety Analysis Set | 323 |
| mITT Analysis Set | 323 |
| Completed | 246 |
| Not completed | 80 |
| Consent withdrawn by subject | 24 |
| Adverse event, non-fatal | 36 |
| Missing | 1 |
| Lack of efficacy | 11 |
| Protocol deviation | 4 |
| No reason provided | 4 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having

completed the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of patients who completed the treatment period are considered as having completed the trial.

Baseline characteristics

Reporting groups

| | |
|---|------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients take one each of placebo tablet and capsule, twice daily (BID) | |
| Reporting group title | Pregabalin |
| Reporting group description: | |
| Patients take one pregabalin capsule and one placebo tablet BID | |
| Reporting group title | DS5565 15 mg QD |
| Reporting group description: | |
| Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD) | |
| Reporting group title | DS5565 15 mg BID |
| Reporting group description: | |
| Patients take one DS-5565 tablet and one placebo capsule BID | |

| Reporting group values | Placebo | Pregabalin | DS5565 15 mg QD |
|------------------------|---------|------------|-----------------|
| Number of subjects | 325 | 324 | 326 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 296 | 294 | 294 |
| From 65-84 years | 29 | 30 | 32 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 303 | 302 | 302 |
| Male | 22 | 22 | 24 |

| Reporting group values | DS5565 15 mg BID | Total | |
|------------------------|------------------|-------|--|
| Number of subjects | 326 | 1301 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 290 | 1174 | |
| From 65-84 years | 36 | 127 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 296 | 1203 | |
| Male | 30 | 98 | |

End points

End points reporting groups

| | |
|---|------------------|
| Reporting group title | Placebo |
| Reporting group description: Patients take one each of placebo tablet and capsule, twice daily (BID) | |
| Reporting group title | Pregabalin |
| Reporting group description: Patients take one pregabalin capsule and one placebo tablet BID | |
| Reporting group title | DS5565 15 mg QD |
| Reporting group description: Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD) | |
| Reporting group title | DS5565 15 mg BID |
| Reporting group description: Patients take one DS-5565 tablet and one placebo capsule BID | |

Primary: Average daily pain score (ADPS) for either dose of DS-5565 versus placebo

| | |
|--|---|
| End point title | Average daily pain score (ADPS) for either dose of DS-5565 versus placebo ^{[1][2]} |
| End point description: Average daily pain scores reported by the patient that best describes his or her worst pain over the previous 24 hours. A daily pain score has a scale of 0 = no pain to 10 = worst possible pain. For patients with no Week 13 data, the baseline observation was carried forward (BOCF). | |
| End point type | Primary |
| End point timeframe: Baseline, Week 13 | |

Notes:

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

Justification: No further statistical analysis was performed to arrive at this summary aggregate data.

[2] - 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: Only pregabalin was included in this endpoint.

| End point values | Placebo | DS5565 15 mg QD | DS5565 15 mg BID | |
|--------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 323 | 324 | 323 | |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| at Baseline | 7.20 (± 1.393) | 7.23 (± 1.357) | 7.24 (± 1.436) | |
| at Week 13 | 5.53 (± 2.462) | 5.51 (± 1.486) | 5.30 (± 2.724) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients who answered "much improved or better" in PGIC at Week 13 receiving either dose of DS-5565 versus placebo

| | |
|-----------------|---|
| End point title | Number of patients who answered "much improved or better" in PGIC at Week 13 receiving either dose of DS-5565 versus placebo ^[3] |
|-----------------|---|

End point description:

Patients rated global impression of change (PGIC) on a categorical scale from 1 = very much improved to 7 = very much worse

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

End point timeframe:

Baseline, Week 13

Notes:

[3] - 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: Pregabalin was not included in this endpoint.

| End point values | Placebo | DS5565 15 mg QD | DS5565 15 mg BID | |
|-----------------------------|-----------------|-----------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 324 | 324 | 323 | |
| Units: Patients | 85 | 120 | 129 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Average score on the fibromyalgia index questionnaire (FIQ) in patients receiving either dose of DS-5565 or placebo

| | |
|-----------------|--|
| End point title | Average score on the fibromyalgia index questionnaire (FIQ) in patients receiving either dose of DS-5565 or placebo ^[4] |
|-----------------|--|

End point description:

The FIQ is composed of 10 items. The first item contains 11 questions related to physical functioning - each question is rated on a 4-point Likert-type scale. Items 2 and 3 ask the patient to mark the number of days that they feel well and the number of days they were unable to work (including housework) because of fibromyalgia (FM) symptoms. Items 4 through 10 are horizontal linear scales marked in 10 increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. A higher score indicates a greater impact of the syndrome on the patient. Scores were collected from patients who completed the assessment at the given time point.

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

End point timeframe:

Baseline, Week 13

Notes:

[4] - 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: Pregabalin was not included in this endpoint.

| End point values | Placebo | DS5565 15 mg QD | DS5565 15 mg BID | |
|--------------------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 324 | 324 | 323 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| at Baseline (n=322,323,320) | 66.02 (± 14.071) | 63.26 (± 13.822) | 64.48 (± 13.615) | |

| | | | | |
|----------------------------|-----------------------|-----------------------|-----------------------|--|
| at Week 13 (n=249,240,246) | 47.80 (\pm 20.248) | 43.86 (\pm 20.714) | 41.04 (\pm 22.115) | |
|----------------------------|-----------------------|-----------------------|-----------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients receiving either dose of DS-5565 or placebo classified as responders at Week 13

| | |
|-----------------|---|
| End point title | Number of patients receiving either dose of DS-5565 or placebo classified as responders at Week 13 ^[5] |
|-----------------|---|

End point description:

Patients classified as responders are those with a substantial reduction in ADPS in Week 13 (BOCF) compared to baseline.

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

End point timeframe:

Baseline, Week 13

Notes:

[5] - 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: Pregabalin was not included in this endpoint.

| End point values | Placebo | DS5565 15 mg QD | DS5565 15 mg BID | |
|-----------------------------|-----------------|-----------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 324 | 324 | 323 | |
| Units: Patients | | | | |
| 30% Responders | 122 | 121 | 125 | |
| 50% Responders | 68 | 77 | 89 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Average daily pain score (ADPS) for pregabalin

| | |
|-----------------|---|
| End point title | Average daily pain score (ADPS) for pregabalin ^[6] |
|-----------------|---|

End point description:

Average daily pain scores reported by the patient that best describes his or her worst pain over the previous 24 hours. A daily pain score has a scale of 0 = no pain to 10 = worst possible pain. For patients with no Week 13 data, the baseline observation was carried forward (BOCF).

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

End point timeframe:

Baseline, Week 13

Notes:

[6] - 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: Pregabalin was not included in this endpoint.

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Pregabalin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 319 | | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| at Baseline | 7.22 (± 1.326) | | | |
| at Week 13 | 5.12 (± 2.510) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events that emerge or get worse on or after the first dosing of double blind study medication and during study treatment up to 4 weeks after the last dose of double blind study medication

Adverse event reporting additional description:

Total number of treatment-emergent adverse events (TEAEs) counts all occurrences in all subjects. In the system organ class and preferred term summarization, a patient was counted only once when one or more events were reported, so the occurrences mirror the number of patients.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Patients take one pregabalin capsule and one placebo tablet BID

| | |
|-----------------------|------------|
| Reporting group title | Pregabalin |
|-----------------------|------------|

Reporting group description:

Patients take one pregabalin capsule and one placebo tablet BID

| | |
|-----------------------|-----------------|
| Reporting group title | DS5565 15 mg QD |
|-----------------------|-----------------|

Reporting group description:

Patients take one each of placebo tablet and capsule in the morning and one placebo capsule in the evening with one DS-5565 tablet, once daily (QD)

| | |
|-----------------------|------------------|
| Reporting group title | DS5565 15 mg BID |
|-----------------------|------------------|

Reporting group description:

Patients take one DS-5565 tablet and one placebo capsule BID

| Serious adverse events | Placebo | Pregabalin | DS5565 15 mg QD |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 324 (2.78%) | 2 / 319 (0.63%) | 5 / 324 (1.54%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Uraemic encephalopathy | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Convulsion | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Seizure like phenomena | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 319 (0.31%) | 0 / 324 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 1 / 319 (0.31%) | 0 / 324 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 1 / 324 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 1 / 324 (0.31%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 0 / 324 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 1 / 324 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 1 / 324 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 324 (0.00%) | 0 / 319 (0.00%) | 1 / 324 (0.31%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 324 (0.31%) | 0 / 319 (0.00%) | 0 / 324 (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 |

| | | | |
|---|------------------|--|--|
| Serious adverse events | DS5565 15 mg BID | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 323 (1.55%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Uraemic encephalopathy | | | |
| subjects affected / exposed | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure like phenomena | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo | Pregabalin | DS5565 15 mg QD |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 214 / 324 (66.05%) | 243 / 319 (76.18%) | 247 / 324 (76.23%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 22 / 324 (6.79%) | 49 / 319 (15.36%) | 26 / 324 (8.02%) |
| occurrences (all) | 22 | 49 | 26 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 17 / 324 (5.25%) | 56 / 319 (17.55%) | 47 / 324 (14.51%) |
| occurrences (all) | 17 | 56 | 47 |
| Headache | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 50 / 324 (15.43%) 50 | 41 / 319 (12.85%) 41 | 39 / 324 (12.04%) 39 |
| Somnolence subjects affected / exposed occurrences (all) | 9 / 324 (2.78%) 9 | 40 / 319 (12.54%) 40 | 29 / 324 (8.95%) 29 |
| General disorders and administration site conditions Drug withdrawal syndrome subjects affected / exposed occurrences (all) | 10 / 324 (3.09%) 10 | 12 / 319 (3.76%) 12 | 15 / 324 (4.63%) 15 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 4 / 324 (1.23%) 4 | 18 / 319 (5.64%) 18 | 11 / 324 (3.40%) 11 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 11 / 324 (3.40%) 11 | 18 / 319 (5.64%) 18 | 25 / 324 (7.72%) 25 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 11 / 324 (3.40%) 11 | 11 / 319 (3.45%) 11 | 18 / 324 (5.56%) 18 |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 14 / 324 (4.32%) 14 | 10 / 319 (3.13%) 10 | 20 / 324 (6.17%) 20 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 13 / 324 (4.01%) 13 | 19 / 319 (5.96%) 19 | 13 / 324 (4.01%) 13 |

| | | | |
|---|-------------------------|--|--|
| Non-serious adverse events | DS5565 15 mg BID | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 247 / 323 (76.47%) | | |
| Investigations Weight increased subjects affected / exposed occurrences (all) | 34 / 323 (10.53%) 34 | | |
| Nervous system disorders | | | |

| | | | |
|--|-------------------------|--|--|
| Dizziness subjects affected / exposed occurrences (all) | 36 / 323 (11.15%) 36 | | |
| Headache subjects affected / exposed occurrences (all) | 31 / 323 (9.60%) 31 | | |
| Somnolence subjects affected / exposed occurrences (all) | 39 / 323 (12.07%) 39 | | |
| General disorders and administration site conditions Drug withdrawal syndrome subjects affected / exposed occurrences (all) | 21 / 323 (6.50%) 21 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 15 / 323 (4.64%) 15 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 20 / 323 (6.19%) 20 | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 7 / 323 (2.17%) 7 | | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 16 / 323 (4.95%) 16 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 14 / 323 (4.33%) 14 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 29 July 2014 | Made multiple changes based on sponsor decision and FDA feedback. Amendment occurred before first subject first visit, so all changes were incorporated into the initial informed consent. |
| 29 January 2015 | Clarified and added eligibility criteria and screening methods. and increased screening window. |
| 07 April 2016 | Modified inclusion exclusion criteria to reflect DSMB's recommendation to screen for suicidality. |
| 15 December 2016 | Changed order of objectives and statistical analysis plan. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported