# 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 | 2013-005161-40 |
| Trial protocol | SE DE DK CZ FI NL |
| Global end of trial date | 14 July 2016 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 04 November 2017 |
| First version publication date | 25 August 2017 |
| Version creation reason | • Correction of full data set<br>The date the last subject completed this trial was actually on 14-Jul-2016, so the global end of trial date is adjusted accordingly. |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | DS5565-A-E309 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02146430 |
| 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 Application, Daiichi Sankyo Development Ltd, +44 1753482800, euregaffairs@dsd-eu.com |
| Scientific contact | Clinical Trial Application, Daiichi Sankyo Development Ltd, +44 1753482800, euregaffairs@dsd-eu.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 | 02 June 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 14 July 2016 |
| 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 Practices which has its foundation in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 27 October 2014 |
| 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 | Netherlands: 12 |
| Country: Number of subjects enrolled | Norway: 69 |
| Country: Number of subjects enrolled | Sweden: 16 |
| Country: Number of subjects enrolled | Czech Republic: 77 |
| Country: Number of subjects enrolled | Denmark: 26 |
| Country: Number of subjects enrolled | Finland: 7 |
| Country: Number of subjects enrolled | France: 25 |
| Country: Number of subjects enrolled | Germany: 168 |
| Country: Number of subjects enrolled | Canada: 120 |
| Country: Number of subjects enrolled | Serbia: 62 |
| Country: Number of subjects enrolled | United States: 711 |
| Worldwide total number of subjects | 1293 |
| EEA total number of subjects | 400 |

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) | 1183 |
| From 65 to 84 years | 109 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Of 2318 patients, 1293 from 11 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 and /or capsule |
| Investigational medicinal product code | |
| Other name | Matching Placebo |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo for oral administration matching tablet for DS-5565 and matching capsule for pregabalin

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

Arm description:

Patients take one pregabalin capsule and one placebo tablet BID

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Pregabalin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Pregabalin 150 mg capsule for oral administration

| | |
|---|---|
| Investigational medicinal product name | Placebo tablet and /or capsule |
| Investigational medicinal product code | |
| Other name | Matching Placebo |
| Pharmaceutical forms | Tablet, Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo for oral administration matching tablet for DS-5565 and matching capsule for pregabalin

| | |
|---|---|
| **Arm title** | DS-5565 QD |

Arm description:

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

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

Dosage and administration details:

DS-5565 15 mg tablet for oral administration

| | |
|---|---|
| Investigational medicinal product name | Placebo tablet and /or capsule |
| Investigational medicinal product code | |
| Other name | Matching Placebo |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo for oral administration matching tablet for DS-5565 and matching capsule for pregabalin

| **Arm title** | DS-5565 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 15 mg tablet for oral administration

| | |
|---|---|
| Investigational medicinal product name | Placebo tablet and /or capsule |
| Investigational medicinal product code | |
| Other name | Matching Placebo |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo for oral administration matching tablet for DS-5565 and matching capsule for pregabalin

| **Number of subjects in period 1** | Placebo | Pregabalin | DS-5565 QD |
|---|---|---|---|
| Started | 323 | 323 | 324 |
| Safety Analysis Set | 318 | 318 | 320 |
| Modified intent to treat set (mITT) | 318 | 317 | 319 |
| Completed double-blind treatment period | 256 | 236 | 242 |
| Completed | 256 | 236 | 242 |
| Not completed | 67 | 87 | 82 |
| Consent withdrawn by subject | 27 | 29 | 30 |
| Adverse event, non-fatal | 20 | 40 | 32 |
| Reason missing or not reported | 2 | 3 | 4 |
| Lack of efficacy | 13 | 11 | 8 |

| | | | |
|---|---|---|---|
| Protocol deviation | 5 | 4 | 8 |

| **Number of subjects in period 1** | DS-5565 BID |
|---|---|
| Started | 323 |
| Safety Analysis Set | 320 |
| Modified intent to treat set (mITT) | 319 |
| Completed double-blind treatment period | 224 |
| Completed | 224 |
| Not completed | 99 |
| Consent withdrawn by subject | 34 |
| Adverse event, non-fatal | 49 |
| Reason missing or not reported | 5 |
| Lack of efficacy | 5 |
| Protocol deviation | 6 |

## 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 | DS-5565 QD |
| Reporting group description: | |
| Patients take one each of placebo tablet and capsule in the morning and one DS-5565 tablet once daily (QD) with a placebo capsule in the evening | |
| Reporting group title | DS-5565 BID |
| Reporting group description: | |
| Patients take one DS-5565 tablet and one placebo capsule BID | |

| Reporting group values | Placebo | Pregabalin | DS-5565 QD |
|---|---|---|---|
| Number of subjects | 323 | 323 | 324 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 298 | 298 | 300 |
| From 65-84 years | 25 | 24 | 24 |
| 85 years and over | 0 | 1 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 48.6 | 49.5 | 50.3 |
| standard deviation | ± 11.76 | ± 11.53 | ± 10.88 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 299 | 292 | 286 |
| Male | 24 | 31 | 38 |

| Reporting group values | DS-5565 BID | Total | |
|---|---|---|---|
| Number of subjects | 323 | 1293 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 287 | 1183 | |
| From 65-84 years | 36 | 109 | |
| 85 years and over | 0 | 1 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 49.5 | | |
| standard deviation | ± 11.77 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 291 | 1168 | |
| Male | 32 | 125 | |

## 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 | DS-5565 QD |
| Reporting group description: | |
| Patients take one each of placebo tablet and capsule in the morning and one DS-5565 tablet once daily (QD) with a placebo capsule in the evening | |
| Reporting group title | DS-5565 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 of 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. | |
| 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 statistical analyses were performed to arrive at the aggregate summary 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: Pregabalin was reported separately

| End point values | Placebo | DS-5565 QD | DS-5565 BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 317 | 318 | 318 | |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=317,318,318) | 7.19 (± 1.3) | 7.13 (± 1.358) | 7.19 (± 1.295) | |
| Week 13 (MI, n=317,319,318) | 5.47 (± 0.132) | 5.16 (± 0.134) | 5.19 (± 0.136) | |

### 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 outcome measure

| End point values | Placebo | DS-5565 QD | DS-5565 BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 318 | 319 | 319 | |
| Units: Patients | 78 | 94 | 71 | |

### 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 outcome measure

| End point values | Placebo | DS-5565 QD | DS-5565 BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 318 | 319 | 319 | |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=316,316,318) | 65.2 (± 13.629) | 64.51 (± 13.92) | 64.21 (± 13.175) | |

| | | | | |
|---|---|---|---|---|
| Week 13 (n=255,240,224) | 49.81 (± 20.149) | 47.65 (± 19.4) | 48.87 (± 18.928) | |

### 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 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 outcome measure

| End point values | Placebo | DS-5565 QD | DS-5565 BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 318 | 319 | 319 | |
| Units: Patients | | | | |
| 30% responders | 101 | 106 | 100 | |
| 50% responders | 57 | 71 | 57 | |

### 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 of 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.

| 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 reported separately

| End point values | Pregabalin | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 317 | | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| Baseline | 7 (± 1.323) | | | |
| Week 13 | 5.22 (± 0.134) | | | |

## 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:

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 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 | DS-5565 QD |

Reporting group description:

Patients take one DS-5565 tablet once daily (QD) with a placebo capsule, and a placebo capsule and tablet at the other dosing session

| | |
|---|---|
| Reporting group title | DS-5565 BID |

Reporting group description:

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

| Serious adverse events | Placebo | Pregabalin | DS-5565 QD |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 318 (3.46%) | 2 / 318 (0.63%) | 5 / 320 (1.56%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 318 (0.00%) | 1 / 318 (0.31%) | 0 / 320 (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 | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 1 / 320 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 1 / 320 (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 |
| Salivary gland calculus | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 318 (0.00%) | 1 / 318 (0.31%) | 0 / 320 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 1 / 320 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 1 / 320 (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 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 1 / 318 (0.31%) | 0 / 320 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back disorder | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Back pain | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 1 / 320 (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 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 318 (0.00%) | 0 / 318 (0.00%) | 1 / 320 (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 |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 318 (0.31%) | 0 / 318 (0.00%) | 0 / 320 (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** | DS-5565 BID | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 320 (2.50%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 320 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Salivary gland calculus | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back disorder | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| **Infections and infestations** | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious colitis | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 320 (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 | DS-5565 QD |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 207 / 318 (65.09%) | 247 / 318 (77.67%) | 227 / 320 (70.94%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 16 / 318 (5.03%) | 36 / 318 (11.32%) | 21 / 320 (6.56%) |
| occurrences (all) | 16 | 26 | 31 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 20 / 318 (6.29%) | 65 / 318 (20.44%) | 53 / 320 (16.56%) |
| occurrences (all) | 20 | 65 | 53 |
| Headache | | | |
| subjects affected / exposed | 36 / 318 (11.32%) | 48 / 318 (15.09%) | 45 / 320 (14.06%) |
| occurrences (all) | 36 | 48 | 45 |
| Somnolence | | | |
| subjects affected / exposed | 7 / 318 (2.20%) | 37 / 318 (11.64%) | 25 / 320 (7.81%) |
| occurrences (all) | 7 | 37 | 25 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 318 (3.14%) | 23 / 318 (7.23%) | 23 / 320 (7.19%) |
| occurrences (all) | 10 | 23 | 23 |
| Oedema peripheral | | | |
| subjects affected / exposed | 11 / 318 (3.46%) | 19 / 318 (5.97%) | 14 / 320 (4.38%) |
| occurrences (all) | 11 | 19 | 14 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 19 / 318 (5.97%) | 27 / 318 (8.49%) | 27 / 320 (8.44%) |
| occurrences (all) | 19 | 27 | 27 |
| Dry mouth | | | |
| subjects affected / exposed | 5 / 318 (1.57%) | 21 / 318 (6.60%) | 15 / 320 (4.69%) |
| occurrences (all) | 5 | 21 | 15 |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 318 (4.40%) | 10 / 318 (3.14%) | 10 / 320 (3.13%) |
| occurrences (all) | 14 | 10 | 10 |

| | | | |
|---|---|---|---|
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | 7 / 318 (2.20%)<br>7 | 13 / 318 (4.09%)<br>13 | 16 / 320 (5.00%)<br>16 |

| **Non-serious adverse events** | DS-5565 BID | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 249 / 320 (77.81%) | | |
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all) | 26 / 320 (8.13%)<br>36 | | |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br>Somnolence<br>subjects affected / exposed<br>occurrences (all) | 71 / 320 (22.19%)<br>71<br>55 / 320 (17.19%)<br>55<br>39 / 320 (12.19%)<br>39 | | |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 36 / 320 (11.25%)<br>36<br>11 / 320 (3.44%)<br>11 | | |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br>Dry mouth<br>subjects affected / exposed<br>occurrences (all)<br>Diarrhoea | 36 / 320 (11.25%)<br>36<br>18 / 320 (5.63%)<br>18 | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 16 / 320 (5.00%)<br>16 | | |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | <br><br>22 / 320 (6.88%)<br>22 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 July 2014 | Clarify study objectives, endpoints, pain assessment and study procedures |
| 29 January 2015 | Update and clarify screening procedures and duration. Update and provide further direction on how to deal with borderline pregnancy results. |
| 07 April 2016 | Modify and clarify discontinuation criteria |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported