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	19 August 2016

Results information

Result version number	v1
This version publication date	25 August 2017
First version publication date	25 August 2017

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	19 August 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
Protocol deviation	5	4	8

Lack of efficacy	13	11	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
Protocol deviation	6
Lack of efficacy	5

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 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 Units: years			
arithmetic mean	48.6	49.5	50.3
standard deviation	± 11.76	± 11.53	± 10.88
Gender categorical Units: Subjects			
Female	299	292	286
Male	24	31	38

Reporting group values	DS-5565 BID	Total	
Number of subjects	323	1293	
Age categorical Units: Subjects			
Adults (18-64 years)	287	1183	
From 65-84 years	36	109	
85 years and over	0	1	
Age continuous Units: years			
arithmetic mean	49.5		
standard deviation	± 11.77	-	
Gender categorical 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 Insomnia subjects affected / exposed occurrences (all)	7 / 318 (2.20%) 7	13 / 318 (4.09%) 13	16 / 320 (5.00%) 16

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

subjects affected / exposed occurrences (all)	16 / 320 (5.00%) 16		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 22 / 320 (6.88%) 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