



Clinical trial results: An Open-Label Extension Study of DS-5565 for 52 Weeks in Pain Associated with Fibromyalgia Summary

EudraCT number	2013-005164-26
Trial protocol	GB SE DK AT SK EE CZ ES LT HU LV PT SI FI BG PL
Global end of trial date	19 April 2017

Results information

Result version number	v1 (current)
This version publication date	18 April 2018
First version publication date	18 April 2018

Trial information

Trial identification

Sponsor protocol code	DS5565-A-E312
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02234583
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, New Jersey, 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	25 July 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to assess the long-term safety of DS-5565 in subjects with fibromyalgia (FM).

This is an open-label study of DS-5565 in subjects who either completed participation in a preceding Phase 3 study of DS-5565 in fibromyalgia (FM); ie, DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311 or are de novo subjects. Eligible subjects will be assigned to receive open-label DS-5565 for 52 weeks, with a 4-week follow-up period. All subjects will receive DS-5565 15 mg once daily (QD) for the first three weeks of the treatment period. After three weeks, subjects may be titrated to 15 mg twice daily (BID) based on protocol-specified criteria.

Protection of trial subjects:

The study was conducted in compliance with ethical principles that have their origin in the Declaration of Helsinki and in accordance with the following as appropriate:

- European Union Commission Directive (2001/20/EC Apr 2001)
- European Union Commission Directive (2005/28/EC Apr 2005)
- ICH E6 Good Clinical Practice (GCP) Guideline
- US Food and Drug Administration (FDA) Regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2015
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	Norway: 42
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Slovenia: 7
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Denmark: 12

Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Latvia: 19
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Canada: 52
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	New Zealand: 18
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	South Africa: 19
Country: Number of subjects enrolled	Ukraine: 132
Country: Number of subjects enrolled	United States: 1482
Worldwide total number of subjects	2088
EEA total number of subjects	353

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)	1878
From 65 to 84 years	208
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 2485 patients enrolled, 2088 were treated in 28 countries and comprise the safety analysis set.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DS-5565 15 mg QD Modal

Arm description:

Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg once daily (QD).

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

Dosage and administration details:

Oral administration of 15 mg tablets once daily (QD)

Arm title	DS-5565 15 mg BID Modal
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Arm description:

Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg twice daily (BID).

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

Dosage and administration details:

DS-5565 15 mg twice daily (BID)

Number of subjects in period 1	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal
Started	847	1241
Completed	434	685
Not completed	413	556
Consent withdrawn by subject	109	157
Adverse event, non-fatal	172	156

Lost to follow-up	-	1
Lack of efficacy	58	103
Protocol deviation	35	42
No reason provided	39	97

Baseline characteristics

Reporting groups

Reporting group title	DS-5565 15 mg QD Modal
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Reporting group description:

Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg once daily (QD).

Reporting group title	DS-5565 15 mg BID Modal
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Reporting group description:

Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg twice daily (BID).

Reporting group values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal	Total
Number of subjects	847	1241	2088
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	51.4 ± 11.18	49.3 ± 11.94	-
Gender categorical Units: Subjects			
Female	770	1130	1900
Male	77	111	188
Baseline HADS Anxiety Subscale Score Units: Subjects			
Non-case (0-7)	526	666	1192
Borderline case (8-10)	160	260	420
Case (11 or more)	100	239	339
Missing	61	76	137
Baseline HADS Depression Subscale Score Units: Subjects			
Non-case (0-7)	555	757	1312
Borderline case (8-10)	130	211	341
Case (11 or more)	101	197	298
Missing	61	76	137
History of Psychological Disorder or Depression Units: Subjects			
Yes	271	492	763
No	576	749	1325

End points

End points reporting groups

Reporting group title	DS-5565 15 mg QD Modal
Reporting group description: Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg once daily (QD).	
Reporting group title	DS-5565 15 mg BID Modal
Reporting group description: Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg twice daily (BID).	

Primary: Number of Patients with Treatment-emergent Adverse Events (TEAEs) as a Measure of Safety

End point title	Number of Patients with Treatment-emergent Adverse Events (TEAEs) as a Measure of Safety ^[1]
End point description: Note: Further measures of safety and relatedness to drug are found in the AE module.	
End point type	Primary
End point timeframe: Baseline to Week 52	
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 analysis was performed for this summary data.	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	847	1241		
Units: Patients	669	1056		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average Daily Pain Score (ADPS) at Week 13 (Rollover)

End point title	Change from Baseline in Average Daily Pain Score (ADPS) at Week 13 (Rollover)
End point description: The primary efficacy assessment was subject-reported pain intensity, recorded in an electronic daily diary using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain).	
End point type	Secondary
End point timeframe: Baseline, Week 13	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	794		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.03 (± 1.747)	-1.08 (± 1.800)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ADPS at Week 52 (Rollover)

End point title	Change from Baseline in ADPS at Week 52 (Rollover)
End point description: The primary efficacy assessment was subject-reported pain intensity, recorded in an electronic daily diary using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain).	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	428		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.14 (± 2.089)	-1.06 (± 1.995)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ADPS at Week 13 (De Novo)

End point title	Change from Baseline in ADPS at Week 13 (De Novo)
End point description: The primary efficacy assessment was subject-reported pain intensity, recorded in an electronic daily diary using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain).	
End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	237		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-3.66 (\pm 2.109)	-3.26 (\pm 2.326)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ADPS at Week 52 (De Novo)

End point title	Change from Baseline in ADPS at Week 52 (De Novo)
End point description: The primary efficacy assessment was subject-reported pain intensity, recorded in an electronic daily diary using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain).	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	121		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-4.41 (\pm 1.975)	-3.39 (\pm 2.597)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 13 in Average Daily Sleep Interference Score (ADSIS) - (Rollover)

End point title	Change from Baseline to Week 13 in Average Daily Sleep Interference Score (ADSIS) - (Rollover)
End point description: ADSIS is assessed on an 11-point numeric rating scale ranging from 0=pain does not interfere with sleep to 10=pain completely interferes with sleep, unable to sleep.	

Note: The ADSIS was the mean value of all available reporting of the respective week. As Baseline was used: For Rollover subjects, scores from the End-of-Tapering visit in the preceding study, and for De Novo subjects, scores recorded during the 7 days prior to start of treatment.

Note: Subjects were reported under their Modal treatment, ie, the treatment they received most frequently.

End point type	Secondary
End point timeframe:	
Baseline, Week 13	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	794		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.06 (± 1.710)	-1.41 (± 1.942)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in ADSIS (Rollover)

End point title	Change from Baseline to Week 52 in ADSIS (Rollover)
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End point description:

ADSI is assessed on an 11-point numeric rating scale ranging from 0=pain does not interfere with sleep to 10=pain completely interferes with sleep, unable to sleep.

Note: The ADSIS was the mean value of all available reporting of the respective week. As Baseline was used: For Rollover subjects, scores from the End-of-Tapering visit in the preceding study, and for De Novo subjects, scores recorded during the 7 days prior to start of treatment.

Note: Subjects were reported under their Modal treatment, ie, the treatment they received most frequently.

End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	428		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.25 (± 1.968)	-1.31 (± 2.102)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 13 in ADSIS (De Novo)

End point title	Change from Baseline to Week 13 in ADSIS (De Novo)
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End point description:

ADSIIS is assessed on an 11-point numeric rating scale ranging from 0=pain does not interfere with sleep to 10=pain completely interferes with sleep, unable to sleep.

Note: The ADSIS was the mean value of all available reporting of the respective week. As Baseline was used: For Rollover subjects, scores from the End-of-Tapering visit in the preceding study, and for De Novo subjects, scores recorded during the 7 days prior to start of treatment.

Note: Subjects were reported under their Modal treatment, ie, the treatment they received most frequently.

End point type	Secondary
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End point timeframe:

Baseline, Week 13

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	237		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-3.98 (± 2.126)	-3.64 (± 2.297)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in ADSIS (De Novo)

End point title	Change from Baseline to Week 52 in ADSIS (De Novo)
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End point description:

ADSIIS is assessed on an 11-point numeric rating scale ranging from 0=pain does not interfere with sleep to 10=pain completely interferes with sleep, unable to sleep.

Note: The ADSIS was the mean value of all available reporting of the respective week. As Baseline was used: For Rollover subjects, scores from the End-of-Tapering visit in the preceding study, and for De Novo subjects, scores recorded during the 7 days prior to start of treatment.

Note: Subjects were reported under their Modal treatment, ie, the treatment they received most frequently.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	121		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-4.61 (\pm 1.996)	-3.54 (\pm 2.537)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Improvement in Overall Status at Week 52 as Assessed by Patient Global Impression of Change (PGIC) - (Rollover)

End point title	Number of Patients with Improvement in Overall Status at Week 52 as Assessed by Patient Global Impression of Change (PGIC) - (Rollover)
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End point description:

This instrument shows pain intensity in the setting of chronic pain. The 7-point PGIC measures change in the subject's overall status using the following categorical scale: 1) very much improved, 2) much improved, 3) minimally improved, 4) no change, 5) minimally worse, 6) much worse, and 7) very much worse.

End point type	Secondary
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End point timeframe:

Week 52

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	578	962		
Units: Patients	418	696		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Improvement in Overall Status at Week 52 as Assessed by PGIC (De Novo)

End point title	Number of Patients with Improvement in Overall Status at Week 52 as Assessed by PGIC (De Novo)
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End point description:

This instrument shows pain intensity in the setting of chronic pain. The 7-point PGIC measures change in the subject's overall status using the following categorical scale: 1) very much improved, 2) much improved, 3) minimally improved, 4) no change, 5) minimally worse, 6) much worse, and 7) very much worse.

End point type	Secondary
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End point timeframe:

Week 52

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	279		
Units: Patients	191	217		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Hospital Anxiety Depression Scale (HADS) Depression and Anxiety Scores (Rollover)

End point title	Change from Baseline to Week 52 in Hospital Anxiety Depression Scale (HADS) Depression and Anxiety Scores (Rollover)
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End point description:

The HADS questionnaire is a self-assessment scale to assess symptoms of anxiety and depression. The instrument consists of 7 questions related to anxiety and 7 related to depression, each rated on a 4-point scale (score of 0 to 3). Scores for anxiety and depression are independently summed to compute HADS-Anxiety and HADS-Depression subscale scores, with ranges from 0 to 21, where higher scores indicate greater severity.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	497		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Anxiety Subscale Score	-0.5 (± 3.25)	0.1 (± 3.27)		
Depression Subscale Score	-1.0 (± 3.80)	-1.3 (± 3.61)		

Statistical analyses

Secondary: Change from Baseline to Week 52 in HADS Depression and Anxiety Scores (De Novo)

End point title	Change from Baseline to Week 52 in HADS Depression and Anxiety Scores (De Novo)
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End point description:

The HADS questionnaire is a self-assessment scale to assess symptoms of anxiety and depression. The instrument consists of 7 questions related to anxiety and 7 related to depression, each rated on a 4-point scale (score of 0 to 3). Scores for anxiety and depression are independently summed to compute HADS-Anxiety and HADS-Depression subscale scores, with ranges from 0 to 21, where higher scores indicate greater severity.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	137		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Anxiety Subscale Score	-1.9 (± 3.78)	-1.3 (± 3.32)		
Depression Subscale Score	-2.6 (± 4.34)	-1.7 (± 3.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-Instrument 5 Dimensions (EQ-5D) - (Rollover)

End point title	Change from Baseline in EuroQol-Instrument 5 Dimensions (EQ-5D) - (Rollover)
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End point description:

The EQ-5D is an instrument that shows high construct validity and responsiveness in patients with chronic pain and has been used specifically in FM. The EQ-5D includes a descriptive section with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are combined into an overall health utilities index, and an NRS (100 mm VAS) that measures perception of overall health, with 0 indicating worst health and 100 representing best imaginable health.

End point type	Secondary
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End point timeframe:

Baseline, Week 52

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	497		
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.0404 (\pm 0.15612)	0.0608 (\pm 0.16397)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D (De Novo)

End point title	Change from Baseline in EQ-5D (De Novo)
End point description: The EQ-5D is an instrument that shows high construct validity and responsiveness in patients with chronic pain and has been used specifically in FM. The EQ-5D includes a descriptive section with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are combined into an overall health utilities index, and an NRS (100 mm VAS) that measures perception of overall health, with 0 indicating worst health and 100 representing best imaginable health.	
End point type	Secondary
End point timeframe: Baseline, Week 52	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	137		
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.1703 (\pm 0.16944)	0.1739 (\pm 0.20900)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Short Form 36 (SF-36) Transformed Scores (Rollover)

End point title	Change from Baseline in Short Form 36 (SF-36) Transformed Scores (Rollover)
End point description: The SF-36 is a health survey that asks 36 questions to measure functional health and well-being from the subject's point of view. It is a measure of physical and mental health used across various disease areas, including FM. The SF-36 provides scores for 8 health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) as well as psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. The scores from all parameters were then transformed into a single score, and change from baseline calculated.	

Note: Subjects were reported under their Modal treatment, ie, the treatment they received most frequently.

Note: High scores are better than low scores; thus, positive changes indicate improvement.

End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	497		
Units: Transformed scores on a scale				
arithmetic mean (standard deviation)	1.526 (\pm 8.8842)	0.653 (\pm 8.9221)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 Transformed Scores (De Novo)

End point title	Change from Baseline in SF-36 Transformed Scores (De Novo)
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End point description:

The SF-36 is a health survey that asks 36 questions to measure functional health and well-being from the subject's point of view. It is a measure of physical and mental health used across various disease areas, including FM. The SF-36 provides scores for 8 health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) as well as psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. The scores from all parameters were then transformed into a single score, and change from baseline calculated.

Note: Subjects were reported under their Modal treatment, ie, the treatment they received most frequently.

Note: High scores are better than low scores; thus, positive changes indicate improvement.

End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	136		
Units: Transformed scores on a scale				
arithmetic mean (standard deviation)	6.205 (\pm 11.5925)	3.636 (\pm 9.9236)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A treatment emergent adverse event (TEAE) is any adverse event that emerges on or after the first dosing of open-label extension (OLE) medication and during the study.

Adverse event reporting additional description:

Total number of TEAEs counts all occurrences in all patients. In the system organ class and preferred term summary, a patient was counted once when one or more events were reported, so the number of events simply mirrors the number of patients experiencing the preferred term.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	DS-5565 15 mg QD Modal
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Reporting group description:

Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg once daily (QD).

Reporting group title	DS-5565 15 mg BID Modal
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Reporting group description:

Patients are reported under their modal treatment, ie, the treatment they received most frequently, which was DS-5565 15 mg twice daily (BID). One death was due to an unknown cause, and was not considered related to study drug. One death for unknown cause was listed as an adverse event.

Serious adverse events	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 847 (4.84%)	94 / 1241 (7.57%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	2 / 847 (0.24%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage III			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Castleman's disease			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure fluctuation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 847 (0.12%)	4 / 1241 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Bereavement			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 847 (0.24%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	3 / 847 (0.35%)	3 / 1241 (0.24%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Suicide attempt			
subjects affected / exposed	3 / 847 (0.35%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 847 (0.24%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase abnormal			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaesthetic complication			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Spine malformation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Supraventricular tachycardia subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 847 (0.00%)	3 / 1241 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 847 (0.24%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysarthria			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticulum			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure acute			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	2 / 847 (0.24%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 847 (0.35%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis C			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1241 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1241 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DS-5565 15 mg QD Modal	DS-5565 15 mg BID Modal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	666 / 847 (78.63%)	847 / 1241 (68.25%)	
Investigations			
Weight increased			
subjects affected / exposed	83 / 847 (9.80%)	207 / 1241 (16.68%)	
occurrences (all)	83	207	
Nervous system disorders			
Dizziness			
subjects affected / exposed	132 / 847 (15.58%)	148 / 1241 (11.93%)	
occurrences (all)	132	148	
Headache			
subjects affected / exposed	122 / 847 (14.40%)	157 / 1241 (12.65%)	
occurrences (all)	122	157	
Somnolence			
subjects affected / exposed	130 / 847 (15.35%)	102 / 1241 (8.22%)	
occurrences (all)	130	102	
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	61 / 847 (7.20%)	135 / 1241 (10.88%)	
occurrences (all)	61	135	
Fatigue			
subjects affected / exposed	76 / 847 (8.97%)	83 / 1241 (6.69%)	
occurrences (all)	76	83	
Oedema peripheral			
subjects affected / exposed	52 / 847 (6.14%)	80 / 1241 (6.45%)	
occurrences (all)	52	80	
Eye disorders			
Vision blurred			
subjects affected / exposed	26 / 847 (3.07%)	56 / 1241 (4.51%)	
occurrences (all)	26	56	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	61 / 847 (7.20%)	113 / 1241 (9.11%)	
occurrences (all)	61	113	
Diarrhoea			

subjects affected / exposed occurrences (all)	40 / 847 (4.72%) 40	97 / 1241 (7.82%) 97	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 847 (4.01%)	63 / 1241 (5.08%)	
occurrences (all)	34	63	
Depression			
subjects affected / exposed	21 / 847 (2.48%)	44 / 1241 (3.55%)	
occurrences (all)	21	44	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	35 / 847 (4.13%)	87 / 1241 (7.01%)	
occurrences (all)	35	87	
Arthralgia			
subjects affected / exposed	32 / 847 (3.78%)	87 / 1241 (7.01%)	
occurrences (all)	32	87	
Pain in extremity			
subjects affected / exposed	27 / 847 (3.19%)	64 / 1241 (5.16%)	
occurrences (all)	27	64	
Fibromyalgia			
subjects affected / exposed	26 / 847 (3.07%)	61 / 1241 (4.92%)	
occurrences (all)	26	61	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	43 / 847 (5.08%)	134 / 1241 (10.80%)	
occurrences (all)	43	134	
Nasopharyngitis			
subjects affected / exposed	47 / 847 (5.55%)	110 / 1241 (8.86%)	
occurrences (all)	47	110	
Urinary tract infection			
subjects affected / exposed	51 / 847 (6.02%)	105 / 1241 (8.46%)	
occurrences (all)	51	105	
Sinusitis			
subjects affected / exposed	36 / 847 (4.25%)	88 / 1241 (7.09%)	
occurrences (all)	36	88	
Viral infection			

subjects affected / exposed	14 / 847 (1.65%)	27 / 1241 (2.18%)	
occurrences (all)	14	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2014	Protocol V2.0, dated 31 Jul 2014, corrected minor editorial errors, as well as the following content revisions: Clarified secondary objectives Clarified the study site for open-label study Clarified Sponsor decision to update sample size determination Added Sponsor decision to edit Exclusion Criteria Clarified secondary endpoints Clarified study procedures for Visit 2 Corrected study procedures to be consistent with schedule of events Updated that all subjects needed to complete SF-36 and EQ-5D questionnaires Clarified dosing instruction Included the procedure for evaluating titration possibility Clarified study procedures for De Novo subjects Reworded protocol for clarification regarding the ADPS Updated text on ECGs to include the difference between De Novo and Rollover subjects Added Sponsor decision to add interim analyses Added a description of the electronic device used to capture daily pain score Clarified the language used for recording medical history Updated the changes in study schedule
29 January 2015	Protocol V3.0, dated 29 Jan 2015, corrected minor editorial errors, as well as the following content revisions: Revised the list numbering of Inclusion and Exclusion criteria for De Novo subjects Added scanning laser ophthalmoscopy to fundoscopic examination of the eyes as an alternative method Changed the position of creatine kinase as a separate bullet point in the relevant section for clarity Updated birth control methods based on feedback from Health Authority and provided further direction on how to deal with borderline pregnancy results Clarified the usage of acetaminophen/paracetamol Extended the Screening Period for De Novo subjects to 35 days Updated the instruction for performing ECGs Corrected Visit 5 (week 1) to include a visit window of ± 3 Deleted "modified" from Cockcroft-Gault Equation and lean body mass
07 April 2016	Protocol V4.0, dated 07 Apr 2016 corrected minor editorial errors, as well as the following content revisions: Reflected the DSMB's recommendation to implement a protocol amendment due to an increased incidence of suicidal ideation of subjects on study drugs versus placebo Clarified that in the study, the C-SSRS was to be administered at all clinic visits and clarified the correct actions if, based on the C-SSRS and Investigator judgment, a subject was identified as being at risk for suicide

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported