Clinical trial results:
A Randomized, Double-blind, Placebo Controlled Safety Study of DS-5565 for Treatment of Pain Due to Fibromyalgia in Subjects with Chronic Kidney Disease

Summary

EudraCT number	2014-003972-21
Trial protocol	HU CZ ES BG
Global end of trial date	06 July 2017

Results information

Result version number	v1 (current)
This version publication date	23 June 2018
First version publication date	23 June 2018

Trial information

Trial identification

Sponsor protocol code	DS5565-A-U307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02496884
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Clinical Trial Information Contact, Daiichi Sankyo, Inc., 1 9089926400, eu_cta@dsi.com
Scientific contact	Clinical Trial Information Contact, Daiichi Sankyo, Inc., 1 9089926400, 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	08 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of subjects with FM and moderate to severe renal dysfunction during 13 weeks of renally-adjusted dosing of DS-5565 compared to placebo, followed by a short-term (4-week) safety follow-up.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guidelines.

An independent DSMB was created to further protect the rights, safety, and well-being of subjects who were participating in this study by monitoring their progress and results. The independent DSMB was composed of qualified scientists, who were not investigators in the study and not otherwise directly associated with the sponsor.

Additional protection was provided by special monitoring of liver enzyme elevations and liver dysfunction performed by a Hepatic Adjudication Committee (HAC), which was comprised of three qualified hepatologists who also were not investigators in the study and not otherwise directly associated with the sponsor. The HAC completed assessments on an ongoing basis. Adjudication of hepatic events was based on evaluation of electronic case report forms (eCRFs) and source documents, as available, including but not limited to hospital discharge summaries, diagnostic imaging, histopathology, consultation, and laboratory reports.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	26 June 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	Romania: 3
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	56
EEA total number of subjects	9

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)	22
From 65 to 84 years	29
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Randomized patients were recruited in four countries: Bulgaria (5), Romania (3), Spain (1), and the United States (47).

Pre-assignment

Screening details:

Of 231 patients enrolled, 175 discontinued before being randomized. Reasons for discontinuing before randomization included: screen failure (164), adverse events (1), withdrawal by patient (7), other, counted twice as enrolled (2), and other, no reason provided (1). The remaining 56 patients were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	M-CKD Placebo

Arm description:

Patients with M-CKD randomized to receive placebo twice daily (BID) during the treatment period.

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

Dosage and administration details:

Placebo film-coated tablet for oral use

Arm title	M-CKD DS-5565 7.5 mg BID

Arm description:

Patients with M-CKD randomized to receive DS-5565 BID during the treatment period.

Arm type	Experimental
Investigational medicinal product name	DS-5565 Tablet
Investigational medicinal product code	SUB60040
Other name	Mirogabalin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-5565 7.5 mg film-coated tablet for oral use

Arm title	S-CKD Placebo

Arm description:

Patients with severe chronic kidney disease (S-CKD) randomized to receive placebo once daily (QD) during the treatment period.

Arm type	Placebo

Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	Placebo comparator
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo film-coated tablet for oral use

Arm title	S-CKD DS-5565 7.5 mg QD

Arm description:

Patients with S-CKD randomized to receive DS-5565 QD during the treatment period.

Arm type	Experimental
Investigational medicinal product name	DS-5565 Tablet
Investigational medicinal product code	SUB60040
Other name	Mirogabalin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-5565 7.5 mg film-coated tablet for oral use

Number of subjects in period 1	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo
Started	17	34	1
Safety Analysis Set	17	34	1
Modified Intent-to-Treat Set (mITT)	17	34	1
Pharmacokinetic Analysis Set (PK)	0 [1]	33	0 [2]
Completed Treatment per Protocol	16	27 [3]	1
Completed	15	31	1
Not completed	2	3	0
Consent withdrawn by subject	-	3	-
Counted twice as enrolled	2	-	-

Number of subjects in period 1	S-CKD DS-5565 7.5 mg QD
Started	4
Safety Analysis Set	4
Modified Intent-to-Treat Set (mITT)	4
Pharmacokinetic Analysis Set (PK)	4
Completed Treatment per Protocol	3 [4]
Completed	4
Not completed	0
Consent withdrawn by subject	-
Counted twice as enrolled	-

Notes:

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

Justification: Some patients who did not complete treatment per protocol were included in the safety follow-up.

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

Justification: Some patients who did not complete treatment per protocol were included in the safety follow-up.

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

Justification: Some patients who did not complete treatment per protocol were included in the safety follow-up.

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

Justification: Some patients who did not complete treatment per protocol were included in the safety follow-up.

Baseline characteristics

Reporting groups	
Reporting group title	M-CKD Placebo
Reporting group description:	
Patients with M-CKD randomized to receive placebo twice daily (BID) during the treatment period.	
Reporting group title	M-CKD DS-5565 7.5 mg BID
Reporting group description:	
Patients with M-CKD randomized to receive DS-5565 BID during the treatment period.	
Reporting group title	S-CKD Placebo
Reporting group description:	
Patients with severe chronic kidney disease (S-CKD) randomized to receive placebo once daily (QD) during the treatment period.	
Reporting group title	S-CKD DS-5565 7.5 mg QD
Reporting group description:	
Patients with S-CKD randomized to receive DS-5565 QD during the treatment period.	

Reporting group values	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo
Number of subjects	17	34	1
Age categorical Units: Subjects			
Adults (18-64 years)	8	12	1
From 65-84 years	9	18	0
85 years and over	0	4	0
Age continuous Units: years			
arithmetic mean	64.4	68.4	53.0
standard deviation	± 11.39	± 13.92	± 0
Gender categorical Units: Subjects			
Female	16	28	1
Male	1	6	0
Chinese ethnicity Units: Subjects			
Yes	0	0	0
No	17	34	1
Race (alternative categorization) Units: Subjects			
White	14	29	0
Non-White	3	5	1
Baseline Average Daily Pain Score (ADPS)			
Patients were asked to rate their pain on a scale of 0-10, where 0=no pain and 10=worse pain experienced. The number of patients with an ADPS in each of two categories was recorded: less than 7 and more than 7.			
Units: Subjects			
ADPS less than 7	8	9	1
ADPS 7 or more	9	25	0

Baseline Average Daily Pain Score (ADPS)			
Patients were asked to rate their pain on a scale of 0-10, where 0=no pain and 10=the most pain experienced. The average ADPS at baseline was recorded.			
Units: score on a scale			
arithmetic mean	6.99	7.21	5.70
standard deviation	± 1.353	± 0.962	± 0

Reporting group values	S-CKD DS-5565 7.5 mg QD	Total	
Number of subjects	4	56	
Age categorical			
Units: Subjects			
Adults (18-64 years)	1	22	
From 65-84 years	2	29	
85 years and over	1	5	
Age continuous			
Units: years			
arithmetic mean	74.0		
standard deviation	± 12.25	-	
Gender categorical			
Units: Subjects			
Female	0	45	
Male	4	11	
Chinese ethnicity			
Units: Subjects			
Yes	0	0	
No	4	56	
Race (alternative categorization)			
Units: Subjects			
White	2	45	
Non-White	2	11	
Baseline Average Daily Pain Score (ADPS)			
Patients were asked to rate their pain on a scale of 0-10, where 0=no pain and 10=worse pain experienced. The number of patients with an ADPS in each of two categories was recorded: less than 7 and more than 7.			
Units: Subjects			
ADPS less than 7	2	20	
ADPS 7 or more	2	36	
Baseline Average Daily Pain Score (ADPS)			
Patients were asked to rate their pain on a scale of 0-10, where 0=no pain and 10=the most pain experienced. The average ADPS at baseline was recorded.			
Units: score on a scale			
arithmetic mean	6.53		
standard deviation	± 0.822	-	

End points

End points reporting groups

Reporting group title	M-CKD Placebo
Reporting group description:	
Patients with M-CKD randomized to receive placebo twice daily (BID) during the treatment period.	
Reporting group title	M-CKD DS-5565 7.5 mg BID
Reporting group description:	
Patients with M-CKD randomized to receive DS-5565 BID during the treatment period.	
Reporting group title	S-CKD Placebo
Reporting group description:	
Patients with severe chronic kidney disease (S-CKD) randomized to receive placebo once daily (QD) during the treatment period.	
Reporting group title	S-CKD DS-5565 7.5 mg QD
Reporting group description:	
Patients with S-CKD randomized to receive DS-5565 QD during the treatment period.	

Primary: Number of patients experiencing a Treatment Emergent Adverse Event (TEAE)

End point title	Number of patients experiencing a Treatment Emergent Adverse Event (TEAE)[1]
End point description:	
A TEAE is any adverse event that emerges 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 (having been absent prior to treatment) or worsens relative to the pre-double blind treatment state. Relationship of TEAEs to study drug was assessed by the investigator. Clinically significant changes from baseline in clinical laboratory evaluations, neurological examinations, and electrocardiograms are reported as TEAEs.	
End point type	Primary
End point timeframe:	
baseline through follow-up period 4 weeks after the last dose of study medication, within 25 months	

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 on these summary statistics.

End point values	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo	S-CKD DS-5565 7.5 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	34	1	4
Units: Patients				
Patients with at least one TEAE	8	16	0	3
Patients with a drug-related TEAE	1	9	0	0
Patients with a serious TEAE	0	1	0	0
Patients with a drug-related serious TEAE	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Patients Answering Yes to any question on the Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Patients Answering Yes to any question on the Columbia-Suicide Severity Rating Scale (C-SSRS)[2]

End point description:

The C-SSRS is described as a scale developed at Columbia University that has 2-6 questions each in categories of Suicidal Ideation, Intensity of Ideation, Suicidal Behavior, and Actual Attempts. The higher the score, the higher the suicide risk.

End point type	Primary

End point timeframe:

Screening, Baseline, Post-baseline (through Week 13)

Notes:

[2] - 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 patients answered Yes, so it was not possible to perform analysis on these summary statistics.

End point values	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo	S-CKD DS-5565 7.5 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	34	1	4
Units: Patients				
Yes at Screening	0	0	0	0
Yes at Baseline	0	0	0	0
Yes at Post-baseline	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Weekly Average of Individual Daily Pain Scores (ADPS)

End point title	Mean Weekly Average of Individual Daily Pain Scores (ADPS)

End point description:

Each day participants will rate their worst pain over the last 24 hours on a scale from 0-10, where 0=no pain and 10=worst pain imaginable. Each week individual pain scores will be averaged, and the mean weekly score for the treatment group will be calculated.

End point type	Secondary

End point timeframe:

through Week 13

End point values	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo	S-CKD DS-5565 7.5 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	34	1	4
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline Period	6.99 (± 1.353)	7.21 (± 0.962)	5.70 (± 0)	6.53 (± 0.822)
Week 1	6.26 (± 1.526)	6.10 (± 1.628)	2.0 (± 0)	6.88 (± 0.150)
Week 2	6.03 (± 1.681)	5.73 (± 2.055)	1.70 (± 0)	6.60 (± 0.800)
Week 3	5.77 (± 1.720)	5.55 (± 1.949)	1.70 (± 0)	6.80 (± 0.400)
Week 4	5.41 (± 1.914)	5.43 (± 1.986)	1.30 (± 0)	6.75 (± 0.500)
Week 5	5.45 (± 1.648)	5.46 (± 2.078)	0.70 (± 0)	6.90 (± 0.987)
Week 6	5.16 (± 1.751)	5.16 (± 2.180)	1.4 (± 0)	6.43 (± 1.914)
Week 7	5.03 (± 2.096)	5.09 (± 2.143)	1.20 (± 0)	6.67 (± 1.528)
Week 8	5.15 (± 2.034)	5.04 (± 2.225)	1.00 (± 0)	6.73 (± 1.518)
Week 9	5.09 (± 1.816)	4.81 (± 2.243)	1.00 (± 0)	6.47 (± 1.909)
Week 10	4.86 (± 2.060)	4.97 (± 2.195)	0.90 (± 0)	6.53 (± 1.747)
Week 11	4.28 (± 1.987)	4.80 (± 2.308)	0.70 (± 0)	6.73 (± 1.124)
Week 12	4.17 (± 2.158)	4.69 (± 2.199)	0.80 (± 0)	6.63 (± 2.274)
Week 13	4.28 (± 2.454)	4.15 (± 1.844)	1.00 (± 0)	6.80 (± 2.227)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC)

End point title	Patient Global Impression of Change (PGIC)

End point description:

At the end of treatment, patients rate their overall status on a scale of 1-7, where 1=very much improved and 7=very much worse using the standard PGIC questionnaire. The PGIC is a validated outcome measure for treatment of pain in the acute pain setting.

End point type	Secondary

End point timeframe:

at Week 13 / end of treatment

End point values	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo	S-CKD DS-5565 7.5 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	34	1	4
Units: Patients				
1-3 Improved	12	20	1	1
4 No change	3	8	0	3
5-7 Worsened	1	0	0	0
Missing	1	6	0	0

Statistical analyses

Statistical analysis title	PGIC<=2 (Much improved or better)
Statistical analysis description: Frequency Difference vs Placebo	
Comparison groups	M-CKD DS-5565 7.5 mg BID v M-CKD Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Newcombe-Wilson
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.4
upper limit	30

Statistical analysis title	CKD PGIC <=2 (much Improved or better)
Statistical analysis description: Frequency difference vs Placebo	
Comparison groups	S-CKD Placebo v S-CKD DS-5565 7.5 mg QD
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Newcombe-Wilson
Point estimate	-100
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100
upper limit	12.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

13 weeks

Adverse event reporting additional description:

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 mirrors the number of participants, as they experienced the preferred term one or more times.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	M-CKD Placebo

Reporting group description:

Patients with M-CKD randomized to receive placebo twice daily (BID) during the treatment period.

Reporting group title	M-CKD DS-5565 7.5 mg BID

Reporting group description:

Patients with M-CKD randomized to receive DS-5565 BID during the treatment period.

Reporting group title	S-CKD Placebo

Reporting group description:

Patients with severe chronic kidney disease (S-CKD) randomized to receive placebo once daily (QD) during the treatment period.

Reporting group title	S-CKD DS-5565 7.5 mg QD

Reporting group description:

Patients with S-CKD randomized to receive DS-5565 QD during the treatment period.

Serious adverse events	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (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

Serious adverse events	S-CKD DS-5565 7.5 mg QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 4 (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: 1 %

Non-serious adverse events	M-CKD Placebo	M-CKD DS-5565 7.5 mg BID	S-CKD Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)	16 / 34 (47.06%)	0 / 1 (0.00%)
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	0 / 17 (0.00%)	2 / 34 (5.88%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)	2 / 34 (5.88%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Pulmonary mass			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Asthma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Investigations			

Weight increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 34 (5.88%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	3 / 34 (8.82%)	0 / 1 (0.00%)
occurrences (all)	1	3	0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	2 / 34 (5.88%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0

Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Neutrophilia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 17 (5.88%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0

Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	3 / 34 (8.82%)	0 / 1 (0.00%)
occurrences (all)	1	3	0
Lobar pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0

Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 17 (0.00%)	2 / 34 (5.88%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	3 / 17 (17.65%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	S-CKD DS-5565 7.5 mg QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)		
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary mass			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Nervousness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Investigations Weight increased subjects affected / exposed occurrences (all) Creatinine renal clearance decreased subjects affected / exposed occurrences (all) Hepatic enzyme increased subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Post-traumatic pain subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Cardiac disorders Bundle branch block left subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neutrophilia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Ecchymosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Lobar pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Viral infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hyperuricaemia subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2016	• Excluded patients identified at screening as being at risk for suicide • Modified discontinuation criteria to provide extra safety measures for patients identified as being at risk for suicide
31 May 2016	• Changed sponsor's name from Daiichi Sankyo Development Limited to Daiichi Sankyo, Inc. • Updated birth control to highly effective methods, as follows: Female patients (or female partners of male patients) who are of child bearing potential should use a highly effective method of contraception throughout their participation in the study, such as hormonal methods associated with inhibition of ovulation, intra-uterine device, surgical sterilization (including partner's vasectomy) and sexual abstinence. • Amended prohibited medications, by: o Requiring patient instructions to take no prohibited medication during the baseline period, prior to randomization, or during the subsequent treatment period, and that using prohibited medications could cause them to be discontinued from the study o Requiring psychiatric consultation before change or wash-out of psychiatric medication
14 March 2017	Modified the protocol to require the following: • Notification to the patients that Mini-international Neuropsychiatric Interview (MINI, version 6) and C-SSRS will be administered at any time during the study (including unscheduled visits) along with psychiatric evaluation at the investigator's discretion • Any time the investigator or staff suspects potential mood disturbance, suicide risk, and/or substantial changes in psychosocial environment, the C-SSRS and MINI is to be administered, with a referral for psychiatric care • Patients assessed as having current severe or uncontrolled major depressive or anxiety disorders and/or suicidal risk are discontinued from the study and given immediate psychiatric care

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported