



## Clinical trial results:

**Phase III clinical trial to evaluate the efficacy and safety of chondroitin sulphate and glucosamine sulphate in combination versus placebo in patients with osteoarthritis of the knee.**

### Summary

EudraCT number	2013-000444-26
Trial protocol	ES
Global end of trial date	21 August 2014

### Results information

Result version number	v1 (current)
This version publication date	13 March 2016
First version publication date	13 March 2016

### Trial information

#### Trial identification

Sponsor protocol code	TM-CS+SG/301
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01893905
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Tedec-Meiji Farma, S.A.
Sponsor organisation address	Ctra. M-300, Km. 30,500, Alcalá de Henares (Madrid), Spain, 28802
Public contact	Departamento Investigación Clínica, Tedec-Meiji Farma, S.A., 34 918870980, m.gimeno@tedecmeiji.com
Scientific contact	Departamento Investigación Clínica, Tedec-Meiji Farma, S.A., 34 918870980, m.gimeno@tedecmeiji.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	03 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 August 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of the combination of chondroitin sulphate + glucosamine sulphate (CS+SG) manufactured by Tedec-Meiji Farma, S.A. compared to placebo in patients with osteoarthritis of the knee.

Protection of trial subjects:

Acetaminophen upon demand, maximum 4g/day, was allowed for pain relief if necessary.

Any other rescue medication considered necessary for any pathology during the study, was administered based on investigator judgment based on the clinical condition of the patient

Background therapy:

Acetaminophen upon demand, maximum 4g/day, as rescue medication.

Evidence for comparator:

According to EMA Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis, if a drug is intended to be approved for pain relief, a placebo-controlled design is recommended.

In addition, the comparator choice was proposed by the Spanish Agency for Medicines and Medical Devices(AEMPS).

Actual start date of recruitment	15 May 2013
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	Spain: 158
Worldwide total number of subjects	158
EEA total number of subjects	158

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)	58
From 65 to 84 years	100
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment started in June 2013 and the last follow-up was performed on August 2014. This study enrolled patients from the Rheumatology and Traumatology Departments belonging to 10 centres located in Spain.

### Pre-assignment

Screening details:

A total of 193 patients were screened, of whom 29 (15%) were screening failures. At the screening visit, the patients were assessed by the blinded physician for fulfilment of the selection criteria, demographic characteristics and medical history. Knee radiographs were also obtained.

### Pre-assignment period milestones

Number of subjects started	158
Number of subjects completed	158

### Period 1

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

Blinding implementation details:

Test and control treatments were presented in the form of sachets with powder to be dissolved in water. External appearance of the sachets from the two groups was the same, in order to make both treatments indistinguishable.

The trial medication was packaged and labelled separately for each patient. It contained the corresponding randomisation number according to a list previously generated and with no identification of the treatment.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Placebo of chondroitin sulfate + glucosamine sulfate orally administered once a day for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Powder for oral solution (sachets). One sachet was administered once daily during a period of 24 weeks.

<b>Arm title</b>	CS+SG
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Arm description:

Chondroitin sulfate + glucosamine sulfate orally administered once a day for 24 weeks.

Arm type	Experimental
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Investigational medicinal product name	Chondroitin sulfate 1200mg + glucosamine sulfate 1500mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Powder for oral solution (sachets). One sachet was administered once daily during a period of 24 weeks.

<b>Number of subjects in period 1</b>	Placebo	CS+SG
Started	78	80
Completed	64	55
Not completed	14	25
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	9
Other	3	1
Lack of adherence to treatment	-	2
Lost to follow-up	-	1
Lack of efficacy	7	5
Protocol deviation	1	6

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo of chondroitin sulfate + glucosamine sulfate orally administered once a day for 24 weeks.	
Reporting group title	CS+SG
Reporting group description:	
Chondroitin sulfate + glucosamine sulfate orally administered once a day for 24 weeks.	

Reporting group values	Placebo	CS+SG	Total
Number of subjects	78	80	158
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	67.6	65.49	
standard deviation	± 8.9	± 8.17	-
Gender categorical			
Units: Subjects			
Female	67	65	132
Male	11	15	26
Race/ethnicity			
Units: Subjects			
Caucasian	77	79	156
Other	1	1	2
Body Mass Index			
Units: kg/m <sup>2</sup>			
arithmetic mean	27.99	28.56	
standard deviation	± 3.26	± 3.49	-
Time to first osteoarthritis symptoms			
Units: Years			
arithmetic mean	6.12	6.35	
standard deviation	± 5.2	± 5.91	-
Mean global pain on VAS			
Units: cm			
arithmetic mean	62.05	62.15	
standard deviation	± 11.77	± 11	-

WOMAC global on VAS Units: cm arithmetic mean standard deviation	52.37 ± 14.53	52.69 ± 12	-
WOMAC pain on VAS Units: cm arithmetic mean standard deviation	53.38 ± 14.37	52.76 ± 12.5	-
WOMAC stiffness on VAS Units: cm arithmetic mean standard deviation	52.28 ± 17.53	49.71 ± 16.45	-
WOMAC function on VAS Units: cm arithmetic mean standard deviation	52.08 ± 15.56	53.02 ± 12.85	-
Patient's Global Assessment on VAS Units: cm arithmetic mean standard deviation	59.91 ± 14.05	63.45 ± 13.67	-
Investigator's Global Assessment on VAS Units: cm arithmetic mean standard deviation	57.35 ± 14.37	57.06 ± 11.87	-

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo of chondroitin sulfate + glucosamine sulfate orally administered once a day for 24 weeks.	
Reporting group title	CS+SG
Reporting group description: Chondroitin sulfate + glucosamine sulfate orally administered once a day for 24 weeks.	

### Primary: Absolute Change in Global Pain Reduction (VAS) at the End of Follow-up

End point title	Absolute Change in Global Pain Reduction (VAS) at the End of Follow-up
End point description: Global Pain was assessed two times in each visit using the VAS (visual analogue scale) for which 0=no pain and 100=worst pain imaginable. Reduction of Global Pain according to VAS is defined in absolute and relative terms as follows: - Absolute change in Global Pain at the end of treatment is calculated as the difference between the Global Pain reported in the last visit and the baseline visit. A negative change indicates a reduction in Global Pain, while a positive change indicates an increment in Global Pain. - Relative change in Global Pain at the end of treatment is calculated as the percentual change between the Global Pain reported in the last visit and the baseline visit. A negative change indicates a reduction in Global Pain, while a positive change indicates an increment in Global Pain.	
End point type	Primary
End point timeframe: 24 weeks	

End point values	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	-20.57 ( $\pm$ 2.41)	-11.86 ( $\pm$ 2.42)		

### Statistical analyses

Statistical analysis title	Statistical Analysis Primary Endpoint
Statistical analysis description: Analysis was performed based on the modified intention-to-treat population. The imputation method for handling missing data was MMRM. The alpha error adjustment and sample size necessary to conduct the interim analysis were estimated according to Pocock approach.	
Comparison groups	Placebo v CS+SG



Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0314
Method	Mixed models analysis

### Primary: Relative Change in Global Pain Reduction (VAS) at the End of Follow-up

End point title	Relative Change in Global Pain Reduction (VAS) at the End of Follow-up
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End point description:

Global Pain was assessed two times in each visit using the VAS (visual analogue scale) for which 0=no pain and 100=worst pain imaginable. Reduction of Global Pain according to VAS is defined in absolute and relative terms as follows:

- Absolute change in Global Pain at the end of treatment is calculated as the difference between the Global Pain reported in the last visit and the baseline visit. A negative change indicates a reduction in Global Pain, while a positive change indicates an increment in Global Pain.
- Relative change in Global Pain at the end of treatment is calculated as the percentual change between the Global Pain reported in the last visit and the baseline visit. A negative change indicates a reduction in Global Pain, while a positive change indicates an increment in Global Pain.

End point type	Primary
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End point timeframe:

24 weeks

End point values	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: Percentage of change				
arithmetic mean (standard deviation)	-33.16 ( $\pm$ 3.98)	-18.9 ( $\pm$ 3.99)		

### Statistical analyses

Statistical analysis title	Statistical Analysis Primary Endpoint
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Statistical analysis description:

Analysis was performed based on the modified intention-to-treat population. The imputation method for handling missing data was MMRM.

The alpha error adjustment and sample size necessary to conduct the interim analysis were estimated according to Pocock approach.

Comparison groups	Placebo v CS+SG
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0475
Method	Mixed models analysis

## Secondary: Responders OMERACT-OARSI 2004 at the End of Follow-up

End point title	Responders OMERACT-OARSI 2004 at the End of Follow-up
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End point description:

Percentage of subjects with a clinical response according to Osteoarthritis Research Society International (OARSI) 2004 criteria at the end of follow-up. Patients were classified as responders if the pain or physical function score decreased at least 50% and at least 20mm on the Visual Analogue Scale, or if two of the following three findings were recorded: a decrease in pain of at least 20% or at least 10mm on the VAS, a decrease in physical function of at least 20% and at least 10mm on the VAS, or an increase in the score of the patient's global assessment by at least 20% and at least 10mm on the VAS.

End point type	Secondary
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End point timeframe:

24 weeks.

End point values	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: Percentage of responders				
number (not applicable)	56.41	50		

## Statistical analyses

Statistical analysis title	Statistical Analysis Secondary Endpoint
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Statistical analysis description:

Analysis was performed based on the modified intention-to-treat population. The imputation method for handling missing data was MMRM.

The alpha error adjustment and sample size necessary to conduct the interim analysis were estimated according to Pocock approach.

Comparison groups	CS+SG v Placebo
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Number of subjects included in analysis	158
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.4195
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Method	Chi-squared
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## Secondary: WOMAC Global (VAS) at the End of Follow-up

End point title	WOMAC Global (VAS) at the End of Follow-up
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End point description:

The WOMAC measures include 5 items for pain intensity, 2 for joint stiffness, and 17 for physical function. These items are measured on a 0-100 VAS for which 0=none and 100=the worst pain intensity/joint stiffness/functional impairment respectively.

End point type	Secondary
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End point timeframe:

24 weeks.

<b>End point values</b>	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	37.37 (± 2.06)	43.27 (± 2.06)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Secondary Endpoint
Comparison groups	Placebo v CS+SG
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0472
Method	Mixed models analysis

### Secondary: WOMAC Pain (VAS) at the End of Follow-up

End point title	WOMAC Pain (VAS) at the End of Follow-up
End point description: The WOMAC measures include 5 items for pain intensity, 2 for joint stiffness, and 17 for physical function. These items are measured on a 0-100 VAS for which 0=none and 100=the worst pain intensity/joint stiffness/functional impairment respectively.	
End point type	Secondary
End point timeframe: 24 weeks.	

<b>End point values</b>	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	37.42 (± 2.22)	44.31 (± 2.23)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Secondary Endpoint
Comparison groups	Placebo v CS+SG

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0443
Method	Mixed models analysis

### Secondary: WOMAC Stiffness (VAS) at the End of Follow-up

End point title	WOMAC Stiffness (VAS) at the End of Follow-up
End point description: The WOMAC measures include 5 items for pain intensity, 2 for joint stiffness, and 17 for physical function. These items are measured on a 0-100 VAS for which 0=none and 100=the worst pain intensity/joint stiffness/functional impairment respectively.	
End point type	Secondary
End point timeframe: 24 weeks.	

End point values	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	34.51 (± 2.49)	42.23 (± 2.5)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Secondary Endpoint
Comparison groups	Placebo v CS+SG
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0231
Method	Mixed models analysis

### Secondary: WOMAC Function (VAS) at the End of Follow-up

End point title	WOMAC Function (VAS) at the End of Follow-up
End point description: The WOMAC measures include 5 items for pain intensity, 2 for joint stiffness, and 17 for physical function. These items are measured on a 0-100 VAS for which 0=none and 100=the worst pain intensity/joint stiffness/functional impairment respectively.	
End point type	Secondary
End point timeframe: 24 weeks.	

<b>End point values</b>	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	37.74 (± 2.06)	43.07 (± 2.07)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Secondary Endpoint
Comparison groups	Placebo v CS+SG
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683
Method	Mixed models analysis

### Secondary: Investigator's Global Assessment (VAS) at the End of Follow-up

End point title	Investigator's Global Assessment (VAS) at the End of Follow-up
End point description:	The WOMAC measures include 5 items for pain intensity, 2 for joint stiffness, and 17 for physical function. These items are measured on a 0-100 VAS for which 0=none and 100=the worst pain intensity/joint stiffness/functional impairment respectively.
End point type	Secondary
End point timeframe:	24 weeks.

<b>End point values</b>	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	35.54 (± 2.12)	42.11 (± 2.12)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Secondary Endpoint
Comparison groups	Placebo v CS+SG

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0391
Method	Mixed models analysis

### Secondary: Patient's Global Assessment (VAS) at the End of Follow-up

End point title	Patient's Global Assessment (VAS) at the End of Follow-up
End point description: The WOMAC measures include 5 items for pain intensity, 2 for joint stiffness, and 17 for physical function. These items are measured on a 0-100 VAS for which 0=none and 100=the worst pain intensity/joint stiffness/functional impairment respectively.	
End point type	Secondary
End point timeframe: 24 weeks.	

End point values	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: cm				
arithmetic mean (standard deviation)	41.38 (± 2.4)	46.21 (± 2.41)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis Secondary Endpoint
Comparison groups	Placebo v CS+SG
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1163
Method	Mixed models analysis

### Secondary: Consumption of Rescue Medication for Osteoarthritis Pain

End point title	Consumption of Rescue Medication for Osteoarthritis Pain
End point description: Consumption of rescue medication for osteoarthritis throughout the study.	
End point type	Secondary
End point timeframe: 24 weeks.	

<b>End point values</b>	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	80		
Units: percentage of patients				
number (not applicable)	92.31	90		

## Statistical analyses

<b>Statistical analysis title</b>	Consumption of Rescue Medication for Pain
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Statistical analysis description:

Analysis was performed based on the modified intention-to-treat population. The imputation method for handling missing data was MMRM.

The alpha error adjustment and sample size necessary to conduct the interim analysis were estimated according to Pocock approach.

Comparison groups	CS+SG v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6098
Method	Chi-squared

## Secondary: Mean Daily Dose of Paracetamol Consumption

End point title	Mean Daily Dose of Paracetamol Consumption
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End point description:

Mean daily dose of paracetamol consumption throughout the study.

End point type	Secondary
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End point timeframe:

Throughout the study.

<b>End point values</b>	Placebo	CS+SG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: g/day				
arithmetic mean (standard deviation)	0.77 ( $\pm$ 0.68)	0.65 ( $\pm$ 0.53)		

## Statistical analyses

<b>Statistical analysis title</b>	Mean Daily Dose of Paracetamol Consumption
Statistical analysis description: Analysis was performed based on the modified intention-to-treat population. The imputation method for handling missing data was MMRM. The alpha error adjustment and sample size necessary to conduct the interim analysis were estimated according to Pocock approach.	
Comparison groups	Placebo v CS+SG
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5038
Method	Wilcoxon (Mann-Whitney)



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 weeks.

Adverse event reporting additional description:

All those patients who have received at least 1 administration of the study product or placebo were included in the safety analysis.

Throughout the study, all adverse events were recorded in the Case Report Form. Adverse events recording, physical examination and analytical parameters were considered as safety variables.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Placebo Group
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Reporting group description:

Placebo group.

Reporting group title	CS+SG group
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Reporting group description: -

Serious adverse events	Placebo Group	CS+SG group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 80 (2.50%)	2 / 80 (2.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
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			
Pulmonary embolism			

subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Diverticulitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
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: 0 %

<b>Non-serious adverse events</b>	Placebo Group	CS+SG group	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	19 / 80 (23.75%)	33 / 80 (41.25%)	
<b>Investigations</b>			
Decreased appetite			
subjects affected / exposed	1 / 80 (1.25%)	0 / 80 (0.00%)	
occurrences (all)	1	0	
<b>Nervous system disorders</b>			
Dizziness			
subjects affected / exposed	1 / 80 (1.25%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	3 / 80 (3.75%)	10 / 80 (12.50%)	
occurrences (all)	3	10	
Somnolence			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
<b>General disorders and administration site conditions</b>			
Asthenia			
subjects affected / exposed	0 / 80 (0.00%)	2 / 80 (2.50%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Oedema peripheral			

subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0	1 / 80 (1.25%) 1	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1	1 / 80 (1.25%) 1	
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1	0 / 80 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Flatulence subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0  2 / 80 (2.50%) 2  1 / 80 (1.25%) 1  1 / 80 (1.25%) 1  0 / 80 (0.00%) 0  2 / 80 (2.50%) 2	3 / 80 (3.75%) 3  2 / 80 (2.50%) 3  3 / 80 (3.75%) 3  4 / 80 (5.00%) 4  1 / 80 (1.25%) 1  2 / 80 (2.50%) 2	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)  Pruritus subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0  2 / 80 (2.50%) 2	1 / 80 (1.25%) 1  2 / 80 (2.50%) 2	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 80 (2.50%)	3 / 80 (3.75%)	
occurrences (all)	2	3	
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 80 (1.25%)	1 / 80 (1.25%)	
occurrences (all)	1	1	
Diarrhoea infectious			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	2 / 80 (2.50%)	2 / 80 (2.50%)	
occurrences (all)	2	2	
Laryngitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	6 / 80 (7.50%)	1 / 80 (1.25%)	
occurrences (all)	6	1	
Pharyngitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Upper respiratory tract infection			

subjects affected / exposed	1 / 80 (1.25%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 80 (1.25%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2013	Inclusion of a new site: Hospital Universitario Fundación Alcorcón (Madrid) and Dr Gavín González as Principal Investigator.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.
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Notes: