



Clinical trial results:

Intra-articular treatment with MEN16132 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double blind, placebo controlled, five parallel group, dose finding study

Summary

EudraCT number	2009-014918-99
Trial protocol	DE IT ES
Global end of trial date	31 May 2011

Results information

Result version number	v1 (current)
This version publication date	09 November 2018
First version publication date	09 November 2018

Trial information

Trial identification

Sponsor protocol code	BKOS-02
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01091116
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A.
Sponsor organisation address	Via Sette Santi 1, Florence, Italy, 50131
Public contact	Corporate Clinical Sciences, Menarini Ricerche S.p.A., 0039 05556809990, acapriati@menarini-ricerche.it
Scientific contact	Corporate Clinical Sciences, Menarini Ricerche S.p.A., 0039 05556809990, acapriati@menarini-ricerche.it

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	31 May 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2011
Global end of trial reached?	Yes
Global end of trial date	31 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of MEN16132 given by intra-articular injections as four different doses/regimens versus placebo

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs will be informed forthwith about these new events and the measures taken. For patients participating in the study, Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements. Details on the insurance company, the insurance number and conditions were made available to patients in the ICF and/or provided in a separate document in accordance with national requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 353
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	423
EEA total number of subjects	423

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)	174
From 65 to 84 years	247
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 23 sites in France (2 sites), Germany (12 sites), Italy (4 sites) and Spain (4 sites). The first patient was enrolled on 24 February 2010 and the last patient completed the study on 31 May 2011.

Pre-assignment

Screening details:

504 patients were screened during the up to 3 weeks screening period of which 423 patients with mild to moderate idiopathic osteoarthritis were randomised. The resulting screening failure rate was 16%.

Period 1

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

Blinding implementation details:

Eligible patients were randomised to one out of five treatment arms, with a 1:1:1:1 randomisation ratio and site balance delivered through IxRS.

Arms

Are arms mutually exclusive?	Yes
Arm title	Low dose

Arm description:

Fasitibant 2x0.125 mg

Arm type	Experimental
Investigational medicinal product name	Fasitibant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Dose: 0.125 mg fasitibant in 1 mL solution for IA injection
single treatment course, consisting of 2 injections at 2-weeks interval: 0.125 mg followed by 0.125 mg

Arm title	Mid dose
------------------	----------

Arm description:

Fasitibant 2x0.25 mg

Arm type	Experimental
Investigational medicinal product name	Fasitibant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Dose: 0.25 mg fasitibant in 1 mL solution for IA injection
single treatment course, consisting of 2 injections at 2-weeks interval: 0.25 mg followed by 0.25 mg

Arm title	High dose
------------------	-----------

Arm description:

Fasitibant 2x0.5 mg

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Fasitibant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details:	
Dose: 0.50 mg fasitibant in 1 mL solution for IA injection single treatment course, consisting of 2 injections at 2-weeks interval: 0.50 mg followed by 0.50 mg	
Arm title	Single high dose
Arm description:	
Fasitibant 1x0.5 mg	
Arm type	Experimental
Investigational medicinal product name	Fasitibant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details:	
Dose: 0.50 mg fasitibant in 1 mL solution for IA injection single treatment course, consisting of 2 injections at 2-weeks interval: 0.50 mg followed by placebo	
Arm title	Placebo
Arm description:	
2x placebo; single treatment course, consisting of 2 injections at 2-weeks interval	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details:	
Intra-articular injection of 2 doses of Placebo control at 2-week interval	

Number of subjects in period 1	Low dose	Mid dose	High dose
Started	83	88	84
Completed	77	80	73
Not completed	6	8	11
Consent withdrawn by subject	6	8	11

Number of subjects in period 1	Single high dose	Placebo
Started	84	84
Completed	80	73
Not completed	4	11
Consent withdrawn by subject	4	11

Baseline characteristics

Reporting groups	
Reporting group title	Low dose
Reporting group description:	
Fasitibant 2x0.125 mg	
Reporting group title	Mid dose
Reporting group description:	
Fasitibant 2x0.25 mg	
Reporting group title	High dose
Reporting group description:	
Fasitibant 2x0.5 mg	
Reporting group title	Single high dose
Reporting group description:	
Fasitibant 1x0.5 mg	
Reporting group title	Placebo
Reporting group description:	
2x placebo; single treatment course, consisting of 2 injections at 2-weeks intervall	

Reporting group values	Low dose	Mid dose	High dose
Number of subjects	83	88	84
Age categorical			
Units: Subjects			
Age ≥ 40	83	88	84
Age continuous			
Age			
Units: years			
arithmetic mean	66.7	65.9	65.1
standard deviation	± 9.0	± 9.5	± 9.7
Gender categorical			
Units: Subjects			
Female	44	46	51
Male	39	42	33
Radiographic Osteoarthritis severity			
Based on Kellgren & Lawrence radiologic scale criteria (Grade 1 to 4): narrowing of joint space osteophytic stuctures sclerosis deformity of bone contour			
Units: Subjects			
Grade 1	0	0	0
Grade 2	52	45	44
Grade 3	31	43	40
Grade 4	0	0	0
missing information	0	0	0
Duration of osteoarthritis symptoms			
Units: Years			
arithmetic mean	9.7	8.0	7.9
standard deviation	± 9.2	± 6.3	± 6.6
WOMAC VA 3.1 A score (Total pain)			

Western Ontario and McMaster Universities osteoarthritis index (WOMAC). The WOMAC VA 3.1 A score (total pain, range 0-500 mm) is the sum of VAS subscores (0-100 mm) attributed by the patient to each of the 5 questions referring to osteoarthritic pain experienced during the preceding 48 hours (pain domain).
The higher is the WOMAC VA 3.1 A ore, the higher is the intensity of pain symptoms (0 = no pain ; 500 = extreme pain).
A decrease of the WOMAC VA 3.1 A score following tratment administration indicates a reduction of pain symptom.

Units: mm			
arithmetic mean	288	282	293
standard deviation	± 80	± 68	± 73

Reporting group values	Single high dose	Placebo	Total
Number of subjects	84	84	423
Age categorical			
Units: Subjects			
Age ≥ 40	84	84	423

Age continuous			
----------------	--	--	--

Age

Units: years			
arithmetic mean	65.3	65.1	-
standard deviation	± 8.7	± 8.5	

Gender categorical			
Units: Subjects			
Female	56	55	252
Male	28	29	171

Radiographic Osteoarthritis severity			
--------------------------------------	--	--	--

Based on Kellgren & Lawrence radiologic scale criteria (Grade 1 to 4):
narrowing of joint space
osteophytic stuctures
sclerosis
deformity of bone contour

Units: Subjects			
Grade 1	0	0	0
Grade 2	41	42	224
Grade 3	42	42	198
Grade 4	0	0	0
missing information	1	0	1

Duration of osteoarthritis symptoms			
Units: Years			
arithmetic mean	8.2	6.5	-
standard deviation	± 8.4	± 6.4	

WOMAC VA 3.1 A score (Total pain)			
-----------------------------------	--	--	--

Western Ontario and McMaster Universities osteoarthritis index (WOMAC). The WOMAC VA 3.1 A score (total pain, range 0-500 mm) is the sum of VAS subscores (0-100 mm) attributed by the patient to each of the 5 questions referring to osteoarthritic pain experienced during the preceding 48 hours (pain domain).
The higher is the WOMAC VA 3.1 A ore, the higher is the intensity of pain symptoms (0 = no pain ; 500 = extreme pain).
A decrease of the WOMAC VA 3.1 A score following tratment administration indicates a reduction of pain symptom.

Units: mm			
arithmetic mean	283	284	-
standard deviation	± 72	± 79	

End points

End points reporting groups

Reporting group title	Low dose
Reporting group description: Fasitibant 2x0.125 mg	
Reporting group title	Mid dose
Reporting group description: Fasitibant 2x0.25 mg	
Reporting group title	High dose
Reporting group description: Fasitibant 2x0.5 mg	
Reporting group title	Single high dose
Reporting group description: Fasitibant 1x0.5 mg	
Reporting group title	Placebo
Reporting group description: 2x placebo; single treatment course, consisting of 2 injections at 2-weeks intervall	

Primary: WOMAC VA 3.1 A Score (Total Pain)

End point title	WOMAC VA 3.1 A Score (Total Pain)
End point description: The primary endpoint was the WOMAC VA 3.1 A sub score (total pain) decrease over the 3 weeks after first drug administrations compared with baseline (ITT population).	
End point type	Primary
End point timeframe: over the 3 weeks after the first administration	

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	88	83	83
Units: mm				
arithmetic mean (standard deviation)				
1 week post dose	-60 (± 84)	-58 (± 82)	-52 (± 92)	-67 (± 91)
2 weeks post dose	-69 (± 89)	-65 (± 81)	-71 (± 102)	-73 (± 96)
3 weeks post dose	-103 (± 107)	-99 (± 86)	-99 (± 104)	-103 (± 99)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: mm				
arithmetic mean (standard deviation)				

1 week post dose	-63 (\pm 103)			
2 weeks post dose	-75 (\pm 93)			
3 weeks post dose	-103 (\pm 112)			

Statistical analyses

Statistical analysis title	Statistical Analysis for primary endpoint
Comparison groups	Low dose v Mid dose v High dose v Single high dose v Placebo
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5263
Method	ANCOVA

Secondary: WOMAC VA 3.1.B Score (Knee Stiffness)

End point title	WOMAC VA 3.1.B Score (Knee Stiffness)
-----------------	---------------------------------------

End point description:

A decrease of the WOMAC VA 3.1 B score following treatment administration indicates a reduction of joint stiffness. The change at Week 13 from baseline is reported.

WOMAC VA 3.1.B score(range 0-200) is the sum of VAS scores (0-100 mm)attributed by the patient to each of the 2 questions referring to joint stiffness experienced during the preceding 48 hours. The higher is the WOMAC VA 3.1 B score, the higher is joint stiffness (0 = no stiffness ; 200 = extreme stiffness).

End point type	Secondary
----------------	-----------

End point timeframe:

up to 3 months after first dose

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	87	84	83
Units: mm				
arithmetic mean (standard deviation)				
Baseline	105.7 (\pm 47.36)	101.8 (\pm 39.7)	109.4 (\pm 46.21)	107.3 (\pm 43.3)
Week 13	61.5 (\pm 52.2)	66.1 (\pm 47.4)	64.5 (\pm 50.1)	66.2 (\pm 49.3)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	84			

Units: mm				
arithmetic mean (standard deviation)				
Baseline	108.7 (± 47.67)			
Week 13	63.4 (± 51.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: WOMAC VA 3.1. C Score (Function)

End point title	WOMAC VA 3.1. C Score (Function)
-----------------	----------------------------------

End point description:

A decrease of the WOMAC VA 3.1 C score following treatment administration indicates an improvement in performing daily activities. WOMAC VA 3.1.C scores at baseline and at Week 13 are reported.

Knee function evaluated by WOMAC VA 3.1 C score (range 0-1700) is the sum of VAS scores (range 0-100 mm) attributed by the patient to each of 17 questions referring to difficulty in performing daily activities experienced during the preceding 48 hours.

The higher is the WOMAC VA 3.1 C score, the higher is functional impairment in daily activities (0 = no difficulty ; 1700 = extreme difficulty).

End point type	Secondary
----------------	-----------

End point timeframe:

up to 3 months after first dose

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	88	83	82
Units: mm				
arithmetic mean (standard deviation)				
Baseline	928.7 (± 336.2)	915.5 (± 285.2)	906.7 (± 318.19)	938.7 (± 300.63)
Week 13	537.5 (± 415.9)	598.0 (± 396.9)	574.6 (± 407.0)	594.8 (± 444.3)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: mm				
arithmetic mean (standard deviation)				
Baseline	936.5 (± 343.8)			
Week 13	557.6 (± 389.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Treatment Responders According to OMERACT-OARSI Responder Criteria

End point title	Percentage of Treatment Responders According to OMERACT-OARSI Responder Criteria
End point description: Osteoarthritis Research Society International (OARSI). Response defined as: a decrease in WOMAC pain or physical-function score by 50% or more and by 20 or more points on the visual analogue scale OR if two of the following three findings are recorded: a decrease in the WOMAC pain score by 20% or more and by 10 or more points on the visual analogue scale; a decrease in the WOMAC physical-function score by 20% or more and by 10 or more points on the scale; an improvement in the score on the patient's global assessment by 20% or more and by 10 or more points on the scale	
End point type	Secondary
End point timeframe: up to 3 months after first dose	

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	88	83	83
Units: Percentage of patients				
number (not applicable)				
Week 1	44.6	35.6	36.6	41.5
Week 2	46.3	36.0	37.0	47.6
Week 3	61.8	67.5	54.4	57.3
Week 13	64.2	66.7	59.8	64.6

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Percentage of patients				
number (not applicable)				
Week 1	44.4			
Week 2	53.8			
Week 3	57.7			
Week 13	53.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment

End point title	Patient Global Assessment
-----------------	---------------------------

End point description:

Patient global assessment evaluated using a VAS scale score attributed by the patient (range 0-100 mm).

Efficacy assessed as change at each time-point post-dosing (week 1, 2 ,3, 13) versus baseline (week 0). A decrease of patient global assessment score indicates an improvement of osteoarthritis symptoms.

End point type	Secondary
----------------	-----------

End point timeframe:

up to 3 months after first dose

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	88	83	83
Units: mm				
arithmetic mean (standard deviation)				
Week1	-4.2 (± 21.8)	-3.3 (± 20.4)	0.9 (± 18.5)	-6.3 (± 23.6)
Week 2	-4.7 (± 19.6)	-0.4 (± 21.4)	-0.3 (± 20.6)	-7.4 (± 21.9)
Week 3	-8.4 (± 25.3)	-4.6 (± 21.3)	-6.4 (± 21.5)	-10.2 (± 24.7)
Week 13	-14.8 (± 26.4)	-7.5 (± 22.3)	-8.8 (± 23.6)	-11.4 (± 22.9)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: mm				
arithmetic mean (standard deviation)				
Week1	-7.8 (± 22.2)			
Week 2	-9.0 (± 24.6)			
Week 3	-11.7 (± 24.0)			
Week 13	-16.3 (± 28.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: WOMAC VA 3.1A - Total Pain Score by Body Mass Index [BMI ≤ 25]

End point title	WOMAC VA 3.1A - Total Pain Score by Body Mass Index [BMI ≤ 25]
-----------------	--

End point description:

Analysis in normal-weight population (BMI ≤ 25) of the WOMAC VA 3.1A score (range 0-500 mm) is reported.

A decrease of the WOMAC VA 3.1 A score following treatment administration indicates a reduction of pain symptom.

End point type	Secondary
----------------	-----------

End point timeframe:

over the 3 weeks after the first administration

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	15	6	9
Units: mm				
arithmetic mean (standard deviation)				
1 week post dose 1	-11.4 (± 53.91)	-72.4 (± 55.78)	-109.0 (± 91.97)	-109.0 (± 86.66)
2 weeks post dose 1	9.2 (± 97.88)	-90.7 (± 70.94)	-99.2 (± 39.89)	-63.8 (± 90.05)
3 weeks post dose 1	-22.4 (± 100.02)	-110.7 (± 80.72)	-107.8 (± 46.16)	-112.9 (± 93.52)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mm				
arithmetic mean (standard deviation)				
1 week post dose 1	2.7 (± 75.21)			
2 weeks post dose 1	-31.2 (± 71.80)			
3 weeks post dose 1	-62.3 (± 83.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: WOMAC VA 3.1A - Total Pain Score by Body Mass Index -[BMI > 25]

End point title	WOMAC VA 3.1A - Total Pain Score by Body Mass Index -[BMI > 25]
-----------------	---

End point description:

Analysis in over-weight population (BMI > 25) of the WOMAC VA 3.1A score (range 0-500 mm) is reported.

A decrease of the WOMAC VA 3.1 A score following treatment administration indicates a reduction of pain symptom

End point type	Secondary
----------------	-----------

End point timeframe:

over the 3 weeks after the first administration

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	36	38	30
Units: mm				
arithmetic mean (standard deviation)				
1 week post dose 1	-76.5 (± 81.73)	-62.9 (± 81.14)	-56.4 (± 88.08)	-67.4 (± 86.99)
2 weeks post dose 1	-88.2 (± 83.18)	-78.2 (± 75.67)	-81.5 (± 105.08)	-81.6 (± 90.11)
3 weeks post dose 1	-103.4 (± 95.6)	-122.1 (± 69.96)	-114.1 (± 106.00)	-99.6 (± 83.74)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: mm				
arithmetic mean (standard deviation)				
1 week post dose 1	-58.0 (± 70.92)			
2 weeks post dose 1	-83.9 (± 72.71)			
3 weeks post dose 1	-103.3 (± 85.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Event Reports

End point title	Adverse Event Reports
-----------------	-----------------------

End point description:

Incidence of spontaneously reported adverse events

End point type	Secondary
----------------	-----------

End point timeframe:

up to 4 months after screening

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	88	83	83
Units: Subjects				
Non-serious adverse events	31	38	36	28
Serious adverse events	1	2	3	3
Blood / Lymph system	0	0	0	1
Cardiac disorders	2	3	1	2
Eye disorders	0	0	0	1
Gastrointestinal disorders	5	3	2	2
General / administration site conditions	3	4	6	3
Infections / infestations	11	11	10	10
Injury / poisoning / procedural complications	3	4	5	2
Investigations	2	3	3	2
Metabolism and nutrition disorders	1	0	0	0
Musculoskeletal and connective tissue disorders	6	11	11	10
Nervous system disorders	6	3	5	3
Psychiatric disorders	1	0	2	0
Renal and Urinary disorders	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	1	0	0
Skin and subcutaneous tissue disorders	1	0	1	1
Surgical and medical procedures	1	0	1	1
Vascular disorders	4	4	2	4
Social circumstances	0	1	0	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Subjects				
Non-serious adverse events	33			
Serious adverse events	2			
Blood / Lymph system	0			
Cardiac disorders	1			
Eye disorders	0			
Gastrointestinal disorders	2			
General / administration site conditions	3			
Infections / infestations	10			
Injury / poisoning / procedural complications	3			
Investigations	3			
Metabolism and nutrition disorders	2			
Musculoskeletal and connective tissue disorders	12			

Nervous system disorders	3			
Psychiatric disorders	0			
Renal and Urinary disorders	2			
Respiratory, thoracic, and mediastinal disorders	0			
Skin and subcutaneous tissue disorders	1			
Surgical and medical procedures	1			
Vascular disorders	2			
Social circumstances	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically Significant Abnormal Laboratory Tests

End point title	Clinically Significant Abnormal Laboratory Tests
End point description:	
Percentage of patients with Abnormal Laboratory Tests judged Clinically Significant by Investigators. The following hematochemical and urinary parameters were analysed: Red Blood Cells Count, Haematocrit, Haemoglobin, Platelets, MCV, MCH, MCHC, White Blood Cells, Sodium, Chloride, Potassium, Total calcium, AST (SGOT), ALT (SGPT), GGT, Alkaline phosphatase, Total Bilirubin, Direct Bilirubin, Creatinine, BUN, CPK, LDH, Glucose, Total proteins, Albumin.	
End point type	Secondary
End point timeframe:	
up to 4 months from screening	

End point values	Low dose	Mid dose	High dose	Single high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	88	84	84
Units: Subjects				
number (not applicable)				
Blood GGT	0	0	1	0
Blood Alkaline Phosphatase	0	0	1	0
Blood Total Bilirubin	0	0	1	0
Blood Creatinine	0	1	0	0
Blood Glucose	0	0	0	1
Blood Potassium	0	0	1	0
Blood Sodium	0	0	0	0
Blood Fibrin D dimer	1	0	0	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Subjects				

number (not applicable)				
Blood GGT	1			
Blood Alkaline Phosphatase	0			
Blood Total Bilirubin	0			
Blood Creatinine	0			
Blood Glucose	1			
Blood Potassium	1			
Blood Sodium	1			
Blood Fibrin D dimer	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Four months of safety observation

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	10.0
--------------------	------

Reporting groups

Reporting group title	Low dose
-----------------------	----------

Reporting group description:

Fasitibant 2x0.125 mg

Reporting group title	Mid dose
-----------------------	----------

Reporting group description:

Fasitibant 2x0.25 mg

Reporting group title	High dose
-----------------------	-----------

Reporting group description:

Fasitibant 2x0.5 mg

Reporting group title	Single high dose
-----------------------	------------------

Reporting group description:

Fasitibant 1x0.5 mg

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

2x placebo; single treatment course, consisting of 2 injections at 2-weeks intervall

Serious adverse events	Low dose	Mid dose	High dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 83 (1.20%)	2 / 88 (2.27%)	3 / 83 (3.61%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 88 (1.14%)	0 / 83 (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

Supraventricular-tachycardia subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia subjects affected / exposed	0 / 83 (0.00%)	1 / 88 (1.14%)	0 / 83 (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
Surgical and medical procedures Knee operation subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatectomy subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders Cerebral infarction subjects affected / exposed	1 / 83 (1.20%)	0 / 88 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders Vertigo subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders Uretic stenosis			

subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterocele			
subjects affected / exposed	0 / 83 (0.00%)	0 / 88 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Single high dose	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 83 (3.61%)	2 / 84 (2.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular-tachycardia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee operation			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatectomy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Uretic stenosis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterocele			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Low dose	Mid dose	High dose
Total subjects affected by non-serious adverse events subjects affected / exposed	17 / 83 (20.48%)	18 / 88 (20.45%)	21 / 83 (25.30%)
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	1 / 88 (1.14%) 1	3 / 83 (3.61%) 3
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	2 / 88 (2.27%) 2	0 / 83 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 83 (3.61%) 3	1 / 88 (1.14%) 1	1 / 83 (1.20%) 1
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	3 / 88 (3.41%) 3	3 / 83 (3.61%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Osteoarthritis subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 4 0 / 83 (0.00%) 0 1 / 83 (1.20%) 1	5 / 88 (5.68%) 5 3 / 88 (3.41%) 3 3 / 88 (3.41%) 3	7 / 83 (8.43%) 7 0 / 83 (0.00%) 0 2 / 83 (2.41%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 5 1 / 83 (1.20%) 1	5 / 88 (5.68%) 5 1 / 88 (1.14%) 2	4 / 83 (4.82%) 4 3 / 83 (3.61%) 3

Non-serious adverse events	Single high dose	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 83 (18.07%)	16 / 84 (19.05%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 83 (4.82%)	2 / 84 (2.38%)	
occurrences (all)	4	2	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 83 (0.00%)	2 / 84 (2.38%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 83 (7.23%)	3 / 84 (3.57%)	
occurrences (all)	7	3	
Back pain			
subjects affected / exposed	2 / 83 (2.41%)	3 / 84 (3.57%)	
occurrences (all)	2	3	
Osteoarthritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 83 (4.82%)	5 / 84 (5.95%)	
occurrences (all)	5	6	
Urinary tract infection			
subjects affected / exposed	0 / 83 (0.00%)	2 / 84 (2.38%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported