Clinical trial results:
A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, FOUR PARALLEL ARM, DOSE-FINDING STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE INTRA-ARTICULAR INJECTIONS OF FASITIBANT IN PATIENTS WITH SYMPTOMATIC OSTEOARTHRITIS OF THE KNEE.

Summary

EudraCT number	2013-004999-35
Trial protocol	DE IT CZ
Global end of trial date	10 February 2015

Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016
Summary attachment (see zip file)	CSR Synopsis (BKOS-04 Synopsis Version 1.0_16OCT2015.pdf)

Trial information

Trial identification

Sponsor protocol code	BKOS-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02205814
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	Dr. Angela Capriati, Clinical Research, Menarini Ricerche S.p.A., 0039 05556809990, acapriati@menarini-ricerche.it
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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	18 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2015
Global end of trial reached?	Yes
Global end of trial date	10 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate fasitibant, given as single IA injection at three different doses versus placebo, as an efficacious symptom modifying treatment of knee OA.

Protection of trial subjects:

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 will be made available to patients in the ICF and/or provided as a separate document, in accordance with national requirements.
Fasitibant is intended to be administered intra-articular in the knee joint. By delivering the drug substance directly to the site of interest, optimum activity can be obtained. This allows minimizing the dose and also the risk of systemic side effects. In all completed clinical studies the local tolerability of treatment injection was very good, without any difference between fasitibant and placebo. As far as the placebo group is concerned, it is worth noting that a high placebo effect has been reported in clinical studies on osteoarthritis symptomatic treatment, with the highest efficacy rate for IA placebo administration. For this reason, the inclusion of a placebo arm is justified and aligned with regulatory guidelines, for drugs intended to treat osteoarthritis.
Finally, the use of paracetamol/acetaminophen as rescue medication along the study, as recommended by guidelines on OA management, is intended to minimize the discomfort of patients who are allocated to non-efficacious doses of fasitibant, if any, or to placebo.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Czech Republic: 72
Country: Number of subjects enrolled	Germany: 324
Country: Number of subjects enrolled	Italy: 9

Worldwide total number of subjects	436
EEA total number of subjects	405

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)	206
From 65 to 84 years	230
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on 28th April 2014. The first patient was randomised on 6th May 2014. The last patient completed the study on 6th January 2015. The study was conducted in 25 study sites in Czech Republic, Germany, Italy and US.

Pre-assignment

Screening details:

A total of 645 patients entered a 2-week Screening period (including wash out); 209 of them were screen failed. One patient randomised to PLACEBO did not receive the study treatment (counted for ITT but not in safety population). Five patients received the study treatment without randomisation (not counted for ITT (n=431), but in safety population.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline Fasitibant Low Dose

Arm description:

At Visit 2 immediately before randomisation to low dose of fasitibant

Arm type	Baseline
Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

not applicable for baseline group

Arm title	Baseline Fasitibant Intermediate Dose

Arm description:

At Visit 2 immediately before randomisation to intermediate dose of fasitibant

Arm type	Baseline
Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

not applicable for baseline group

Arm title	Baseline Fasitibant High Dose

Arm description:

At Visit 2 immediately before randomisation to high dose of fasitibant

Arm type	Baseline

Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

not applicable for baseline group

Arm title	Baseline Placebo

Arm description:

At Visit 2 immediately before randomisation to placebo

Arm type	Baseline
Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

not applicable for baseline group

Number of subjects in period 1	Baseline Fasitibant Low Dose	Baseline Fasitibant Intermediate Dose	Baseline Fasitibant High Dose
Started	110	110	108
Completed	108	108	107
Not completed	2	2	1
Protocol deviation	2	2	1

Number of subjects in period 1	Baseline Placebo
Started	108
Completed	108
Not completed	0
Protocol deviation	-

Period 2

Period 2 title	12 Week Post-Treatment Follow Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Eligible patients were randomised at the end of the 2-week run-in period and after rechecking eligibility criteria, as per treatment code by the IVRS/IWRS in accordance with the randomisation list. Double-blind conditions were secured by the identical appearance and viscosity of the fasitibant and placebo solutions. The blind remained in effect until the database was completed and locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fasitibant Low Dose

Arm description:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant low dose and will be followed up for a period of 12 weeks post-treatment.

Arm type	Experimental
Investigational medicinal product name	Fasitibant
Investigational medicinal product code	MEN 16132
Other name	Fasitibant chloride bis-hydrochloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant 1 mg/mL (1 mL solution for IA injection) into the target knee.

Arm title	Fasitibant Intermediate Dose

Arm description:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant intermediate dose and will be followed up for a period of 12 weeks post-treatment.

Arm type	Experimental
Investigational medicinal product name	Fasitibant
Investigational medicinal product code	MEN16132
Other name	Fasitibant chloride bis-hydrochloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant 2.5 mg/mL (1 mL solution for IA injection) into the target knee.

Arm title	Fasitibant High Dose

Arm description:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant high dose and will be followed up for a period of 12 weeks post-treatment.

Arm type	Experimental
Investigational medicinal product name	Fasitibant
Investigational medicinal product code	MEN 16132
Other name	Fasitibant chloride bis-hydrochloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant 5 mg/mL (1 mL solution for IA injection) into the target knee.

Arm title	Placebo

Arm description:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of placebo and will be followed up for a period of 12 weeks post-treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of placebo (1 mL solution for IA injection) into the target knee.

Number of subjects in period 2	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose
Started	108	108	107
Completed	108	108	107

Number of subjects in period 2	Placebo
Started	108
Completed	108

Baseline characteristics

Reporting groups	
Reporting group title	Baseline Fasitibant Low Dose
Reporting group description:	
At Visit 2 immediately before randomisation to low dose of fasitibant	
Reporting group title	Baseline Fasitibant Intermediate Dose
Reporting group description:	
At Visit 2 immediately before randomisation to intermediate dose of fasitibant	
Reporting group title	Baseline Fasitibant High Dose
Reporting group description:	
At Visit 2 immediately before randomisation to high dose of fasitibant	
Reporting group title	Baseline Placebo
Reporting group description:	
At Visit 2 immediately before randomisation to placebo	

Reporting group values	Baseline Fasitibant Low Dose	Baseline Fasitibant Intermediate Dose	Baseline Fasitibant High Dose
Number of subjects	110	110	108
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age, continuous			
Units: years			
arithmetic mean	65.3	63.2	64.7
standard deviation	± 7.61	± 8.73	± 8.43
Gender categorical			
Gender categorical			
Units: Subjects			
Female	62	72	64
Male	48	38	44
Ethnicity			
Non Hispanic or Latino			
Units: Subjects			
Not Hispanic or Latino	109	109	107
Hispanic or Latino	1	1	1
BMI			
BMI			
Units: kg/m2			

arithmetic mean	27.1	26.5	27.1
standard deviation	± 2.12	± 2.83	± 2.35
WOMAC A			
The validated Western Ontario and McMaster University questionnaire (WOMAC) was used to measure total knee pain choosing its visual analogue scale version (VAS). The WOMAC VA 3.1 A subscore (WOMAC A) ranges from 0 to 500 mm (summing up five VAS 0-100 mm) with higher scores indicating more pain.			
Units: units on a scale			
arithmetic mean	286.5	282.7	278.3
standard deviation	± 40.4	± 40.08	± 38.11
WOMAC INDEX			
The WOMAC VA 3.1 Index score (WOMAC INDEX) is the sum of WOMAC A (total pain), WOMAC B (stiffness) and WOMAC C (functional impairment) subscores. The WOMAC INDEX score ranges from 0 to 2400 mm, with higher scores indicating higher disease burden.			
Units: units on a scale			
arithmetic mean	1321.5	1275.4	1282.6
standard deviation	± 278.88	± 283.6	± 274.5
EQ VAS			
The EQ visual analogue scale (EQ VAS) recorded the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 'the best health you can imagine' on top (equal to 100) and 'the worst health you can imagine' at the bottom (equal to 0).			
Units: units on a scale			
arithmetic mean	63.1	64.3	67.4
standard deviation	± 20.54	± 17.21	± 18.18

Reporting group values	Baseline Placebo	Total	
Number of subjects	108	436	
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			
Age, continuous			
Units: years			
arithmetic mean	64.4		
standard deviation	± 8.5	-	
Gender categorical			
Gender categorical			
Units: Subjects			
Female	66	264	
Male	42	172	

Ethnicity			
Non Hispanic or Latino			
Units: Subjects			
Not Hispanic or Latino	106	431	
Hispanic or Latino	2	5	
BMI			
BMI			
Units: kg/m2			
arithmetic mean	27		
standard deviation	± 2.6	-	
WOMAC A			
The validated Western Ontario and McMaster University questionnaire (WOMAC) was used to measure total knee pain choosing its visual analogue scale version (VAS). The WOMAC VA 3.1 A subscore (WOMAC A) ranges from 0 to 500 mm (summing up five VAS 0-100 mm) with higher scores indicating more pain.			
Units: units on a scale			
arithmetic mean	275.5		
standard deviation	± 39.81	-	
WOMAC INDEX			
The WOMAC VA 3.1 Index score (WOMAC INDEX) is the sum of WOMAC A (total pain), WOMAC B (stiffness) and WOMAC C (functional impairment) subscores. The WOMAC INDEX score ranges from 0 to 2400 mm, with higher scores indicating higher disease burden.			
Units: units on a scale			
arithmetic mean	1293.5		
standard deviation	± 239.73	-	
EQ VAS			
The EQ visual analogue scale (EQ VAS) recorded the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 'the best health you can imagine' on top (equal to 100) and 'the worst health you can imagine' at the bottom (equal to 0).			
Units: units on a scale			
arithmetic mean	65.7		
standard deviation	± 19.47	-	

End points

End points reporting groups

Reporting group title	Baseline Fasitibant Low Dose
Reporting group description:	
At Visit 2 immediately before randomisation to low dose of fasitibant	
Reporting group title	Baseline Fasitibant Intermediate Dose
Reporting group description:	
At Visit 2 immediately before randomisation to intermediate dose of fasitibant	
Reporting group title	Baseline Fasitibant High Dose
Reporting group description:	
At Visit 2 immediately before randomisation to high dose of fasitibant	
Reporting group title	Baseline Placebo
Reporting group description:	
At Visit 2 immediately before randomisation to placebo	
Reporting group title	Fasitibant Low Dose
Reporting group description:	
At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant low dose and will be followed up for a period of 12 weeks post-treatment.	
Reporting group title	Fasitibant Intermediate Dose
Reporting group description:	
At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant intermediate dose and will be followed up for a period of 12 weeks post-treatment.	
Reporting group title	Fasitibant High Dose
Reporting group description:	
At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of fasitibant high dose and will be followed up for a period of 12 weeks post-treatment.	
Reporting group title	Placebo
Reporting group description:	
At Visit 2 (T0 – Randomisation and Treatment Administration) patients will receive one intra articular injection of placebo and will be followed up for a period of 12 weeks post-treatment.	

Primary: Change in WOMAC A

End point title	Change in WOMAC A
End point description:	
The validated Western Ontario and McMaster University questionnaire (WOMAC) was used to measure total knee pain choosing its visual analogue scale version (VAS). The WOMAC VA 3.1 A subscore (WOMAC A) ranges from 0 to 500 mm (summing up five VAS 0-100 mm) with higher scores indicating more pain.	
End point type	Primary
End point timeframe:	
from baseline up to 2 weeks after randomisation	

End point values	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	108	107	108
Units: units on a scale				
arithmetic mean (standard deviation)	-106.1 (± 101.88)	-131.5 (± 96.41)	-115.9 (± 104.61)	117.2 (± 90.15)

Statistical analyses

Statistical analysis title	Mixed linear model for repeated measures

Statistical analysis description:

Fourhundred evaluable patients were supposed to provide approximately 80% power in rejecting the null hypothesis of equality between any dose of fasitibant and placebo based on previous results and an overall significance level of 5% (two-sided).

Comparison groups	Fasitibant Low Dose v Fasitibant Intermediate Dose v Fasitibant High Dose v Placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - The primary efficacy variable was analysed on the ITT population. Multiplicity was adjusted using the Hochberg procedure. The continuous efficacy variable was analysed over time. The minimum efficacy was defined as at least 40% pain reduction over placebo (considered for sample size calculation).

Secondary: Change in WOMAC INDEX

End point title	Change in WOMAC INDEX

End point description:

The WOMAC VA 3.1 Index score (WOMAC INDEX) is the sum of WOMAC A (total pain), WOMAC B (stiffness) and WOMAC C (functional impairment) subscores. The WOMAC INDEX score ranges from 0 to 2400 mm, with higher scores indicating higher disease burden.

End point type	Secondary

End point timeframe:

from baseline up to 6 weeks after randomisation

End point values	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	108	107	108
Units: units on a scale				
arithmetic mean (standard deviation)	-566.3 (± 525.63)	-653.8 (± 516.31)	-547.6 (± 522.37)	-581.3 (± 503.37)

Statistical analyses

Statistical analysis title	Mixed linear model for repeated measures

Statistical analysis description:

Fourhundred evaluable patients were supposed to provide approximately 80% power in rejecting the null hypothesis of equality between any dose of fasitibant and placebo based on previous results and an overall significance level of 5% (two-sided).

Comparison groups	Fasitibant Low Dose v Fasitibant Intermediate Dose v Fasitibant High Dose v Placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[2] - All secondary efficacy variables were analysed on the ITT population only. Multiplicity was adjusted using the Hochberg procedure. The continuous secondary efficacy variables were analysed over time and were treated in the same way as the primary efficacy variable with respective output.

Secondary: Responder Rate According to OMERACT-OARSI Criteria

End point title	Responder Rate According to OMERACT-OARSI Criteria

End point description:

Percentage of responders according to Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) criteria. Patients with at least 50 % improvement in pain or in function scores are considered responders. Alternatively, patients are considered responders if they show at least 20% improvement in at least two of the following scores: pain, function and Patients's Global Assessment (PGA) scores.

End point type	Secondary

End point timeframe:

from baseline up to 6 weeks after randomisation

End point values	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	108	107	108
Units: percentage of responders				
Week 1 after randomisation	52	57	64	56
Week 2 after randomisation	59	72	63	69
Week 4 after randomisation	66	72	65	67
Week 6 after randomisation	71	74	67	68

Statistical analyses

No statistical analyses for this end point

Secondary: Euro Quality of Life Questionnaire (EQ-5D-5L) Responder Rate

End point title	Euro Quality of Life Questionnaire (EQ-5D-5L) Responder Rate

End point description:

Response based on change ≥ 20 % from baseline for EQ-5D-5L index value

End point type	Secondary

End point timeframe:

from baseline up to 6 weeks after randomisation

End point values	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	108	108	107	108
Units: Percentage of Responders				
Week 2 after randomisation	19	19	21	24
Week 6 after randomisation	23	28	25	21

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For all patients receiving the study treatment (safety population, N=435), adverse event data were collected over a period of maximal 15 weeks (including the 12 week post-treatment period and the screening period up to a maximum of 3 weeks).

Adverse event reporting additional description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Fasitibant Low Dose

Reporting group description:

Patients receiving at least one single injection of low dose fasitibant

Reporting group title	Fasitibant Intermediate Dose

Reporting group description:

Patients receiving at least one single injection of intermediate dose fasitibant

Reporting group title	Fasitibant High Dose

Reporting group description:

Patients receiving at least one single injection of high dose fasitibant

Reporting group title	Placebo

Reporting group description:

Patients receiving at least one single injection of placebo.

Serious adverse events	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 110 (1.82%)	2 / 110 (1.82%)	2 / 108 (1.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 108 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			

subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 108 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 108 (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
Humerus fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	0 / 108 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	0 / 108 (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			
Hernia repair			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 108 (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
Malignant breast lump removal			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 108 (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
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 108 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 107 (3.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			

subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Knee arthroplasty			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant breast lump removal			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Fasitibant Low Dose	Fasitibant Intermediate Dose	Fasitibant High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 110 (25.45%)	46 / 110 (41.82%)	36 / 108 (33.33%)
Investigations			
Ligament sprain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 110 (1.82%)	0 / 108 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	0 / 108 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	1 / 108 (0.93%)
occurrences (all)	2	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 110 (2.73%)	3 / 110 (2.73%)	1 / 108 (0.93%)
occurrences (all)	4	4	1
General disorders and administration site conditions			
Injection site haematoma			
subjects affected / exposed	0 / 110 (0.00%)	2 / 110 (1.82%)	0 / 108 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 110 (1.82%)	0 / 108 (0.00%)
occurrences (all)	0	2	0
Diarrhea			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	2 / 108 (1.85%)
occurrences (all)	1	1	2
Toothache			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	1 / 108 (0.93%)
occurrences (all)	1	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 110 (3.64%)	7 / 110 (6.36%)	5 / 108 (4.63%)
occurrences (all)	6	7	6
Back pain			
subjects affected / exposed	2 / 110 (1.82%)	4 / 110 (3.64%)	5 / 108 (4.63%)
occurrences (all)	2	5	5
Joint swelling			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	1 / 108 (0.93%)
occurrences (all)	1	1	1
Muscle spasms			

subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	2 / 108 (1.85%)
occurrences (all)	1	0	2
Musculoskeletal pain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 110 (1.82%)	0 / 108 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	1 / 108 (0.93%)
occurrences (all)	2	0	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	2 / 110 (1.82%)	0 / 108 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	4 / 110 (3.64%)	17 / 110 (15.45%)	11 / 108 (10.19%)
occurrences (all)	4	18	11
Rhinitis			
subjects affected / exposed	2 / 110 (1.82%)	1 / 110 (0.91%)	2 / 108 (1.85%)
occurrences (all)	2	1	2
Urinary tract infection			
subjects affected / exposed	3 / 110 (2.73%)	1 / 110 (0.91%)	2 / 108 (1.85%)
occurrences (all)	3	1	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 107 (41.12%)		
Investigations			
Ligament sprain			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 0 / 107 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 2 / 107 (1.87%) 2		
General disorders and administration site conditions Injection site haematoma subjects affected / exposed occurrences (all)	 1 / 107 (0.93%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	 2 / 107 (1.87%) 2 3 / 107 (2.80%) 3 2 / 107 (1.87%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain	 8 / 107 (7.48%) 8 6 / 107 (5.61%) 6 2 / 107 (1.87%) 2 1 / 107 (0.93%) 1		

subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0 0 / 107 (0.00%) 0		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 0 / 107 (0.00%) 0 13 / 107 (12.15%) 13 0 / 107 (0.00%) 0 3 / 107 (2.80%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2014	There was one substantial amendment to study protocol version 1.0 (dated 09DEC2013) in order to accomplish all changes that were requested by the competent authorities for study approval. Main changes are summarised below: 1) The duration of the follow up for safety evaluation of fasitibant was extended up to 12 weeks after treatment administration. 2) The obligation to adopt the double barrier contraception method was integrated in the corresponding Inclusion Criterion. 3) Additional cardiac safety monitoring was included (12-lead ECG prior to and 2 hours post intraarticular injection) in the protocol. 4) The exclusion of patients taking any concomitant medications that are CYP3A4 substrates and/or moderate or strong CYP3A4 inhibitors starting from 4 weeks prior to randomisation and along study duration was added as Exclusion Criterion, considering the potential of fasitibant to be a time dependent CYP 3A4 inhibitor. Patients taking weak CYP3A4 inhibitors could be included in the study. Medications metabolised by CYP3A4 as well as grapefruit juice were included in the prohibited medication/food restrictions required by the protocol. All above changes were implemented in the study protocol version 2.0 (dated 26 FEB 2014).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported