



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 |
| Scientific contact | Dr. Angela Capriati, Clinical Research, 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 | 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 (\pm 101.88) | -131.5 (\pm 96.41) | -115.9 (\pm 104.61) | 117.2 (\pm 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 (\pm 525.63) | -653.8 (\pm 516.31) | -547.6 (\pm 522.37) | -581.3 (\pm 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 occurrences (all) | 2 / 110 (1.82%) 2 | 0 / 110 (0.00%) 0 | 0 / 108 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 2 / 110 (1.82%) 2 | 0 / 110 (0.00%) 0 | 1 / 108 (0.93%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 3 / 110 (2.73%) 4 | 3 / 110 (2.73%) 4 | 1 / 108 (0.93%) 1 |
| General disorders and administration site conditions Injection site haematoma subjects affected / exposed occurrences (all) | 0 / 110 (0.00%) 0 | 2 / 110 (1.82%) 2 | 0 / 108 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) | 0 / 110 (0.00%) 0 1 / 110 (0.91%) 1 1 / 110 (0.91%) 1 | 2 / 110 (1.82%) 2 1 / 110 (0.91%) 1 1 / 110 (0.91%) 2 | 0 / 108 (0.00%) 0 2 / 108 (1.85%) 2 1 / 108 (0.93%) 1 |
| 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 | 4 / 110 (3.64%) 6 2 / 110 (1.82%) 2 1 / 110 (0.91%) 1 | 7 / 110 (6.36%) 7 4 / 110 (3.64%) 5 1 / 110 (0.91%) 1 | 5 / 108 (4.63%) 6 5 / 108 (4.63%) 5 1 / 108 (0.93%) 1 |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 26 February 2014 | <p>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.</p> <p>Main changes are summarised below:</p> <ol style="list-style-type: none">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. <p>All above changes were implemented in the study protocol version 2.0 (dated 26 FEB 2014).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported