MENARINI RICERCHE

SYNOPSIS
STUDY CODE: BKOS-04
EudraCT No: 2013-004999-35

ALBATROSS-3
A Locally-injected Bradykinin Antagonist for the TReatment of OSteoarthritiS

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.

Sponsor:	Menarini Ricerche S.p.A. Clinical Research Department Via Sette Santi 1 50131 Florence - Italy
Test Drug:	Fasitibant chloride bis-hydrochloride
Indication Studied:	Symptomatic osteoarthritis of the knee
Study Phase:	Phase II
Study Initiation Date (First Patient In):	06 May 2014
Study Completion Date (Last Patient Out):	06 January 2015
Coordinating Investigator:	Prof. Karel Pavelka Institute of Rheumatology Charles University, Prague
Sponsor's Representative and Sponsor's Responsible Medical Officer	Angela Capriati MD, PhD Corporate Director of Clinical Research
Report Version	Final 1.0 (16 OCT 2015)
Report Date:	16 OCT 2015

This study was performed in accordance with the principles of Good Clinical Practice (GCP), the Declaration of Helsinki (and subsequent amendment) and the applicable regulatory requirements, including the archiving of essential documents.

1. SYNOPSIS

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Title of Study: 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.

Study Code: BKOS-04

Acronym/nick name:Albatross-3 - **A** **L**ocally injected **B**radykinin **A**ntagonist for **TR**eatment of **OS**teoarthriti**S**

Investigator(s) and Study Centre(s): The study was conducted in 25 study sites in Czech Republic, Germany, Italy and US. The list of Principal Investigators is provided in Appendix 16.1.4. The Coordinating Investigator was Professor Karel Pavelka, Institute of Rheumatology, Charles University Prague-Czech Republic.

Publication (Reference): not applicable

Studied Period (Years): Date of first patient screened: 28th April 2014 Date of first patient randomised: 06th May 2014 Date of last patient completed: 06th January 2015	**Phase of Development:** II

Objectives:

Primary objective:

To evaluate fasitibant, given as single intra-articular (IA) injection at three different doses *versus* placebo, as an efficacious symptom modifying treatment of knee osteoarthritis (OA).

Secondary objectives:

- To assess the dose-effect relationship of fasitibant to support the choice of the dose to be studied in a subsequent clinical phase III study.
- To evaluate the safety and tolerability of single IA fasitibant doses of 1 mg, 2.5 mg and 5 mg as 1 mL solution to patients with symptomatic knee OA.
- To evaluate fasitibant population pharmacokinetics (pop-PK) in patients with symptomatic OA of the knee and the exposure-response relationship (PK/PD).

Methodology: This was a multicenter, randomised, double-blind, placebo-controlled, four parallel arm study, testing three doses of fasitibant (1mg, 2.5mg and 5mg) *versus* placebo. Eligible patients were randomised in a 1:1:1:1 ratio to receive one of the three possible doses of fasitibant or placebo.

The individual study duration lasted up to 14 weeks, encompassing:

1. *Screening period,* for study eligibility assessment;
2. *Randomisation and Treatment visit,* with IA administration of study treatment and collection of blood sample for PK analyses;

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

3. *Follow-up period*, with efficacy and PK evaluation, and safety and tolerability monitoring (lasting twelve weeks from treatment administration).

Clinical efficacy evaluation was based on patient reported outcomes, i.e. patient assigned scores recorded at pre-specified time-points (baseline, week 1, 2, 4, 6 and 12 after IA injection):

- WOMAC VA 3.1, with each assessment referred by the patient to the previous 48 hours and recorded on a visual analogue scale, namely:
  - A subscore (total pain): sum of 5 VA scales (0-500)
  - B subscore (stiffness): sum of 2 VA scales (0-200)
  - C subscore (functional impairment): sum of 17 VA scales (0-1700)
  - Index: sum of subscores A+B+C (0-2400)
- Pain at rest: 1 VA scale (0-100)
- Pain after 15-meter walk: 1 VA scale (0-100)
- Patient Global Assessment: 1 VA scale (0-100)
- AUC_{0w-2w} and AUC_{0w-6w} of WOMAC VA 3.1 A subscore (total pain).
- Responses to treatment according to Minimal Clinically Important Improvement (MCII) criteria over 2 and 6 weeks after randomisation and at each post-treatment time point, for WOMAC VA 3.1 A subscore (total pain), WOMAC VA 3.1 C subscore (functional impairment) and Patient Global Assessment, in terms of: - absolute MCII; change from baseline ≥ 15 mm (by using normalized scale 0-100); - relative MCII; change from baseline ≥ 20%.
- Response to treatment according to Patient Acceptable Symptom State (PASS) criterion, over 2 and 6 weeks after randomisation and at each post-treatment time point defined as WOMAC VA 3.1 A subscore (total pain), WOMAC VA 3.1 C subscore (functional impairment) and Patient Global Assessment < 40 mm (by using normalized scale 0-100).
- Response to treatment according to OMERACT-OARSI criteria over 2 and 6 weeks after randomisation, and at each post-treatment time point until week 6.
- Use of rescue medication (time to first use of rescue medication, and consumption and number of days analysed by time-point).
- Response based on change ≥ 20 % from baseline for EuroQoL5 (EQ-5D-5L) index value over 2 and 6 weeks after randomisation and at week 2 and 6.

For the PK evaluation the following blood samples for fasitibant plasma concentration measurements were taken at pre-defined time points from baseline up to 4 weeks after treatment administration as reported in the flow chart under § 9.5.1.

The following safety assessments were performed: vital signs (including blood pressure [BP], pulse rate [PR], respiratory rate [RR], body temperature [T], 12 lead-electrocardiogram (ECG), laboratory safety analyses (haematology, clinical biochemistry, urinalysis, and pregnancy test, if applicable), physical examination, knee examination (including local tolerability at target knee) and occurrence

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

of Adverse Events (AEs).

Number of Subjects (planned and analysed):

Planned (to be randomised): 400 patients. The enrolment was competitive.
Enrolled: 645 patients.
Randomised: 431 patients.
Safety analysis: 435 patients.
Efficacy analysis: 431 (Intention-to-treat, ITT), 381 (Per Protocol, PP)
PK/PD analysis: 430 patients
PK-analysis: 323 patients

Diagnosis and Main Criteria for Inclusion:

Patients with history of symptomatic primary osteoarthritis of the knee with documented Kellgren Lawrence Grade 2 to 3 radiological severity, and BMI < 30 kg/m² for which an IA treatment is indicated. In addition the patients should have an adequate hematological, renal and hepatic function and do not use confounding pharmacological or non-pharmacological treatments.

Test Product, Dose, Mode of Administration, and Batch Number:

Pre-filled syringes with 1 ml solution of Fasitibant 1 mg/ml, 2.5 mg/ml, and 5 mg/ml, for IA injection:
IMP bulk batch no. fasitibant 1 mg: FAS PM0171
IMP bulk batch no. fasitibant 2.5 mg: FAS PM0172
IMP bulk batch no. fasitibant 5 mg: FAS PM0173
IMP batch numbers: J0414031, J0414032, J0414061 and J0414071

Duration of Treatment:

Both, the test product and the reference therapy had to be administered as one single IA (target knee joint) injection.

Reference Therapy, Dose, Mode of Administration, and Batch Number:

Pre-filled syringes with Placebo 1 ml solution for IA injection (fully matching fasitibant):
Placebo bulk batch no: FAS PM0170
IMP batch numbers: J0414031, J0414032, J0414061 and J0414071

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Criteria for Evaluation:

Efficacy:

The primary clinical efficacy endpoint was evaluated by measuring the change of WOMAC VA 3.1 A (total pain) subscore from baseline (Visit 2) over 2 weeks after randomisation.

The secondary clinical efficacy endpoints were evaluated by measuring the change from baseline (Visit 2) over 2 weeks (excluding WOMAC 3.1 A) and over 6 weeks after randomisation, and at each post-treatment time-point until week 6, of the WOMAC VA 3.1 subscore A, A1, B, C, global index, pain at rest, pain after 15 meter walk, patient global assessment. Finally, treatment responses according to the MCII, PASS, OMERACT-OARSI criteria, EuroQoL5 questionnaire and the use of rescue medication were also evaluated.

Pharmacokinetic:

The following pharmacokinetic parameters were assessed:
- Time course of fasitibant plasma concentrations.
- Population pharmacokinetic parameters of fasitibant including CL/F, Vd/F and Ka from synovial fluid to systemic circulation.
- Individual AUC, C_{max} and $t_{1/2}$.

Safety:

The assessment of safety and tolerability of study treatments includes the:

- Incidence, intensity (severity), seriousness and treatment causality of adverse events reported after study medication intake (i.e. treatment emergent signs and symptoms –TESS).
- Frequency of clinical significant changes in vital signs (blood pressure [BP]; pulse rate [PR]; respiratory rate [RR]; body temperature [T]), 12-lead electrocardiogram (ECG) parameters and laboratory safety battery tests (haematology, clinical biochemistry and urinalysis).
- Frequency of investigator judgements in physical examinations including local tolerability and target knee examination.

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Statistical Methods:

Sample Size Determination:

Assuming 10% screening failures, approximately 440 patients will be screened in order to randomise a total of 400 male and female patients with symptomatic knee osteoarthritis. A total number of 400 evaluable patients were supposed to provide approximately 80% power in rejecting the null hypothesis of equality between any dose of fasitibant and placebo on the basis of the following assumptions relative to the primary efficacy endpoint:

- expected mean reduction of WOMAC A NR score *versus* baseline in the placebo group = -10.5 (on a numeric scale 0-50);
- expected mean therapeutic gain over placebo in primary outcome = 40% (i.e.: -4.2);
- common standard deviation for change from each time point (i.e. 1 week and 2 week after treatment administration) to baseline for all groups= 9.1;
- overall significance level = 5% two-sided.

A detailed description of the statistical methods applied in this study was given in the final Statistical Analysis Plan (SAP, Appendix 16.1.9). The SAP was finalised prior to assigning the randomisation code to the study data.

Analysis populations were as follows:

- Intention-to-treat (ITT) population: all randomised patients.
- Per Protocol (PP) population: all patients of the ITT population with no major protocol violations.
- Safety population: all patients receiving the study treatment
- PK population: all randomised patients who have at least one fasitibant plasma concentration data available with complete dosing and sampling history, and covariate documentation.

All efficacy analyses were performed on the ITT population. The PP population was used to perform confirmatory analyses on the primary efficacy evaluation.

Statistical Analysis:

Study variables were described using the following statistics:

- Continuous variables: number of non-missing observations (N), arithmetic mean, standard deviation (SD), minimum, median, maximum;
- Categorical variables: number of non-missing observations and column percentages (N, %);

The behaviour over time of study variables were summarised by treatment, as follows:

- Continuous variables: descriptive statistics for each time point and for the absolute differences to baseline;
- Discrete variables: descriptive statistics for each time point.

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Primary efficacy analysis:

The primary variable was analysed by a mixed linear model for repeated measures in order to test the differences in treatment efficacy, as quantified by WOMAC VA 3.1 A (total pain) subscore, over 2 weeks after treatment administration, between each fasitibant treatment group *versus* placebo. This model included terms of treatment, visits, interaction between visits and treatment, as well as the baseline WOMAC VA 3.1 A (total pain) subscore as covariate. Multiplicity was corrected by using the Hochberg adjustment.

The primary analysis has been done on the ITT population and was repeated on the PP population using the same procedure.

Secondary efficacy analyses:

All secondary efficacy variables were analysed on the ITT population only:

- Over time analysis for continuous variables was performed as described for the primary efficacy analysis.
- Punctual time analysis for continuous variables was performed using ANCOVA model including terms of treatment and corresponding baseline value as covariates.
- Responder to treatment criteria were analysed over time and at each time point using generalised estimating equations for repeated binary outcomes and single outcomes, respectively.
- Time to first use of RM was analysed by Kaplan-Meier (KM).

Pharmacokinetic analyses:

The population PK and population PK/PD analyses were based on multiple regressions using Non-Linear Mixed Effect Models. The PK/PD analysis of efficacy was assessed on the WOMAC VA 3.1 A (total pain) subscore in the fasitibant and placebo groups. The significance of the effect of fasitibant exposure was tested using the Likelihood Ratio Test (LRT) at $p<0.05$, i.e. a decrease of the objective function of at least 3.84.

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Results

Baseline characteristics of study population:

The demographics and baseline characteristics were comparable between treatment groups and placebo.

On average, study patients were 64.4 ± 8.34 years of age, with a mean body weight of 77.3 ± 11.4 kg, and mean BMI of 26.9 ± 2.50 kg/m² without any clinically significant differences between treatment groups and placebo.

The included patients were to 61% of female gender. All women of childbearing potential (n=10), underwent a pregnancy test at Screening and before treatment administration, which resulted in all cases as negative.

There were no significant clinically differences regarding baseline characteristics of the target knee between all treatment groups and placebo. All patients of the ITT-population had symptomatic primary osteoarthritis (OA) of the knee according to the American College of Rheumatology (ACR) criteria for ≥ 3 months, and with X-ray documented Kellgren Lawrence Grade 2 to 3 radiological severities, and an average time from onset of OA symptoms of 8.5 ± 7.06 years, without any relevant differences between treatment groups and placebo.

All WOMAC VA 3.1 pain, stiffness and function scores as well as the WOMAC 3.1 VA pain subscore A1 (walking on a flat surface) were not significant different at baseline between all treatment groups and placebo. The WOMAC VA 3.1 A (total pain) subscore at baseline was on average of moderate intensity (280.8 ± 39.61 mm, VAS 0-500 mm). The average interfering pain score at baseline was negligible (6.8 ± 7.26 mm, VAS 0-100 mm) in all treatment groups and placebo.

Efficacy Results:

Primary Endpoint:

Fasitibant (1 mg, 2.5 mg and 5 mg) given as single IA injections did not significantly differentiate from placebo for WOMAC VA 3.1 A (total pain) score over two weeks post administration in the ITT-Population (n=431):

- At week 1 after randomisation, the mean change of WOMAC VA 3.1 A (total pain) subscore from baseline was -91.8 (-32.7 %) for fasitibant 1 mg; -110.0 (-39.5%) for fasitibant 2.5 mg and -109.8 (-39.7%) for fasitibant 5 mg and was at no fasitibant dose significant different from placebo -93.7 (-34.5%). Thus, only a trend to a dose-dependent pain reduction was observed at week 1 after randomisation with maximal pain reduction in the fasitibant 5mg dose group.
- At week 2 after randomisation, the mean change of WOMAC VA 3.1 A (total pain) subscore from baseline was -106.1 (-37.5 %) for fasitibant 1 mg; -131.5 (-47.4%) for fasitibant 2.5 mg and -115.9 (-42.2%) for fasitibant 5 mg and hence was at no fasitibant dose significant different from placebo -117.2 (-42.9%).

The lack of efficacy has been confirmed in the PP-Population (n=381):

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

- At week 1 after randomisation; the mean change of WOMAC VA 3.1 A (total pain) subscore from baseline was -94.5 (-33.4%) for fasitibant 1mg, -110.6 (-39.9%) for fasitibant 2.5 mg and -116.8 (-41.9%) for fasitibant 5 mg; pain reduction was at no dose significant different from placebo -92.2 (-33.6%). Again, only a trend to a dose-dependent pain reduction was observed at week 1 after randomisation with maximal pain reduction in the fasitibant 5mg dose group.
- At week 2 after randomisation; the mean change of WOMAC VA 3.1 A (total pain) subscore from baseline was -110.7 (-39.0%) for fasitibant 1 mg; -134.3 (-48.5%) for fasitibant 2.5 mg and -124.6 (-45.3%) for fasitibant 5 mg and hence was at no fasitibant dose significant different from placebo -119.4 (-43.4%).

Secondary Endpoints:

All main secondary endpoints showed a trend to improvement respect to basal values in all treatment groups post IA injection; however without reaching statistical significance *over* placebo for any of the administered fasitibant doses for the following assessments:

- Changes from baseline over 2 weeks (excluding WOMAC VA 3.1 A) and over 6 weeks after randomisation, and at each post-treatment time-point until week 6:
  - WOMAC VA 3.1 A subscore (total pain): VAS subscore 0-500 mm;
  - WOMAC VA 3.1 A1 subscore (walking pain on a flat surface): VAS 0-100 mm;
  - WOMAC VA 3.1 B subscore (stiffness): VAS subscore 0-200 mm;
  - WOMAC VA 3.1 C subscore (functional impairment): VAS subscore 0-1700 mm;
  - WOMAC VA 3.1 Index (sum of subscores A+ B+C): VAS total score 0-2400 mm;
  - Pain at rest: VAS 0-100 mm;
  - Pain after 15-meter walk: VAS 0-100 mm;
  - Patient Global Assessment: VAS 0-100 mm;
- AUC_{0w-2w} and AUC_{0w-6w} of WOMAC VA 3.1 A subscore (total pain).
- Responses to treatment according to Minimal Clinically Important Improvement (MCII) criteria over 2 and 6 weeks and at each post-treatment time point after randomisation, for WOMAC VA 3.1 A subscore (total pain), WOMAC VA 3.1 C subscore (functional impairment) and Patient Global Assessment, in terms of:
  - absolute MCII; change from baseline $\geq$ 15 mm (by using normalized scale 0-100);
  - relative MCII; change from baseline $\geq$ 20%.
- Response to treatment according to Patient Acceptable Symptom State (PASS) criterion, over 2 and 6 weeks and at each post-treatment time point after randomisation defined as WOMAC VA 3.1 A subscore (total pain), WOMAC VA 3.1 C subscore (functional impairment) and Patient Global Assessment < 40 mm (by using normalized scale 0-100).
- Response to treatment according to OMERACT-OARSI criteria over 2 and 6 weeks after randomisation, and at each post-treatment time point until week 6.
- Response based on change $\geq$ 20 % from baseline for EuroQoL5 (EQ-5D-5L) index value over 2 and 6 weeks after randomisation and at week 2 and 6.

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Rescue medication

The rescue medication consumption declined in all treatment groups up to week 2 after IA injection without any significant difference *versus* placebo; at the same time the number of days of rescue medication used did not change within each treatment group.

The time to first use of rescue medication discriminated significant from placebo in the fasitibant 5 mg dose group (Kaplan-Meier analysis; p< 0.0154, adjusted p-value = 0.0462). However, the use of rescue medication returned to baseline values at 4 weeks post administration in all treatment groups.

Subgroup analysis

Fasitibant (1 mg, 2.5 mg and 5 mg) did not significant discriminate from placebo from baseline over 2 and 6 weeks in the following subgroups of the ITT population:

- patients of female gender (n=263),
- patients ≤ 65 years (n=229),
- patients with BMI ≥ 25kg/m^2 (n=335),
- patients with BMI ≤ Median 27.5 kg/m^2 (n=218) and
- patients with a baseline total pain score ≥ 300 mm (n=145).

Pharmacokinetic Results:

Population pharmacokinetic (pop-PK) analysis

A two-compartment model with first order absorption from the synovial compartment and linear elimination from the central compartment best described the data.

Clearance was affected by body size and age, with lower clearance (and higher exposure) for those of lower weight and/or advanced age. The inclusion of lean body mass (LBM) as predictor of clearance was sufficient to explain body size effect. Apparent clearance (CL/F) for a typical patient aged 65 years with a LBM of 50 Kg was 48 mL/h. This was in line with previously observed estimate of the parameter from BKOS-03 (i.e. 43 mL/h). As expected, the volume of distribution of the central compartment was found to increase with body size. Apparent volume of the central compartment (Vc/F) for a typical patient with a LBM of 50 Kg was 6.11 L.

Fasitibant systemic exposure in terms of Cmax and AUC was found to increase proportionally with dose similarly to what has been observed in previous BKOS-03 study.

Exposure-response (PK/PD) analysis

No relationship between the WOMAC VA 3.1 A subscore (total pain) and fasitibant exposure could be detected at p<0.05.

Safety Results:

Treatment Emergent Signs and Symptoms (TESS)

In total, 265 TESS were reported in 186 patients (42.8%). In detail, TESSs were reported for 39 (35.5%) patients in the fasitibant 1 mg group, 55 (50%) patients in the fasitibant 2.5 mg group, 46

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

(42.6 %) patients in the fasitibant 5 mg group, and 46 (43%) patients in the placebo group. Overall, for 23 patients with TESS 29 treatment- related TESSs were reported [6 in the fasitibant 1 mg group, 6 in the fasitibant 2.5 mg group, 4 in the fasitibant 5 mg group and 13 related events in the placebo group]. Twenty seven of these treatment-related TESSs resolved spontaneously and two did not resolve during the study.

The most common TESSs were reported in the "Infections and Infestations" SOC (74 TESSs in 72 patients [16.6%]), the most frequent being nasopharyngitis that occurred with no dose dependence in all treatment groups and was comparable to placebo group. The second most common TESSs were reported in the "Musculoskeletal and Connective tissue Disorders" SOC (67 TESSs in 58 patients [13.3%]), the most frequent being arthralgia and back pain which were experienced uniformly in all treatment groups and placebo.

No dose-related trend was noted for the incidence of adverse events in the study. Overall, a slightly higher incidence in the active treatment groups was noted just for the 2.5 mg group than under placebo (50% *vs* 43%). In contrast, treatment-related TESSs were more frequent in the placebo group (n=13) than in each treatment group, as stated above.

In general, most TESSs were of mild or moderate intensity; only 12 TESSs across all treatment groups were rated as being of severe intensity. Ten patients (2.3%) across all treatment groups experienced 12 (13*) serious adverse events (SAEs) with most SAEs in the placebo group (n=5). These SAEs were judged as either not related (n=11) (12*) or unlikely related (n=1) by investigators.

**Note: Data according to Sponsor's upgrade of the event "breast cancer female" (patient 04905054-allocated to fasitibant 1 mg) from non-serious to serious adverse event.*

No deaths have been reported in this study.

Laboratory

There were no clinically relevant differences in the average values of any haematology, serum biochemistry or urinary parameters across all treatment groups at Screening and 6 week post IA treatment administration or at any pre-defined time point up to 12 weeks after treatment administration.

In 10 patients, 16 abnormal lab values [increase of creatine phosphokinase (n=2), Gamma-glutamyl transpeptidase (n=4), increased fasting glucose (n=2), direct bilirubine (n=2), of total bilirubine, ALT, AST, ALP, C-reactive protein and uric acid (n=1 each) were reported and judged by the investigators as clinically significant. In five cases these clinically significant abnormal lab values were detected at Screening, i.e. before the administration of any study medication. The other five findings occurred at 6 weeks after IA injection or at unscheduled visits and all were judged by investigator as not related to study treatment.

Vital signs

There were no clinically significant changes of average values in vital signs between and any follow-up visit or at any pre-defined time point up to 12 weeks after treatment administration.

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Almost all individual abnormal changes of vital signs recorded during the study were judged by the investigators as not clinically significant, with the exception of two patients with clinical significant abnormalities in the fasitibant 5mg group. One patient had an elevated systolic blood pressure one week post treatment. Since this patient had a history of hypertension for several years, the elevated blood pressure was judged as not related to study treatment by the investigator. Another patient had a diastolic hypotension one week after treatment administration, judged by the investigator as abnormal clinical significant. However, no hypotension associated signs and symptoms were recorded for this patient during the whole study.

Physical examination:
There were no clinical relevant differences in physical examination results between the treatment groups along the entire study period.

Tolerability of target knee with injection:
The intra-articular injection of the study medication was well tolerated by almost all patients of the safety population with the exception of two patients in the 5 mg group. In 5 patients the tolerability test was not done.

Electrocardiography:
Over 40 % of patients across all treatment groups had non-clinically relevant abnormalities of ECGs at Screening (40.1%) and baseline (42.1%).
The incidence of these non-clinically relevant abnormalities of ECGs did not significantly change during the post-treatment period (up to 6 weeks after treatment administration), and there was no clinically relevant difference across all treatment groups.
Two patients, allocated to the fasitibant 1 mg group, had an abnormal ECG judged as abnormal clinically significant. One patient had an atrioventricular block first degree judged as clinical significant at Visit 2 - 2hours after treatment administration. The event was considered by the investigator as mild, certainly related to study treatment and did resolve during the study. Another patient had an intermittent tachyarrhythmia absoluta at 6 weeks after treatment administration considered by the investigator as moderate and unlikely related to study treatment. The event necessitated treatment and according to the investigator it did not resolve during the study.
No clinically significant QTc prolongation was observed in any treatment group.

Name of Sponsor/Company: Menarini Ricerche S.p.A.	**Individual Study Table Referring to part of the Dossier**	**(for National Authority Use only)**
Name of Finished Product: -/-	**Volume:**	
Name of Active Ingredient: Fasitibant chloride bis-hydrochloride (Fasitibant)	**Page:**	

Conclusions:

In summary, the primary efficacy analysis has not shown any statistical significant evidence of superiority of fasitibant at any dose *over* placebo on pain reduction from baseline over 2 weeks after randomisation.

The lack of efficacy has been confirmed for the Per-Protocol population and by subgroup analyses for gender, age, BMI and pain intensity. All main secondary endpoints testing efficacy in terms of reduction in knee pain and stiffness, improvement in knee function and patient global assessment score as well as rescue medication consumption were not met. However, the time to first use of rescue medication discriminated significant from placebo in the fasitibant 5 mg dose group (Kaplan-Meier analysis; $p< 0.0154$; adjusted p-value = 0.0462), which might be considered as an indirect evidence of its efficacy.

In general, single doses of fasitibant were well tolerated without relevant dose-proportionality pattern in the observed safety parameters. Most TESSs were of mild to moderate severity, most of them resolving spontaneously during the study period. Considering the Sponsor's upgrade of the event "breast cancer female" (patient 04905054-allocated to fasitibant 1 mg) from non-serious to serious adverse event, a total of 13 TESSs were rated as Serious Adverse Event (SAE) and judged as either not related (n=12) or unlikely related (n=1) by investigators.

No SAE was considered to have a relationship to the study medication.

No deaths were reported in the study.

No clinically relevant abnormalities were observed in the physical examinations. Only few clinical significant events were reported for vital signs, blood and urinary laboratories analyses, and 12-lead ECGs without relevant dose-proportionality pattern in the observed safety parameters. No clinically significant QTc prolongations were observed in any treatment group.

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