2 SYNOPSIS

Name of Sponsor/Company: Zambon S.p.A., Via Lillo del Duca 10, 20091 Bresso (Milan), Italy

Name of Active Ingredient: Ibuprofen Arginine 600 mg

Title of the study: Evaluation of efficacy and safety of Ibuprofen Arginine 600 mg tid vs. Ibuprofen 600 mg tid in the treatment of pain and inflammation in Osteoarthritis (OA) patients with hypertension pharmacologically stabilized

Investigators: 4 Principal Investigators in Italy

Study centres: 4 investigational study sites in Italy

Publication (reference): Not applicable

Study period: First patient enrolled: 04 Mar 2013; Last patient completed: 09 Dec 2013

Phase of development: IV

Objectives: The objective of the study was to compare Ibuprofen Arginine (IBA) vs. Ibuprofen (IBU) in the change from baseline of daily spontaneous pain in patients suffering from OA and stabilized hypertension.

Methodology:

This study was a multicentre, randomized, open-label, active controlled, parallel group study.

After signing the informed consent, patients with OA and stabilized hypertension by pharmacological treatment in monotherapy or with no more than three antihypertensive drugs association among AT1 antagonists or ACE inhibitors or Calcium-channel-blockers or diuretics (except the monotherapy with Calcium-channel-blockers or diuretics and their association), satisfying all inclusion criteria and none of the exclusion criteria, underwent a 7-day run-in period and were then randomized to a 14-day treatment period with either Ibuprofen Arginine (IBA) apricot 600 mg granules for oral solution (sachet) or Ibuprofen (IBU) 600 mg granules for oral solution (sachet).

The study included a screening visit (Visit 0), scheduled 7 days prior to randomization, a randomization visit (Visit 1/A, Day -1) followed by a further visit on the following Day (Visit 1/B, Day 0), and a 14-day treatment period, during which visits at the clinic took place after 7 (Visit 2, Day 7), 14 (V3/A, Day 14) and 15 (Visit 3/B, Day 15) days from the start of treatment.

Number of subjects (planned and analysed):

	Planned	Randomised	Safety	Completed
Total	128	10	10	10
Ibuprofen arginin (IBA)	64	5	5	5
Ibuprofen (IBU)	64	5	5	5

Study population: the study was prematurely interrupted due to difficulties in enrollment, with 10 randomized patients, 5 in each treatment group. All patients in both groups completed the study.

Extent of exposure and compliance: apart from one patient in the IBA group (patient No. 093), all the other patients in both groups took the study treatment as scheduled.

Diagnosis and main criteria for inclusion:

Male or female patients aged ≥ 50 and ≤ 80 years; patients suffering from knee or hip OA symptoms exacerbation requiring intake of NSAIDs for at least 14 days; hypertensive stabilized patients (sitting office systolic blood pressure [SBP] <160 mmHg and sitting office diastolic blood pressure [DBP] <100 mmHg) since six months under pharmacological treatment in monotherapy or with no more than three antihypertensive drugs association among the following: AT1 antagonists or ACE inhibitors or Calcium-channel-blockers or diuretics (except the monotherapy with Calcium-channel-blockers or diuretics and their association); patients having moderate to severe pain (pain intensity ≥ 50 on a 0-100 VAS) at the randomization visit; signed informed consent; willing and able to comply with study procedures.

Test product, dose and mode of administration, batch no:

Ibuprofen Arginine (IBA) apricot 600 mg granules for oral solution (sachet), given three times daily (i.e. in the morning, in the early afternoon and in the evening) by oral route, dissolved in approximately one glass of water.

Used batch: refer to Appendix 16.1.6.

Duration of treatment: 14 days.

Reference therapy, dose and mode of administration, batch no:

Ibuprofen (IBU) 600 mg granules for oral solution (sachet), given three times daily (i.e. in the morning, in the early afternoon and in the evening) by oral route, dissolved in approximately one glass of water.

Used batch: refer to Appendix 16.1.6.

Criteria for evaluation:

Efficacy

The primary efficacy variable of the study was the change versus baseline of daily spontaneous pain, as measured by VAS, in both treatment arms, assessed by patients on diaries from Day 0 to Day 14.

The secondary efficacy variables scheduled by protocol were:

- Change versus baseline (Day 0) in Office sitting SBP and DBP at Day 7 and 15 measured and recorded with Microlife Watch BP Office Target by the Investigator in the office visit;
- Change versus baseline in Seven Day Average SBP and DBP measured by Home BP Monitoring (HBPM) calculated after 7 (interval day 1 to 7) and after 14 days (interval day 8 to 14) , with Microlife Watch BP 03 (Home mode);
- Change versus baseline in 24-hour average SBP and DBP measured by ABPM (at Day -1 to 0 and at Day 14 to 15) by Microlife Watch BP 03 (Ambulatory mode);
- Change versus baseline (Day -1 to 0) in day-time pulse pressure (SBP-DBP) measured at Day 14 to 15 with Microlife Watch BP 03 (Ambulatory mode);
- Change versus baseline (Day -7 to 15) in ADMA test measured in a centralized laboratory (no data were analysed);
- Change versus baseline (Day 0) in daily morning stiffness by VAS values, assessed daily at morning, at wake up time, by patient from Day 0 to Day 14 - after 14 days of treatment;
- Change versus baseline of Fatigue based on FSS questionnaire at Day 0 and Day 15, - after 14 days of treatment, administered by Investigator.

Note: Due to the study premature terminated with 10 evaluable patients, descriptive statistics were produced only for the following efficacy variables: daily spontaneous pain, daily morning stiffness and FSS. Data of all the other efficacy variables were listed only.

Safety

The safety variables of the study were:

- Monitoring all adverse events (AEs) during the study, starting from the signature of the informed consent throughout the end of the study;
- Physical examination and vital signs, evaluated at any visit;
- Safety laboratory parameters: haematology, clinical chemistry and urinalysis carried out at screening and at the end of the study (V3/B, Day 15);
- A 12-lead ECG performed at screening and at the end of the study (V3/B, Day 15).

Note: Due to the study premature terminated with 10 evaluable patients, descriptive statistics were produced only for adverse events. Data of all the other safety variables were listed only.

Statistical methods:

Descriptive statistics were produced only for the following variables: patient disposition, demographic and other baseline characteristic, daily spontaneous pain, daily morning stiffness, FSS and treatment-emergent AEs. The results were presented in the safety data set, defined as the all randomized patients who received at least one dose of IMP. The results were presented in form of descriptive statistics, i.e. number of observation, mean, standard deviation (SD), median, minimum and maximum for continuous variables, and frequency distributions (number and percentages) for categorical variables.

No inferential statistics in the analysis of changes from baseline and of comparisons between groups were performed. All the other study variables were listed only.

Treatment emergent adverse events (TEAEs) were defined as those AEs that started on or after the study medication intake. All TEAEs were summarised by MedDRA System Organ Class (SOC) and Preferred Term (PT).

Efficacy results:

Primary end-point: daily spontaneous pain

The mean VAS score of daily spontaneous pain decreased from baseline to any post-baseline time point in both groups (except for a small increase at Day 2 in the IBU group). The mean (± SD) change from baseline to Day 14 was -21.0 ± 23.3 mm in the IBA group and -12.4 ± 39.8 mm in the IBU group.

Secondary end-points

Daily morning stiffness

The mean VAS score of daily morning stiffness decreased from baseline to any post-baseline time point in both groups (except for a small increase at Day 1 in the IBA group and at Day 1 and 2 in the IBU group). The mean (± SD) change from baseline to Day 14 was -27.5 ± 28.1 mm in the IBA group and -6.0 ± 28.6 mm in the IBU group.

Fatigue severity scale

The mean FSS score did not change from baseline to the final visit in the IBU group and decreased in the IBA group. The mean (± SD) change from baseline to the final visit was 0.0 ± 10.1 in the IBA group and -10.0 ± 6.2 in the IBU group.

Office blood pressure

There was no evidence of clinically significant changes from the screening visit to any post-baseline time point of both systolic and diastolic blood pressure in all patients in both groups.

Ambulatory BP Monitoring (ABPM)

There was no evidence of clinically significant changes from baseline to Day 14 of 24-hour average systolic and diastolic blood pressure, and of daytime pulse pressure, in all patients in both groups.

Home BP Monitoring (HBPM)

There was no evidence of clinically significant changes from baseline to Day 14 of both systolic and diastolic blood pressure in all patients in both groups.

Safety results:

Adverse events

Two treatment-emergent non-serious AEs were reported in 1 patient (20.0%) in the IBA group. None of patients in the IBU group reported treatment-emergent AEs.

One of the AEs in the IBA group (oedema) was treatment-related and was moderate in intensity, while the other AE (cough) was not treatment-related and was of mild intensity. Both AEs required a specific treatment but did not cause the discontinuation of treatment with the IMP.

Vital signs

There was no evidence of clinically significant changes from the screening visit of any parameter (weight, BMI, circumference of dominating arm, heart rate and respiratory rate) in all patients in both groups.

ECG

There was no evidence of clinically significant changes of ECG results from the screening visit to the final visit in all patients in both groups.

Physical examination

There was no evidence of changes of results of physical examination from the screening visit to the final visit in all patients in both groups.

Conclusions:

- The study was prematurely interrupted due to difficulties in enrolment and no definite conclusions can be made;
- The few available data (5 patients in each group) showed mean improvements from baseline in daily spontaneous pain and daily morning stiffness, being the mean changes more marked in the IBA group than in the IBU group (however with high data variability);
- There was no evidence of clinically significant changes from baseline to Day 14 in office blood pressure, ABPM and HBPM parameters in both groups;
- Both IMPs were well tolerated, with one treatment-related AE in the IBA group.