CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor Company	***Name of finished product***	***Name of active ingredient***
Zambon		Ibuprofen Arginine 600 mg
Study Code: Z7190M01		
Eudract number: 2011-003051-19		

Title of the study

Evaluation of the speed of action of Ibuprofen Arginine in comparison to Ibuprofen in the acute pain relief after mini invasive orthopaedic arthroscopic knee surgery in adults

Principal Investigators and study sites

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Other 9 sites in Italy were opened, but no subjects were included in these sites.

Study Period:	***Phase of Development***
19 March 2012 (First Subject In) /15 July 2014 (Last Subject Out)	Phase IV

Objectives

The objective of the study was to assess of the speed of action and global clinical efficacy of Ibuprofen Arginine (IBA) in comparison with Ibuprofen (IBU) in subjects with postoperative acute pain. The effects of IBA or IBU were assessed, for this first 60-minute observation period, in the absence of intake of any rescue medication.

Study design and Methodology

This was a multicentre, randomized, single blind, blind-observer, active controlled, parallel group study.

After signing the informed consent, subjects with post-surgical acute pain satisfying all inclusion criteria and none of the exclusion criteria were randomized to either IBA apricot 600 mg granules for oral solution (sachets) or IBU 600 mg granules for oral solution (sachets).

The study plan included a screening visit (Visit 0), scheduled within 14 days before the planned date for surgery, and a randomisation/treatment visit (Visit 1), during which pre- and post-treatment assessments were performed. During Visit 1 (randomisation/treatment) subjects who had undergone meniscectomy received a single oral dose of IBA or IBU 600 mg on request when needed during the period following the loco-regional anaesthesia, to assess their pain reduction from the time of the study drug administration over the following 360-minute period.

Subject population

Number of Subjects Planned: 158
Number of Subjects Randomized: 46 (38 Males/8 Females)
Number of Subjects Analysed for Safety: 43 (20 in the IBA group and 23 in the IBU group)
Number of Subjects Analysed for Efficacy (Full Analysis Set): Not applicable (efficacy analyses were performed in the safety set)
Number of Completers 43 (20 in the IBA group and 23 in the IBU group)

Demographic and baseline characteristics

Both groups included more male than female subjects. The vast majority of subjects were Caucasians. The mean values of the demographic parameters were comparable in the two groups.

Summary of major protocol deviations

None of randomised subjects in both groups had major protocol violations

Subjects excluded from analyses

All analyses were based on the safety set

Eligibility Criteria

Inclusion criteria.

1) Male or female subjects aged ≥ 18 and ≤ 65 years;
2) Subjects undergoing mini invasive orthopaedic surgery (meniscectomy) in loco-regional anaesthesia;
3) Subjects having a pain intensity of 50 or more on a 0-100 VAS in the post-surgical period;
4) American Society of Anaesthesiologists (ASA) physical status I and II for the whole study duration;
5) Signed informed consent;
6) Willing and able to comply with study procedures.

Exclusion criteria

1) Ascertained or presumptive hypersensitivity to the active compound and/or any of the formulation excipients;

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2) History of anaphylaxis to drugs or allergic reactions; in particular, history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria, angioedema) to non-steroidal anti-inflammatory drugs (NSAIDs);
3) Obstructive respiratory syndromes (asthma or COPD), nasal polyposis or any other chronic respiratory disease;
4) History of psychosis (e.g. schizophrenia or psychotic depression) or major depression (requiring treatment);
5) Severe neurological diseases, including dementia, anxiety, mental retardation, multiple sclerosis, Parkinson's disease, uncontrolled epilepsy;
6) Transient ischemic attack or cerebrovascular accident within the last three months before the screening visit;
7) Myocardial infarction, unstable angina, arrhythmias, cardiac failure or other chronic cardiac diseases;
8) Significant kidney (serum creatinine ≥ 2.0 mg/dL or 180 µmol/L) or liver disease (serum transaminases ≥ 3 x upper limit of normal);
9) History of gastrointestinal diseases, active peptic ulcer, gastrointestinal bleeding in the preceding 6 months before the screening visit;
10) Inflammatory Bowel Diseases (IBD);
11) Phenylchetonuria;
12) Autoimmune diseases;
13) Blood coagulation disorders or anticoagulants use within the last month before the screening visit;
14) Symptomatic osteoarthritis requiring medical therapy or inflammatory arthritis;
15) Arthroscopic knee surgery within the last 6 months before the screening visit;
16) Body mass index (BMI) ≥ 35 kg/m^2;
17) Use of paracetamol within 24 hours before the randomization visit;
18) Use of muscle relaxants 24 hours before the randomization visit;
19) Use of systemic and topical preparations of NSAIDs within 48 hours before the randomization visit;
20) Use of opioids within 7 days before the randomization visit;
21) Use of systemic and topical preparations of corticosteroids within 14 days before the randomization visit;
22) Any clinical significant abnormal laboratory values as judged by the Investigator;
23) Pregnant or lactating women or women of childbearing age not using a reliable method of contraception (hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months prior to the screening visit; a non-hormonal intrauterine device [IUD] with spermicide), or in postmenopausal status for less than 2 years;
24) Intake of investigational drug within the last 30 days before the screening visit;
25) History of alcohol or drug abuse;
26) Donation of blood in the previous 3 months before the screening visit;
27) Inadequate comprehension of study risks and requirements, or uncooperative subject;
28) Any other clinical condition or disease or history of significant diseases.

Study products

	Ibuprofen Arginine (IBA)	Ibuprofen (IBU)
Dosage	600 mg	600 mg
Batch number	311397 - 3116697	0528TF01 - 14089TF01
Expiry date:	04/2014 - 03/2015	04/2013 - 01/2014

Both IMPs were administered as single dose of one sachet 600 mg of IBA or IBU given by oral route (dissolved in 50 - 100 ml of water) in the post-surgical period, under the control of an Investigator different from that who performed all evaluations.

Study Endpoints

Efficacy (primary/secondary)

Primary endpoint:

The primary endpoint of the study was the time to onset of pain relief (when the subject began to feel any pain relieving effect from the drug) in the first 60 minutes after study medication intake. The effect of IBA or IBU was assessed, for this first 60 minute observation period, in absence of intake of any rescue medication, using a stopwatch clock.

Secondary endpoints:

- The evaluation of Total Pain relief (TOTPAR) by the measurement of the area under the curve (AUC) of pain intensity change from baseline values, assessed by the subjects, using a Visual Analogue Scale (VAS) during the first 60 minutes after study medication intake;

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- The proportion of subjects with at least 50% pain relief;
- The pain relief effect (PR), at each prefixed observation point, using a Pain Relief Rating (PRR) of five points;
- The time to achievement of the "meaningful pain relief" (when the subject felt his/her pain relief was meaningful) using a stopwatch clock;
- The time to the first intake of rescue medication;
- The rate of re-medication (proportion of subjects who required rescue medication);
- The Clinical Global Impression (CGI) of the subject at the end of the study, using a 7-point scale;
- The Pain Intensity Difference (PID) at each observation point (the pain intensity differences from baseline);
- The Sum of Pain Intensity Difference (SPID).

Safety

- Frequency of treatment-emergent adverse events (TEAEs) in the two treatment groups

Statistical methods

Due to the early termination of the study, the following analysis sets were used:

- All enrolled subjects: all subjects enrolled who signed the informed consent form;
- Randomized set: all randomized subjects;
- Safety set (SS): all subjects who took the scheduled dose of study medication.

All analyses were based on the safety set, whereas data listings included all available data for all enrolled subjects.

Continuous variables were summarized by descriptive statistics (number of cases, mean, standard deviation (SD), median, minimum, and maximum). Categorical variables were summarized using counts of subjects and percentages.

Because of the premature interruption of the study with an insufficient number of cases, no inferential statistics/tests of hypothesis were planned.

Mean changes from baseline were calculated, if applicable.

The number and percentage of subjects experiencing TEAEs were summarized by treatment group. TEAEs were coded using the MedDRA dictionary (version 16.1).

SUMMARY

Efficacy results

Time to onset of pain relief

Eighteen subjects (90.0%) in the IBA group and 21 (91.3%) in the IBU group achieved pain relief in the first 60 minutes in absence of rescue medication.

Proportion of subjects with at least 50% pain relief

Eleven subjects (55.0%) in the IBA group and 10 (43.5%) in the IBU group achieved at least 50% of pain relief.

Time to achievement of the "meaningful pain relief"

Eighteen subjects (90.0%) in the IBA group and 19 (82.6%) in the IBU group achieved meaningful pain relief within 360 minutes in absence of rescue medication.

Pain intensity difference (PID) at each time-point

The mean VAS score of daily spontaneous pain decreased from baseline to any post-baseline time-point in both groups. The extent of the decrease was more marked in the IBA group than in the IBU group up to 90 minutes, was similar in the two groups at 120 and 150 minutes, and then was more marked in the IBU group than in the IBA group up to 360 minutes (see Table below).

Table. Pain intensity at any time-point (safety set)

		Ibuprofen Arginin (IBA) (N=20)	**Ibuprofen (IBU) (N=23)**
Baseline	Mean (SD)	62.3 (5.3)	64.0 (10.8)
Changes from baseline			
10 minutes	Mean (SD)	-6.0 (14.4)	-3.9 (10.5)
20 minutes	Mean (SD)	-17.1 (19.0)	-9.5 (12.8)
30 minutes	Mean (SD)	-21.7 (21.8)	-16.3 (16.5)
40 minutes	Mean (SD)	-25.4 (20.6)	-20.8 (21.9)
50 minutes	Mean (SD)	-31.0 (22.7)	-23.3 (21.4)
60 minutes	Mean (SD)	-34.8 (23.4)	-25.0 (23.1)
90 minutes	Mean (SD)	-40.1 (21.1)	-35.3 (21.4)
120 minutes	Mean (SD)	-43.1 (20.5)	-43.3 (16.3)
150 minutes	Mean (SD)	-46.2 (20.4)	-47.2 (15.7)
180 minutes	Mean (SD)	-45.4 (23.3)	-52.1 (16.5)

240 minutes	Mean (SD)	-44.3 (23.5)	-53.3 (18.8)
360 minutes	Mean (SD)	-47.5 (22.1)	-54.1 (21.9)

The mean (± SD) change from baseline to 30 minutes was -21.7 ± 21.8 mm in the IBA group and -16.3 ± 16.5 mm in the IBU group. The mean (± SD) change from baseline to 60 minutes was -34.8 ± 23.4 mm in the IBA group and -25.0 ± 23.1 mm in the IBU group. The mean (± SD) change from baseline to 90 minutes was -40.1 ± 21.1 mm in the IBA group and -35.3 ± 21.4 mm in the IBU group. The mean (± SD) change from baseline to 120 minutes was -43.1 ± 20.5 mm in the IBA group and -43.3 ± 16.3 mm in the IBU group. The mean (± SD) change from baseline to 150 minutes was -46.2 ± 20.4 mm in the IBA group and -47.2 ± 15.7 mm in the IBU group. The mean (± SD) change from baseline to 180 minutes was -45.4 ± 23.3 mm in the IBA group and -52.1 ± 16.5 mm in the IBU group. The mean (± SD) change from baseline to 240 minutes was -44.3 ± 23.5 mm in the IBA group and -53.3 ± 18.8 mm in the IBU group. The mean (± SD) change from baseline to 360 minutes was -47.5 ± 22.1 mm in the IBA group and -54.1 ± 21.9 mm in the IBU group.

Pain relief effect (PR) at any time-point, using a Pain Relief Rating (PRR) of five points

No substantial differences between groups in the frequency distribution of pain relief rating were observed at any time-point. A complete pain relief was observed in 2 subjects (10.0%) in the IBA group at 30 minutes, in 2 subjects (10.0%) in the IBA group and in 2 (8.7%) in the IBU group at 40 minutes, in 3 subjects (15.0%) in the IBA group and in 2 (8.7%) in the IBU group at 50 minutes, and in 5 subjects (25.0%) in the IBA group and in 4 (17.4%) in the IBU group at 60 minutes.

Time to the first intake of rescue medication

None of subjects in both groups required rescue medication in the first 60 minutes.

Rate of re-medication (proportion of subjects who required rescue medication)

Three subjects (15.0%) in the IBA group and 6 (26.1%) in the IBU group required rescue medication after the first 60 minutes.

Clinical Global Impression (CGI)

The results of CGI were similar in the two groups. Ten subjects (50.0%) in the IBA group and 10 (43.5%) in the IBU group were very much improved, 5 subjects (25.0%) in the IBA group and 8 (34.8%) in the IBU group were much improved, 4 subjects (20.0%) in the IBA group and 3 (13.0%) in the IBU group were minimally improved, and none of subjects (0.0%) in the IBA group and 1 (4.3%) in the IBU group were minimally worsened. None of subjects in both groups had a much worse or a very much worse score.

The results of total pain relief (TOTPAR) and of sum of pain intensity difference (SPID) were listed only.

Safety results

One TEAE (hypertension) was reported in 1 subject (5.0%) in the IBA group and one TEAE (nausea) was reported in 1 subject (4.3%) in the IBU group. None of subjects in both groups reported SAEs, treatment-related TEAEs, TEAEs of moderate or severe intensity, or TEAEs leading to study discontinuation.

Conclusions

- The study was prematurely interrupted due to difficulties in enrolment and no definite conclusions can be made;
- Similar rates of subjects in the two groups achieved pain relief in the first 60 minutes in absence of rescue medication (primary endpoint).
- Similar results in the two groups were also observed in the following secondary efficacy endpoints: proportion of subjects with at least 50% pain relief, time to achievement of the “meaningful pain relief”, frequency distribution of pain relief rating, use of rescue medication, CGI.
- The results of pain intensity difference (PID) at each time-point showed that the extent of the decrease was more marked in the IBA group than in the IBU group up to 90 minutes, was similar in the two groups at 120 and 150 minutes, and then was more marked in the IBU group than in the IBA group up to 360 minutes.
- Both IMPs were well tolerated, as none of subjects in both groups had treatment-related TEAEs.

Version and Date of the report

Final Version, 20 May 2015