2. Synopsis

Name of Sponsor/Company: Nycomed Sweden Holding AB	Individual Study Table Referring to Part of the Dossier: IMPD, version 1.0., August 31st 2009
Name of Finished Product: Ibu Rapid (IMP), Nurofen (Comparator)	
Name of Active Ingredient: Ibuprofen	
Title of Study: A controlled, randomized, double-blind, cross-over study of the onset of analgesic effect of two formulations of ibuprofen for the treatment of pain after oral surgery	
Investigators: PPD [redacted]	
Study centre(s): CCI [redacted]	
Publication (reference): See references under section 15 in this report.	
Studied period (years): Date of first enrolment: In Sweden 01-Dec-2009 In Denmark 07-Dec-2009 Date of last patient completed: In Sweden 22-Mar-2010 In Denmark 29-Mar-2010	Phase of development: Phase III
Objectives: The primary aim of the study was to compare the time to onset of substantial analgesic effect of a new formulation of ibuprofen (the investigational product) to that of a conventional tablet (Nurofen®) in patients having removal of impacted or partly impacted third molars. The secondary aim was to compare the analgesic effect and the safety of the two formulations in the above mentioned patient group.	
Methodology (Design): The study was a multi centre, controlled, randomized, double-blind, single dose, cross-over study where each patient received two treatments: A: 2 tablets of Ibuprofen 200 mg fast release tablet formulation (IMP)	

B: 2 tablets of Ibuprofen 200 mg conventional tablet formulation (Nurofen®).

The study was conducted in Denmark and Sweden at clinics at CCI [redacted]

Pre-study visit

Consecutive patients who were referred to one of the clinics participating in this study were examined clinically and radiologically as to the indication for removal third molars. If there was an indication the patients were asked to participate in the study. The patient received verbal and written information about the study as well as information about the surgical procedures including risk of complications.

If the patient agreed to participate the inclusion and exclusion criteria were checked. All of the inclusion criteria and none of the exclusion criteria had to be met in order for the patient to be eligible in the study.

On a separate inclusion form the patient's day, months and year of birth as well as gender were noted. Patients rejecting participation were listed in a log recording the reason for rejection.

Day of first surgery

Only one molar was removed at this time point. Standard local anaesthesias (Xylopylin-adrenalin 2%, Lidocain-adrenalin 2% or Xylocain-adrenalin 2%) were given.

The usual surgical procedure for removal of a third molar was followed. Relevant data from the procedure was noted in a separate case report form.

Postoperatively: At the time when the patient after removal of a third molar for the first time experienced moderate to severe or unendurable pain he or she received the study medication A or B. Patients reported pain intensity and pain relief for two hours after receiving the study medication. By use of a stop watch they reported when they felt the first sign of pain relief and when they felt substantial pain relief. The patient was asked about adverse events.

Follow-up visit:

The patient was asked to come to a follow-up visit at the clinic 5-7 days after receiving of the study medication. Follow-up could also take place as a phone call. The patients were asked about adverse events and these were noted in a separate form.

Day of second surgery:

Only one molar was removed. Standard local anaesthesia (Xylopylin-adrenalin 2%, Lidocain-adrenalin 2% or Xylocain-adrenalin 2%) was given.

The usual surgical procedure for removal of a third molar was followed. Relevant data from the procedure was noted in a separate case report form.

Postoperatively: At the time when the patient after removal of a third molar for the first time experienced moderate to severe pain or unendurable pain he or she was randomized and received study medication A or B. Patients reported pain intensity and pain relief for two hours after receiving the study medication. By use of a stop watch he or she reported when they felt first sign of pain relief and when they felt substantial pain relief. The patient was asked about adverse events.

Follow-up visit:

The patient was asked to come to a follow-up visit at the clinic 5-7 days after receiving of the study medication. Follow-up could also take place as a phone call. The patients were asked about adverse events and these were noted in a separate form.

The patients were advised to have their normal diet on the day of surgery. After the surgery and until two hours after receiving the study medication the patients were allowed to drink water, cold soft drinks and to eat non solid food, e.g. yoghurt.

Number of patients planned: 140 to be randomized aiming for 120 evaluable patients.

Number of patients analysed: In total 144 were randomized, 137 completed the study and hereof 134 completed the study per protocol.

Diagnosis and main criteria for inclusion:

Patients aiming to complete two molar surgeries. The patients were persons of both sex and between 18-40 years of age.

Inclusion criteria:

1) Indication for surgical removal of two impacted or partly impacted mandibular third molars
2) Written informed consent after verbal and written information.

Exclusions criteria:

A. exclusions criteria related to ibuprofen

1) An active gastric or duodenal ulcer
2) Hypersensivity to NSAIDs or ASA
3) Severe liver or kidney disorder
4) Bleeding disorder
5) Treatment with anticoagulantia

B. General exclusion criteria

1) Pregnancy, actual or intended
2) Systemic diseases which could endanger the participating patients
3) Patients who were assumed not to be able to carry out the study for instance patients who were not speaking or writing local language
4) Patients who are regarded to have high risk for alveolitis (dry socket pain) e.g. heavy smokers and diabetic patients
5) Intake of analgesics including NSAIDs for 12 hours before tooth removal of surgery
6) Lack of ability or willingness to comply with the protocol
7) Alcohol intake on the day of surgery.
8) Drug abusers
9) Other circumstances observed during the surgery, at the discretion of the investigator.

Test product: Ibuprofen Rapid (each tablet containing 200 mg ibuprofen) ,

Dose: 400 mg

mode of administration: Oral

Batch Nos:

Ibuprofen Rapid 200 mg, batch nr. G0535B079

Ibuprofen Rapid 200 mg Placebo, batch nr. G0535B078
Duration of treatment: Single dose administration
Reference therapy: Nurofen® (each tablet containing 200 mg ibuprofen) Dose: 400 mg Mode of administration : Oral Batch Nos: Ibuprofen 200 mg, batch nr. 81801-0910-15 Ibuprofen Placebo, batch nr. 81801-0911-01
Criteria for evaluation: Efficacy as time to substantial pain relief recorded as the time of the second stop watch was used for evaluation of the primary endpoint. The secondary endpoints were time to first pain relief (as the time when the first stop watch was stopped), pain intensity and pain relief (measured at time 15, 30, 45, 60, 75, 90, 105 and 120 minutes), general impression (measured at time 120 minutes). Safety was evaluated as for pre-treatment, treatment emergent and serious adverse events
Statistical methods: Apart from an overall total number of screening failures in the subject disposition, data from screening failures has not been reported. Otherwise, data has been reported from all randomized patients. The subject disposition has in addition reported the number of completers, withdrawals and the reason for withdrawal. Demographic data and other baseline characteristics have been tabulated by use of descriptive statistics. The statistical hypothesis (H_0) of the primary and secondary analyses was that there was no difference between the two formulations of Ibuprofen. The alternative was two-sided, i.e. that the two formulations were not equal. All tests were performed with a significance level of 5%. Except when described otherwise below, missing values remain missing. Tabulation of continuous data is shown with mean, median, min, max and standard deviation. Tabulation of categorical data is shown with N and percentage. All efficacy and safety data is tabulated. Selected listings include all relevant data. Graphical display in the form of time-effect and scatter plots is used when possible. The primary endpoint is analyzed both for the FAS (Full Analysis Set) and the PP population. Otherwise, all analyses, summary tables, figures and listings are based on the FAS population only. All statistical analyses and presentation of data are performed using SAS version 9.1.3 or higher. **Primary Endpoint** The primary analysis was a Cox proportional hazards analysis. The model included the factors formulation, period, sequence and patient all as categorical. The patient factor accommodated the cross-over design of the study. If the second watch was not stopped before end of the evaluation period (120 minutes), the time was censored at 120 minutes. Censoring at the 120 minutes was handled in the model. The p-value for the

comparison of the formulations is reported. The comparison was carried out for the FAS and for the PP population. The time until 25%, 50% (median), and 75% of patients had obtained substantial pain relief is presented for each formulation.

The primary endpoint is shown graphically as Kaplan- Meier plots.

As a supportive analysis, number of patients with substantial pain relief has been compared between the two formulations for the time points 15, 30, 45, 60, 75, 90 and 120 minutes. The comparison has been with McNemar's test which is appropriate for a cross-over design.

Secondary Endpoints

The secondary end point, time to first pain relief, was analysed in the same manner as the primary end point.

Pain Intensity

The Pain Intensity (PI) has been recorded as an ordinal response in 5 levels from 0 to 4 at each evaluation time point. To adjust for the different baseline PI levels, the difference from the baseline, called Pain Intensity Difference (PID) has been derived. Due to the cross-over design, a test for difference between the two formulations at each time point has been based on the Wilcoxon signed rank test. PID is presented graphically by time and formulation. Pain Intensity Difference (PID) is tabulated by time and formulation.

Pain relief

The Pain Relief is recorded as an ordinal response in 5 levels from 0 to 4 at each evaluation time point. Due to the cross-over design, a test for difference between the two formulations at each time point is based on the Wilcoxon signed rank test. The pain relief is presented graphically by time and formulation. The Pain Relief is tabulated by time and formulation.

Time to first pain relief

The time to first pain relief was recorded as the time of the first stop watch. The analysis and data presentation is similar to the primary endpoint, but only performed for the FAS population.

General impression

The general impression is recorded as an ordinal variable in 5 levels ranging from poor (1) to excellent (5). Due to the cross-over design, a test for difference between the two formulations has been based on the Wilcoxon signed rank test. General impression has been tabulated for each formulation and for the intra-patient differences.

Safety

The safety data only comprises adverse events. An overall summary of tabulate numbers pre-treatment, treatment emergent and serious events and further show the split in causality and intensity. The adverse events are tabulated by formulation, system organ class and preferred term.

Summary-Conclusions

Efficacy results: The analysis of the primary endpoint, time to substantial pain relief by stop watch for the FAS analysis set, found a median difference, Ibu Rapid – Nurofen®, of -3.8 minutes (83,7 min (Nurofen®)- 79,9 min (Ibu Rapid)). This relatively small difference was not statistically significant. The same non-significant conclusion was found for the PP analysis set.

Among the secondary endpoints, a statistically significantly shorter time to first pain relief by stop watch was found for the FAS analysis set. Similarly, pain relief and pain intensity scores recorded in the diary showed a statistically significantly better performance for Ibu Rapid than for Nurofen® at some time points during the first hour, thus indicating a more rapid onset of Ibu Rapid.

Safety Results: From a safety perspective, both products were well tolerated and most adverse events were related to the surgery.

Conclusion:

The primary endpoint, time to substantial pain relief, showed no significant difference between the two treatments. However for the secondary endpoint there was a significant difference for time to first pain relief in favour of Ibu Rapid compared to Nurofen®. In addition a significant difference for some time points regarding pain relief and pain intensity was seen in favour of Ibu Rapid compared to Nurofen®.

Both treatments were well tolerated and no serious adverse events related to the treatments were observed during the study.

Date of report: 05-July-2010