# 1. SYNOPSIS

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| COMPANY: | Roche (Hungary) Ltd. |
| NAME OF FINISHED PRODUCT: | Bondronat |
| NAME OF ACTIVE SUBSTANCE: | ibandronic acid |
| TITLE OF THE STUDY / REPORT No. / DATE OF REPORT | Open Label Study to Establish the Short Term Efficacy of Intravenous Loading-Doses of Bondronat 6mg in Patients with Breast Cancer and Skeletal Metastases Experiencing Moderate to Severe Pain, within 7 Days after Initiation of Treatment |
| INVESTIGATORS / CENTERS AND COUNTRIES | 13 centers in Hungary |
| PUBLICATION (REFERENCE) | none |
| PERIOD OF TRIAL | Jul 31, 2006 – Dec 19, 2008 CLINICAL PHASE II |
| OBJECTIVES | **Primary:** The primary objective was to establish the pain response of the treatment with ibandronic acid in patients with Breast cancer and painful metastatic bone disease. In this study, pain response was defined as:<br><br>≥ 25% decrease in mean pain score in the observation phase compared to mean pain score at baseline as determined by the "WORST PAIN" scale of the Brief Pain Inventory (BPI), with no more than a 35% increase in mean analgesic consumption in the observation phase compared to mean baseline analgesic consumption.<br><br>**Secondary:** The secondary endpoints consisted of<br><br>• pain response as defined above determined by the "AVERAGE PAIN" scale of the BPI<br>• time to pain response based on the WORST PAIN scale of the BPI<br>• analgesic consumption expressed as opioid equivalents<br>• WHO Performance Score<br>• Interference Scales of the BPI<br>• Patient Global Assessment<br><br>**Safety:** The tolerance of ibandronic acid was evaluated based on spontaneous reporting of adverse events and the monitoring of clinical laboratory results. |
| STUDY DESIGN | This was an open label multicenter non-comparative trial of ibandronic acid. |
| NUMBER OF SUBJECTS | Total enrolled = 182 |

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| DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION | Patients with breast cancer, documented bone metastases and bone pain secondary to bone metastatic disease with a mean pain score of $\geq$ 4 (moderate to severe pain) despite the concomitantly used analgesics |
| TRIAL DRUG: DOSE / ROUTE / REGIMEN | ibandronic acid 6 mg intravenously over 15 minutes on Days 1, 2, and 3 |
| CRITERIA FOR EVALUATION | |
| EFFICACY: | **Primary variable:** The primary efficacy parameter was the pain response to the treatment with ibandronic acid in patients with Breast cancer and painful metastatic bone disease and was defined as a $\geq$ 25% decrease in mean pain score in the observation phase compared to mean pain score at baseline as determined by the "WORST PAIN" scale of the Brief Pain Inventory (BPI), with no more than a 35% increase in mean analgesic consumption in the observation phase compared to mean baseline analgesic consumption.<br>• **Secondary variables:** Pain response defined as a $\geq$ 25% decrease in mean pain score in the observation phase compared to mean pain score at baseline as determined by the "AVERAGE PAIN" scale of the Brief Pain Inventory (BPI), with no more than a 35% increase in mean analgesic consumption in the observation phase compared to mean baseline analgesic consumption<br>• Time to pain response based on the "WORST PAIN" scale of the BPI<br>• Analgesic consumption expressed as opioid equivalents<br>• WHO Performance Score<br>• Interference Scales of the BPI<br>• Patient Global Assessment |
| SAFETY: | Safety and tolerability of ibandronic acid were assessed by collecting adverse events and monitoring of clinical laboratory results. |
| STATISTICAL METHODS: | The analysis of the primary parameter tests the null hypothesis of no change in mean pain score over the period of the study.<br>The primary analyses are based on pain scores.<br>The baseline for pain score is the value obtained at enrollment for the last 24 hours. The baseline for analgesic consumption was based on the assessment of analgesic consumption in the 3 days preceding the first dosing.<br>Observation phase assessment for pain score and analgesic consumption were based on the daily |

measures.

The change of the mean pain score from the baseline was examined by repeated measurement ANOVA model with two sided 95% CI for the mean change between the compared values. The response rates were computed for Days 2, 3, 4, 5, 6, and 7 taking into consideration the maximum allowed increase in analgesic consumption as reported in the CRFs.

Secondary Variables

Pain response based on the AVERAGE PAIN scale of the BPI was evaluated as the primary variable. Kaplan-Meier estimation was used for the "time to" parameters. Mean change from baseline in WHO Performance Score at Day 7 was analyzed by Wilcoxon's matched rank test. Other parameters were assessed by repeated measurement ANOVA model.

Safety Analysis

The safety parameters assessed after first dose were analyzed and presented in terms of listings and summary tables based on the safety population.

EFFICACY RESULTS:

For the primary efficacy variable there was an increase in rates of responders in the ITT population reaching 58.1% at Day 7. Using the McNemar test, the comparison of the response rates on Day 2 and Day 7 in the per protocol population showed a highly significant difference ($p<0.0001$) with 81 subjects becoming a responder and 6 subjects losing response. For 59 + 17 subjects the response state (no response; and response, respectively) did not change.
The response rates according to the "AVERAGE PAIN" scale also increased over time. On Day 2, response rate was 18.5% and it reached 64.6% on Day 7. Using the McNemar test, the comparison of the response rates on Day 2 and Day 7 showed a highly significant difference ($p<0.0001$) with 90 subjects becoming a responder and 8 subjects losing response. For 55 + 25 subjects the response state (no response; and response, respectively) did not change.
The mean time to response evaluated by the "WORST PAIN" scale of the BPI was 3.85 days and the median was 3 days.
The distribution of the WHO performance scores on Day 7 showed a beneficial change compared to Day 2, which was significant with the Wilcoxon's matched rank test. The WHO scores of 18 subjects decreased, in case of 9 subjects the scores increased and for 148 subjects there was no change in the values.
From Day 2 until Day 7 patients reported a continuous decrease in the magnitude their pain interfered with their general activities, walking ability, normal work, and enjoyment of life and for all time points the changes were statistically significant compared to Day 1.
Similarly, patients reported a continuous decrease in the magnitude their pain interfered with their mood and sleep and for all time points beginning at Day 3 the changes were statistically significant compared to Day 1.
Regarding the interference of pain with relations to other people, patients reported a continuous decrease and from Day 4 the change was statistically significant compared to Day 1.
On Day 7 patients were more satisfied with their treatment compared to their assessment on Day 1 and the difference was significant with the Wilcoxon's matched rank test.
The number of patients who were extremely satisfied with their current treatment increased from 2 on Day 1 to 30 on Day 7, whereas the number of patients who were extremely dissatisfied with their current treatment decreased from 13 on Day 1 to 3 on Day 7.

SAFETY RESULTS:

Altogether 60 adverse events were reported. Eight patients experienced serious adverse events and four of these patients died. The study treatment was terminated early for one of the patients experiencing serious adverse events. Only one serous case was assessed as having a causal relationship with the study drug. The majority of adverse events were of Grade 1 intensity. The most commonly reported adverse events were headache and fever. Two laboratory parameters showed a significant change from Day 1 to Day 7. Mean serum creatinine decreased from 74.7 µmol/L to 72.6 µmol/L (p=0.011) and mean creatinine clearance increased from 77.4 mL/min to 80.1 mL/min (p=0.017).

CONCLUSIONS: The results of this phase II study indicates that the daily intravenous administration of ibandronic acid 6 mg for three consecutive days in patients with breast cancer and painful skeletal metastases provides beneficial effect in decreasing pain and interference of pain with daily functions over seven days while maintaining the safety profile of ibandronic acid established for the registered indications and dosing schedules.