2. SYNOPSIS

COMPANY: **ROCHE SA**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Bondronat®	
NAME OF ACTIVE SUBSTANCE(S): Ibandronic Acid	

TITLE OF THE STUDY:
Open Label Study to Evaluate the Efficacy and Safety of Intravenous Loading Dose of 3 x 6mg Ibandronic Acid (Bondronat®) during 3 Consecutive Days in Patients with Breast Cancer and Skeletal Metastases Experiencing Moderate to Severe Pain
(Bone Pain Experience Trial)

STUDY CENTRE(S) and INVESTIGATOR(S):
Among the 25 centers selected in Belgium, 7 recruited patients
Principal Investigator:
[redacted]
And
[redacted]

PUBLICATION (REFERENCE): None

PERIOD OF TRIAL: 30 MARCH 2007 to 19 JANUARY 2008	CLINICAL PHASE: II

OBJECTIVES:
The primary objective was to establish the efficacy in pain relief of ibandronic acid, loading dose, in patients with breast cancer and painful metastatic bone disease over a 7-day period.

The secondary objective was to describe the safety and tolerance of ibandronic acid based on the monitoring of clinical laboratory results, especially serum creatinine level, creatinine clearance and on spontaneous reporting of adverse events.

METHODOLOGY:
Single arm, open label, multicenter study

NUMBER OF SUBJECTS (planned and analyzed):
About 50 evaluable patients were planned to be recruited in approximately 20 centers.
Finally 10 patients (9 evaluable) were recruited in 7 centers

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The target population consisted of patients with metastatic Breast Cancer, documented bone metastases and bone pain secondary to bone metastatic disease with a mean pain score ≥ 4 over a 3-day Baseline period on the WORST PAIN scale of the BPI. Patients had to be treated for their pain with at least a weak Opioid analgesic base on the WHO pain ladder

INCLUSION CRITERIA:

- Written informed consent
- Age ≥ 18 years
- Histological or cytological evidence of breast cancer
- Presence of bone metastases documented on bone X-ray, CT scan or MRI scan
- Mean pain score ≥ 4 during 3-day baseline period on the WORST pain scale of the BPI
- Pain must correspond to areas of bone metastases, not to areas of visceral metastases e.g. liver metastases.
- Minimum 3-week period after the last bisphosphonate treatment
- No change in systemic anti-neoplastic therapy for at least 4 weeks prior to baseline period
- Patients must be on a stable dose of, at least, a weak Opioid analgesic over the 3-day baseline period (maximum 10% variation is allowed)
- ECOG Performance score of 0-3 (patients with PS of 3 must have their score based on bone pain, not underlying neoplastic disease)
- Adequate renal function: creatinine clearance ≥ 50ml/min (Cockcroft formula) and serum creatinine ≤2.0mg/dl (168 µmol/L)
- Normal serum calcium

EXCLUSION CRITERIA:

- Patients with an uncontrolled infection
- Patients who have received a bisphosphonate within 3 weeks of the start of the Baseline period or who are currently receiving another bisphosphonate
- Patients with WBC count ≤ 1800/mm³ and/or platelet count ≤ 75000/ mm³
- Patients with known hypersensitivity to any of the components of ibandronic acid
- Patients who are pregnant or lactating
- Any other medical condition, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interferes with the interpretation of the results.
- Radiotherapy to bone within the 28 days prior inclusion or during the trial duration
- Patients who are currently treated with any other investigational therapy or have received it within 30 days of the first schedule day of dosing (an investigational treatment is defined as one for which there is currently no regulatory-authority approved indication).

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TEST PRODUCT(S), DOSE AND MODE OF ADMINISTRATION:.

Ibandronic acid is a nitrogen containing bisphosphonate currently approved in the European Union (EU), under the trade name of Bondronat®, for metastatic bone disease secondary to breast cancer, and hypercalcemia of malignancy, as both an IV and oral formulation.

Ibandronic acid was supplied as packs containing 3 vials (6 ml glass vial glass type I). The vials are closed with rubber stoppers complying with European Pharmacopea (Ph.Eur.).

Patients fulfilling inclusion/exclusion criteria were to receive a loading dose of 6mg of ibandronic acid intravenously over 15 minutes on days 0, 1 and 2 of the Evaluation Period.

DURATION OF TREATMENT :

3 days

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Not relevant

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CRITERIA FOR EVALUATION:

Efficacy variables

The primary variable was the proportion of patients with bone pain response, defined as a ≥ 25% decrease in mean pain score of Worst Pain over a 7-day evaluation period compared to the mean score of Worst Pain over a 3-day baseline period with a maximum of 10% increase in mean Opioid analgesic consumption over the same 7-day period compared to the mean Opioid analgesic consumption over the 3-day baseline period.

The secondary efficacy variables were:

- Worst pain defined as the bone pain which occurs on movement, during night or spontaneously for unknown reasons determined by the worst pain scale of BPI (Brief Pain Inventory).
- Other pain parameters on the BPI: average pain score during the day and pain score at rest (sleep interference scale of BPI)
- Responder Rate defined as the number of patient with a ≥ 25% reduction in the mean pain score of Worst Pain over a 7-day evaluation period compared to the mean score over a 3-day baseline period
- Quality of life questionnaire measured by the FACT-BP scale
- Opioid analgesic consumption, expressed as Morphine equivalents
- ECOG Index

Safety variables

The safety and tolerance of ibandronic acid were to be assessed by the monitoring of clinical laboratory results, especially serum creatinine level, creatinine clearance and on spontaneous reporting of adverse events.

STATISTICAL METHODS

Sample Size Calculation:

Since this is an open study in a limited number of patients, no hypothesis testing was planned. The sample size of 50 patients was based on clinical judgment, not on statistical considerations. Moreover, the study was prematurely stopped after 10 patients were recruited due to low recruitment rate.

Analysis Plan:

The Intention-to-treat population (ITT) was defined as the patients who received at least one dose of study medication. This was the primary population for the primary efficacy analysis. The safety population consisted of all treated patients, e.g. all patients who received at least one injection of the study drug. Thus the safety population and the ITT population are the same.

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Efficacy:

Summary table are provided with the number of percentage of **patients with bone pain response**. The 95% score confidence intervals of proportion of bone pain response are also provided.

Descriptive statistics were calculated for mean pain score of Worst Pain over the 3-day baseline, mean over the 7-day evaluation period, and for the change in the mean over the 7-day evaluation period from the mean over the 3-day baseline (defined as **patients with response**).

Changes in Worst pain from baseline, evaluated over the 3-day baseline evaluation period, to day 28 are summarized.

Descriptive statistics were calculated for mean over the 3-day baseline of the Average Pain score during the day, mean over the 7-day evaluation period, and for the change in the mean over the 7-day period from the mean over the 3-day baseline.

Changes in Average Pain score during the day from baseline, evaluated over the 3-day baseline evaluation period, to day 28 are summarized.

Descriptive statistics were calculated for mean sleep interference score over the 3-day baseline, over the 7-day evaluation period, and for the change in the mean over the 7-day period from the mean over the 3-day baseline.

Changes in mean sleep interference score from baseline, evaluated over the 3-day baseline evaluation period to day 28, are summarized. ECOG performance status is not summarized due to the too low number of patients.

Descriptive statistics were calculated for mean Opioid analgesic consumption expressed as Morphine equivalents over the 3-day baseline and for the mean over the 7-day evaluation period, and for the change in the mean over the 7-day period from the mean over the 3-day baseline.

Changes in mean Opioid analgesic consumption from baseline, evaluated over the 3-day baseline period to day 28, are summarized. Quality of life questionnaire are not summarized due to the too low number of patients.

Safety:

Descriptive statistics with respect to dose administration are displayed for the ITT population.

Adverse events were analyzed in terms of their type, incidence, severity and relationship to the study drug. Adverse events were coded using MedDRA (Version 10.0).

Tabulations of the number of patients who experienced adverse events as well as CTC grade (version 3.0) of the events are presented by system organ class and preferred term. Patients have only been counted once for each preferred term. In case a patient experienced the same event more than once, the worst severity is presented. Analysis by drug relationship and CTC grade has also been performed.

Serious adverse events (SAEs) are summarized grouped by system organ class and preferred term.

Descriptive statistics were calculated for creatinine clearance over time, as well as for change from Visit 1. Mean evolution of creatinine clearance and change from Visit 1 are graphically displayed.

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SUMMARY AND CONCLUSIONS

First patient was enrolled on 30 March 2007. Last patient completed the study on 19 January 2008. 10 patients were included in the study by 7 different centers. One patient withdrew consent before being treated and was consequently excluded from any analysis. Among the 9 patients treated, 2 discontinued for adverse event (not related to study medication). Among the 10 patients included, it was planned to continue ibandronate therapy in 5 patients, including in the patient who withdrew consent.

EFFICACY RESULTS

Five patients (56%) had a bone pain response (95% CI: 23%-88%).

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Worst pain decreased on average by 21% from baseline to evaluation period and by 27% from baseline to Day 28.

Average pain decreased on average by 4% from baseline to evaluation period and by 41% from baseline to Day 28.

Sleep interference decreased on average by 29% from baseline to evaluation period and by 60% from baseline to Day 28.

Evolution of Opioid analgesic consumption, expressed as Morphine equivalents, is shown in section 14.2.6. There was a 23% decrease of consumption from baseline to d7-d27 (Median: 11.3; SD: 34.9).

SAFETY RESULTS:

A total of 24 AEs occurring in 7 patients were reported during the study. 4 AEs (2 Nausea , 1 arthralgia, 1 restless leg) possibly, probably or definitely related to the study drug were reported in 4 patients. All 4 related AEs were non-serious, of grade 1 and resolved completely without sequelae. A total of 6 SAES were reported in 4 patients. None was considered possibly, probably or definitively related to the study drug. All serious AEs resolved without sequelae.

Serum creatinine is within the normal range for all patients at final visit. Creatinine clearance is within the normal range for all except one patient at final visit. This patient has already an abnormally low value at baseline. The mean creatinine clearance is 89.8 ± 44.6 mL/min at baseline and 87.1 ± 30.9 mL/min at final visit.

CONCLUSIONS:

The safety data gathered here raise no particular safety concerns. No new or unexpected safety findings were identified which would alter the known safety profile of Bondronat in cancer patients with bone metastases. Safety data are in line with the expected safety profile of the study drug (type of adverse events, frequency and severity) and the safety information contained in the current version of the SmPC.

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In conclusion, the results of this trial are in line of what has been previously observed in other studies and show that ibandronic acid may offer patients with metastatic bone disease some alleviation of the debilitating bone pain they often experience and a possible reduction of the opioid analgesic consumption, thus preserving quality of life. However, due to the limited number of patients included into the study, no robust conclusion can be drawn. Efficacy and safety of loading dose of ibandronic acid needs to be further evaluated in prospective, well-controlled trials in order to confirm the utility of this strategy for patients with metastatic bone pain. The results of such trials could be of particular interest to clinicians treating patients with severe pain that is refractory to current analgesic intervention, such as opioids.

DATE OF REPORT: 10 FEBRUARY 2009