SYNOPSIS OF RESEARCH REPORT

COMPANY: Roche Italy NAME OF FINISHED PRODUCT: Bondronat NAME OF ACTIVE SUBSTANCE(S): Ibandronate	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY

Protocol ML 18108 : Evaluation of efficacy and safety of ibandronate as treatment of metastatic bone pain in patients with different tumor types. A randomized phase II study

REPORT No [redacted]

DATE OF REPORT June 2012

INVESTIGATORS / CENTERS AND COUNTRIES

[redacted]

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PUBLICATION (REFERENCE) NA		
PERIOD OF TRIAL April 2005-January 2007	CLINICAL PHASE Phase II	

OBJECTIVES

Primary objective:

- The primary objective is to evaluate the difference in pain responses with treatment with ibandronic acid vs. zoledronic acid in patients with malignancy and

painful metastatic bone disease. In this study, pain response is defined as a:

25% decrease in mean pain score over a 7- day period compared to mean pain score at Screening, with no more than a 25% increase in mean analgesic consumption over the same 7-day period compared to mean Screening analgesic consumption

OR

25% decrease in mean analgesic consumption over a 7-day period compared to mean Screening analgesic consumption with no more than a 25% increase in mean pain score over the same 7- day period compared to mean pain score at Screening that persists for at least 6 weeks, as determined by the "WORST PAIN" scale of the Brief Pain Inventory (BPI).

Secondary objectives:

- Pain response as defined above determined by the "AVERAGE PAIN" scale of the BPI
- Duration of pain response based on the WORST PAIN and AVERAGE PAIN scales of the BPI where duration is defined as the period of time from the first evidence of response (assuming confirmation 6 weeks later) to that time when the mean pain score over a 7-day period on the WORST PAIN scale increases by 25% over Screening for 2 consecutive weeks; when the mean opioid consumption increases by 50% over Screening for 2 consecutive weeks; or when a patient receives radiotherapy for bone pain.

- Time to pain response based on the WORST PAIN and AVERAGE PAIN scales of the BPI
- Interference scales of the BPI
- Analgesic consumption, expressed as opioid equivalents
- Opioid side-effects
- WHO Performance Score
- Quality of life measured by the EORTC QLQ-C30 scale
- A Patient Global Assessment

- An evaluation of the safety and tolerance of ibandronic acid and zoledronic acid will be described based on spontaneous reporting of adverse events and the monitoring of clinical laboratory results.

STUDY DESIGN

Multicenter, randomized, non-comparative, open label, 3 arm efficacy and safety study over 6 months. Efficacy will be assessed for the first 3 months and safety data will be assessed out to 6 months.

NUMBER OF SUBJECTS

210 planned

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Inclusion Criteria:

- Histological or cytological evidence of neoplastic disease (breast cancer, hormone-refractory prostate cancer, lung cancer and all other solid malignancies). Patients with prostate cancer must have progressive neoplastic disease despite at least 3 months of hormonal therapy, defined as a rise in PSA on 3 separate occasions at least 2 weeks apart or clear evidence of new bone metastases

- Presence of bone metastases documented on bone x-ray, bone scintigram, CT scan or MRI scan

- Mean pain score of 5 over a 7-day Screening period on the WORST PAIN scale of the BPI

- Bone pain must correspond to areas of metastases on bone x-ray, bone scintigram, CT scan or MRI scan; patients whose pain is primarily due to visceral disease (e.g., liver metastases) or to neuropathy should be excluded. It is the responsibility of the investigator to insure that each patient's pain is primarily due to bone metastatic disease.

- The use of at least a weak opioid based on the WHO Analgesic ladder

- No change in systemic anti-neoplastic therapy for at least 6 weeks prior to Screening period

- Age >18 years

- WHO 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 as evidenced by serum creatinine □2.0 mg/dL (168 µmol/L)

- Normal serum calcium level

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- Patients or their legal representatives must be able to read, understand and provide informed consent to participate in the trial.

TRIAL DRUG / STROKE (BATCH) No.
Ibandronic acid

DOSE / ROUTE / REGIMEN / DURATION

Arm A : 6 mg IV administered as a 15 minute infusion on Days 1, 2, 3; and continued after 3-4 weeks until week 24

Arm B : 6 mg IV administered as a 15 minute infusion on Days 1, 2, 3; and oral ibandronic acid 50 mg qd given 30 min before breakfast commenced after 3-4 weeks until week 24.

REFERENCE DRUG / STROKE (BATCH) No.
Zoledronic acid

4 mg IV administered as a 15 minute infusion on Day 1 and then every 3-4 weeks until week 24.

CRITERIA FOR EVALUATION

EFFICACY:

25% decrease in mean pain score over a 7-day period compared to mean pain score at Screening, with no more than a 25% increase in mean analgesic consumption over the same 7-day period compared to mean Screening analgesic consumption

OR

25% decrease in mean analgesic consumption over a 7-day period compared to mean Screening analgesic consumption with no more than a 25% increase in mean pain score over the same 7- day period compared to mean pain score at Screening that persists for at least 6 weeks, as determined by the "WORST PAIN" scale of the Brief Pain Inventory (BPI).

□ Pain response as defined above determined by the "AVERAGE PAIN" scale of the BPI

□ Duration of pain response based on the WORST PAIN and AVERAGE PAIN scales of the BPI. If there is no duration end, the duration will be considered censored at the last available primary assessment on study. Patients with no response have duration of 0 days.

- Time to pain response based on the WORST PAIN and AVERAGE PAIN scales of the BPI. Starting date is the date of randomization. Censored times at last available primary assessment will be considered for non-responding patients.
- Interference scales of the BPI
- Analgesic consumption, expressed as opioid equivalents
- Opioid side-effects
- WHO Performance Score
- Quality of life measured by the EORTC QLQ-C30 scale

PHARMACODYNAMICS: NA

PHARMACOKINETICS: NA

SAFETY:
Safety and tolerability (including AEs and safety labs); renal safety.

STATISTICAL METHODS
Fisher's 2-sided exact tests
Power of 85%.
Significance level 5%.

EFFICACY RESULTS

NA

PHARMACODYNAMIC RESULTS

NA

PHARMACOKINETIC RESULTS

NA

SAFETY RESULTS

no side effects

CONCLUSIONS

A total of 21 centers in Italy participated in the recruitment of patients. The study started in April 2005. Enrollment was stopped in August 2005 and a protocol amendment implemented in November 2005.

Protocol amendment : due to the occurrence in the Phase 4 of ONJ case during treatment with Zolendronate iv, protocol was amended to introduce a Dentistry evaluation and a Panoramic radiograph in the screening examination . Patients were advised to avoid invasive dental procedures if possible during treatment. Furthermore study design was modified from "Multicenter, randomized, comparative, open label" to "Multicenter, randomized, non-comparative, open label". Some other minor changes were implemented in the amendment .

Study was prematurely terminated in January 2007 due to lack of patients enrolled in the centers. Only three patients were screened in two centers and randomized to zoledronic acid (arm C). One out of 3 patient received treatment for 4 weeks. For these reasons no efficacy and safety analysis are applicable.