SYNOPSIS OF RESEARCH REPORT [redacted]

PROTOCOL BO18039

COMPANY: F.Hoffmann-La Roche NAME OF FINISHED PRODUCT: Bondronat® NAME OF ACTIVE SUBSTANCE(S): ibandronic acid	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, two arm, placebo controlled study to compare the efficacy of intravenous loading doses followed by maintenance treatment with oral ibandronic acid versus zoledronic acid in patients with skeletal metastases experiencing moderate to severe pain / Protocol BO18039 / Abbreviated Study Report [redacted] October 2007.		
INVESTIGATORS / CENTERS AND COUNTRIES	Multicenter Trial / 34 centers in 14 countries		
PUBLICATION (REFERENCE)	none		
PERIOD OF TRIAL	01 Aug 2005 – 29 Jan 2007	CLINICAL PHASE	III
OBJECTIVES	Primary Objective: To compare the difference in pain responses between treatment with ibandronic acid vs. zoledronic acid in patients with malignancy and painful metastatic bone disease. Secondary Objectives: • Pain response 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. • 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 • Quality of life measured by the FACT-BP scale • Patient Global Assessment Due to the insufficient number of subjects recruited into the study as a result of the premature termination of enrollment, the primary objective could not be achieved. The primary objective of the current report was to present a full analysis of the safety data from this trial.		
STUDY DESIGN	Multicenter, randomized, active-controlled, double-blind, parallel group trial		
NUMBER OF SUBJECTS	BO18039: Enrolled n = 99 No. Evaluated Safety Ibandronic acid group 49		

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	Zoledronic acid group 50
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with malignancies, documented bone metastases and bone pain secondary to bone metastatic disease with a mean pain score of $\geq$ 5 over a 7-day Baseline period on the WORST PAIN scale of the BPI.
TRIAL DRUG / STROKE (BATCH) No.	Ibandronic acid 6 mg/6mL vial / [redacted] Ibandronic acid 50 mg tablets / [redacted] Ibandronic acid placebo tablets / [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Ibandronic acid 6 mg i.v. infusion over 15 minutes Days 1, 2, and 3 followed by maintenance with 50 mg orally every day starting on Day 22. Placebo i.v. infusions were given every 3-4 weeks.
REFERENCE DRUG / STROKE (BATCH) No.	Zoledronic acid 4mg/5mL vial / [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Zoledronic acid 4 mg i.v. infusion over 15 minutes Day 1, followed by placebo infusions Days 2 and 3, followed by maintenance with 4 mg i.v. every 3-4 weeks. Placebo tablets were given daily starting on Day 22.
CRITERIA FOR EVALUATION	
EFFICACY:	Starting on Day 1 of the trials patients recorded their "WORST PAIN" of the BPI, and their "AVERAGE PAIN" of the BPI on an electronic diary nightly. In addition, beginning on Day 1 of the trial patients recorded their analgesic consumption on a paper diary nightly. Additional assessments included: • The Brief Pain Inventory Interference Scales • Opioid side-effects • The EORTC QLQ-C30 Quality of Life instrument • The FACT-BP Questionnaire • WHO PS • Patient global assessment
SAFETY:	Adverse Events, safety laboratory measurements including serum creatinine and urinalysis, skeletal surveys and recording of skeletal related events (SREs)
STATISTICAL METHODS	For the primary variable, Fisher's exact tests were performed comparing the different treatments. Frequency rates and exact 95%-confidence intervals were estimated for each treatment group. The difference in the frequency rates between the treatment groups was estimated together with 97.5%-confidence intervals according to the Anderson-Hauck approach. Odds ratios from logistic regressions on response were estimated to study the impact of stratification factors. For secondary variables time to event methods (Kaplan-Meier and

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Cox regression) were applied and comparisons made with Mantel-Haenszel Chi-square tests. Descriptive statistics for adverse events.

METHODOLOGY:

Ibandronic acid was administered as a loading dose of 6 mg intravenously daily for 3 days, followed by treatment with 50 mg orally every day starting at day 22. Zoledronic acid was administered in a dose of 4 mg intravenously every 3 – 4 weeks, depending on the underlying chemotherapy regimens patients were receiving. Patients received intravenous zoledronic acid placebo on Days 2 and 3 of the first zoledronic acid treatment only. Patients randomized to oral ibandronic acid received i.v placebo infusions every 3-4 weeks. Patients randomized to zoledronic acid received placebo tablets daily starting at day 22. Treatment was continued for 24 weeks. Patients recorded their pain on the WORST PAIN and the AVERAGE PAIN scales of the BPI, as well as daily analgesic use, on a nightly basis. Patients recorded the degree to which their pain interfered with normal functioning and any opioid side-effects weekly. WHO Performance Status, patient quality of life based on the EORTC QLQ-C30 instrument and quality of life based on the FACT-BP, an instrument specifically designed to measure quality of life in patients with bone pain were recorded at Day 8 and Weeks 6, 12, 18 and 24 of the trial. Patients had skeletal surveys performed at baseline and at Weeks 12 and 24 as part of the monitoring of SREs. Adverse events and laboratory safety parameters were assessed throughout.

SAFETY RESULTS:

Overall, 71% of patients in the ibandronic acid treatment group and 82% of patients in the zoledronic acid treatment group reported at least one adverse event during the trials. Gastrointestinal Disorders were the most frequently reported adverse events, the most common being nausea which was reported by 22% of patients in the ibandronic acid group and 8% of patients in the zoledronic acid treatment group. In general, the types of adverse event reported during the trial were similar in the two treatment groups.

The incidence of grade III adverse events during the study was similar in the ibandronic acid and zoledronic acid treatment groups (37% vs 44%, respectively). Anemia (4 ibandronic acid patients, 3 zoledronic acid patients) was the most frequently reported grade III event in either treatment group. Nine ibandronic acid patients and 7 zoledronic acid patients reported at least one grade IV adverse event during the studies. No grade IV adverse events were considered related to ibandronic acid treatment or zoledronic acid treatment.

A total of 11 patients (22%) in the ibandronic acid group and 9 patients (18%) in the zoledronic acid group died. The most common reason for death was for disease progression of the underlying cancer. None of the deaths was considered related to trial treatment.

Serious adverse events were reported by 39% (19/49) of patients in the ibandronic acid group and 32% (16/50) of patients in the zoledronic acid group. The most common individual SAE was anemia reported in 1 ibandronic acid patient and 3 zoledronic acid patients. During the studies, 16% of patients in ibandronic acid group and 12% of patients in the zoledronic acid treatment group discontinued treatment because of one or more adverse events. Adverse events of special interest in this patient population receiving bisphosphonate therapy were skeletal related events and renal events. There were no differences between the treatment groups with respect to the frequency of skeletal related adverse events and the time to first skeletal related event was similar between the two groups. The incidence of renal events in both studies was low and no marked deterioration in renal function was seen in either treatment group during the treatment period. Among the small percentage of subjects for whom a deterioration in renal function was observed, a slight difference between the treatment groups, in favor of the ibandronic acid treatment group,

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was seen with respect to the time to renal deterioration, however this difference was not considered to be of clinical relevance.
The mean changes from baseline in hematology, blood chemistry or urinalysis parameters were similar in the two treatment groups and there were no clinically relevant differences between the treatment groups with respect to grade 3 or grade 4 laboratory test parameter values reported during the study. Changes from baseline values in vital signs parameters were also comparable in the ibandronic acid and zoledronic acid treatment groups.

CONCLUSIONS:

Within the limitations of the early termination of study BO18039, the results demonstrate that a regimen of 3 consecutive i.v. doses of ibandronic acid over 3 days followed by maintenance therapy with oral ibandronic acid 50 mg daily has a comparable safety profile to that of zoledronic acid 4 mg every 3-4 weeks in patients with bone pain due to metastatic bone disease. No new or unexpected safety findings were identified which would alter the known safety profile of ibandronic acid in cancer patients with bone metastases.