SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL MM17385)

COMPANY: Hoffmann-La Roche, Ltd. NAME OF FINISHED PRODUCT: Boniva NAME OF ACTIVE SUBSTANCE(S): Ibandronate	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, double-blind, double-dummy, parallel-group, multicenter study to compare the efficacy and safety of once monthly oral administration of 150-mg ibandronate with once weekly oral administration of 70-mg alendronate in postmenopausal osteoporosis – a non-inferiority trial / Report No.: [redacted] / Date of Report: May 2007		
INVESTIGATORS / CENTERS AND COUNTRIES	This was a multicenter study conducted in the United States, Belgium, Denmark, France, Germany, Hungary, Norway, Poland, Russia, Spain, United Kingdom, South Africa, Argentina, and Brazil.		
PUBLICATION (REFERENCE)	None.		
PERIOD OF TRIAL	March 11, 2005 to November 14, 2006	CLINICAL PHASE	III
OBJECTIVES	**The primary objective**: to investigate if a monthly dose of 150 mg of ibandronate was able to increase bone mineral density (BMD) at the lumbar spine and at the total hip to the same degree as a weekly dose of 70 mg of alendronate after 12 months of treatment. **The secondary objective**: to compare the increase of BMD at the trochanter after treatment with a monthly dose of 150 mg of ibandronate and a weekly dose of 70 mg of alendronate after 12 months of treatment, and to assess the overall tolerability and safety of both regimens.		
STUDY DESIGN	Randomized, double-blind, double-dummy, parallel-group, multicenter, and multinational trial. Eligible patients were randomly assigned to one of two treatment groups (ibandronate monthly dose group or alendronate weekly dose group). The randomization was stratified by country, history of clinical fragility fractures according to the screening interview, and baseline total hip BMD T-scores (total hip BMD T-score ≥ -2.5 or < -2.5.		
NUMBER OF SUBJECTS	1760 randomized, 1733 treated, 1546 completed the trial.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Ambulatory women of 55 to 84 years of age and at least 5 years after menopause with postmenopausal osteoporosis and a mean lumbar spine BMD (L2 to L4) T-score of < -2.5 and ≥ -5.0 at screening (ie, mean BMD of at least two vertebrae [L2 to L4] that were not fractured and not affected by a process [eg, osteoarthritis or an artifact that could not be removed] to such a degree that accurate measurement of BMD would be considered jeopardized by the central reading center).		
TRIAL DRUG / STROKE (BATCH) No.	150-mg ibandronate tablets (batch No.: [redacted]) and placebo tablets supplied by Roche (batch No.: [redacted]).		
DOSE / ROUTE / REGIMEN / DURATION	150 mg of ibandronate tablet administered orally once monthly and alendronate placebo administered orally once weekly for 12 months.		

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REFERENCE DRUG / STROKE (BATCH) No.	70-mg alendronate tablets manufactured by Merck & Co, Inc (batch No.: [redacted]) and marketed as Fosamax® and placebo tablets supplied by Roche (batch No.: [redacted]).
DOSE / ROUTE / REGIMEN / DURATION	70 mg of alendronate tablet administered orally once weekly and ibandronate placebo administered orally once monthly for 12 months.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary efficacy endpoint:** Relative changes (%) in mean lumbar spine (L2 to L4) BMD and total hip BMD at 12 months from their respective baseline value. **Secondary efficacy endpoint:** • Absolute changes (g/cm^2) in mean lumbar spine (L2 to L4) BMD and total hip BMD at 12 months from their respective baseline values. • Relative (%) and absolute changes (g/cm^2) in trochanter BMD at 12 months from the baseline value. • Relative and absolute changes in serum CTX and P1NP in a subset (30%) of the total population at day 7 after baseline, at 3 months, at day 7 after 6 months, and at 12 months from the baseline value.
SAFETY:	Adverse events and laboratory abnormalities.
STATISTICAL METHODS	This was a non-inferiority trial. To determine if the ibandronate monthly treatment regimen was non-inferior to the alendronate weekly treatment regimen, a one-sided 97.5% confidence interval of the mean difference of the relative change in lumbar spine (L2 to L4) BMD and total hip BMD at 12 months from baseline between the tested arms, the monthly ibandronate dose regimen, and the active-control arm, the weekly alendronate regimen, was constructed. The monthly ibandronate dosing regimen was to be considered non-inferior to the weekly alendronate regimen if the lower bound of the one-sided 97.5% confidence interval was greater than or equal to -1.41 percentage point for the lumbar spine BMD and –0.87 percentage point for the total hip BMD.

METHODOLOGY:

Randomized patients were to be treated for 12 months and followed for an additional 15 days. Efficacy was evaluated by taking BMD scan images at 12 months, which were assessed by the central reading center and compared with the respective baseline values. Blood samples for biochemical markers of bone turnover, serum C-terminal telopeptide of type 1 collagen (CTX) and procollagen type 1 N-terminal propeptide (P1NP) concentrations, were taken at baseline, 7 days after baseline, at least 3 weeks after months 3 and 6 dosings, 7 days after month 6 dosing, and at least 3 weeks after month 12 dosing. Safety information was collected throughout the treatment phase and also during the 15-day post-treatment follow-up period.

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EFFICACY RESULTS:

The primary efficacy parameters, namely, the relative changes in mean lumbar spine (L2 to L4) BMD and total hip BMD at 12 months from baseline, were both improved (see the table below). The lower bound of the 95% confidence interval of the mean difference in mean lumbar spine BMD changes at 12 months from baseline between ibandronate and alendronate was -1.13% in the per-protocol population and -1.12% in the intent-to-treat population, which were greater than the non-inferiority level of -1.41%. The lower bound of the 95% confidence interval of the difference in the total hip BMD changes at 12 months from baseline between ibandronate and alendronate was -0.38% in the per-protocol population and -0.43% in the intent-to-treat population, which were greater than the non-inferiority level of -0.87%. Therefore, the null hypothesis of the statistical model was rejected and it was concluded that the monthly 150-mg ibandronate treatment regimen was not inferior to the weekly 70-mg alendronate treatment regimen in the patient population evaluated.

Summary of Results for the Primary Efficacy Analysis: Relative Change (%) in Lumbar Spine (L2 to L4) BMD and Total Hip BMD at 12 Months from Baseline

	Alendronate 70 mg Weekly	Ibandronate 150 mg Monthly
Per-protocol population		
Lumbar spine BMD		
N	717	721
Mean (%) ± SD	5.7758 ± 4.4344	5.1018 ± 4.2923
95% CI of difference in means	-1.1291 to -0.2334 (inferiority margin: -1.41)	
Total hip BMD		
N	714	720
Mean (%) ± SD	3.0294 ± 2.6530	2.9433 ± 2.7870
95% CI of difference in means	-0.3778 to 0.1777 (inferiority margin: -0.87)	
Intent-to-treat population		
Lumbar spine BMD		
N	792	802
Mean (%) ± SD	5.6322 ± 4.3869	4.9362 ± 4.2901
95% CI of difference in means	-1.1212 to -0.2764 (inferiority margin: -1.41)	
Total hip BMD		
N	789	801
Mean (%) ± SD	2.9841 ± 2.6326	2.8357 ± 2.8390
95% CI of difference in means	-0.4276 to 0.1009 (inferiority margin: -0.87)	

Additional analyses for the primary efficacy endpoint (relative change in lumbar spine and total hip BMD at 12 months from baseline) were performed as confirmatory tests in order to assess the robustness of the primary analysis. These included (1) analysis without adjusting for country and baseline BMD effects, (2) analysis using previous fractures as a covariate, (3) repeating the analyses using a non-parametric method, (4) repeating the analysis by carrying forward any month 12 or study termination BMD measurements outside of the month 12 BMD evaluation window to the month 12 BMD analysis, and (5) repeating the analyses on the lumbar spine BMD only by adjusting for geographical country/region and baseline lumbar spine BMD instead of adjusting for baseline total hip BMD. The results of all the above additional analyses of the primary efficacy endpoints support the conclusion of the primary efficacy analysis, ie, monthly 150-mg ibandronate treatment regimen is statistically comparable (non-inferior) to the weekly 70-mg alendronate treatment regimen in patients with postmenopausal osteoporosis.

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Subgroup analyses on the primary efficacy endpoint indicated the following: (1) a low baseline lumbar spine BMD T- score (≥-3.5) or a low baseline total hip BMD T-score (≥-2.5), Lunar BMD measurement device, and US patients tended to show a lower increase in both the lumbar spine and total hip BMD following 12 months of treatment with either ibandronate or alendronate, (2) the percentage increase in mean lumbar spine and total hip BMD at 12 months from baseline was independent of the previous history of fracture and the time elapsed since menopause, (3) the effect of patients' race on the BMD results remained unclear because of small sample size of patients in certain subgroups, and (4) at 12 months, patients ≥ 75 years of age treated with ibandronate showed a higher relative increase in mean lumbar spine BMD, patients ≥ 75 years of age treated with alendronate showed a lower relative increase in mean lumbar spine BMD, than the respective patients < 75 years old. In general, the differences in treatment effects for subgroups analyzed were consistent with the primary analysis.

As a secondary efficacy parameter, the relative change (%) in trochanter BMD at month 12 from baseline was also consistent with the primary efficacy endpoints, with an increase of 4.2% in both treatment arms. In addition, changes in femoral neck BMD at 12 months were assessed as an exploratory efficacy parameter. The 12-month femoral neck BMD increased from baseline by 2.07% and 2.30% in the ibandronate and alendronate arms, respectively. Hence, similar to changes in total hip BMD, comparable increases in both trochanter and femoral neck BMD were observed with the two treatments, suggesting a similar clinical effect of ibandronate and alendronate at the proximal hip.

The serum CTX and P1NP were sampled at multiple time points. In both treatment arms and at almost all sampling time points, the concentrations of serum CTX and P1NP decreased (the relative changes from baseline were negative), suggesting inhibition of bone turnover.

The pre-dose (residual) levels of sCTX and P1NP assessed immediately before dosing at months 3, 6, and 12 were substantially lower at month 3 compared with baseline and this reduction was sustained over the period of 12 months with both treatments. The median reduction from baseline to different pre-dose time points in serum CTX was 68% to 75% in patients treated with ibandronate, compared with 82% to 83% in patients treated with alendronate. Median relative pre-dose reduction in P1NP concentration was also very similar between treatment arms at all times points; 58% to 68% in ibandronate arm and 59% to 67% in the alendronate arm.

The post-dose levels of both sCTX and P1NP were assessed 7 days after the first dosing and 7 days after the month 6 monthly dosing. Rapid and more pronounced reduction in the resorption marker sCTX was observed after the first dose with ibandronate compared with alendronate (by 85% and 48 %, respectively), while post-dose reductions at month 6 were very similar for ibandronate (88%) and alendronate (85%). There were almost no effects seen on P1NP with either treatment 7 days after the first dose, while similar post-dose reductions in P1NP were seen with ibandronate (67%) and alendronate (68%) 7 days after month 6.

Exploratory analyses were performed on several patient response rates to study treatment. With the per-protocol analysis, at 12 months, the percentages of patients with a mean lumbar spine BMD above baseline (90% vs 92%, ibandronate vs alendronate), with a total hip BMD above baseline (87% vs 90%), with a trochanter BMD above baseline (88% vs 86%), and with both lumbar spine and total hip BMD above baseline (79% vs 84%), with a ≥ 6% increase in lumbar spine BMD from baseline (40% vs 46%), and with a ≥ 3% increase in total hip BMD from baseline (49% vs 49%) were comparable in the two treatment arms. These results demonstrated that the majority (up to 90%) of women with postmenopausal osteoporosis treated with either monthly ibandronate or weekly alendronate benefited from the treatment.

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SAFETY RESULTS:

Following 12 months of study treatment, the overall incidence of adverse events was comparable between the ibandronate- and alendronate-treated patients (75.4% vs 73.6%). The body systems mostl affected were the same for the two groups, namely, gastrointestinal disorders, musculoskeletal and connective tissue disorders, infections, and nervous system disorders. The incidence of some frequent adverse events associated with gastrointestinal symptoms, including upper abdominal pain, nausea, gastritis, and abdominal pain, showed a lower incidence in the ibandronate arm than in the alendronate arm.

Bisphosphonates, including the monthly ibandronate treatment regimen, are known to be associated with a group of adverse events previously termed as “acute phase reaction-like symptoms”. In the current report, in order to further clarify this group of adverse events, they are more specifically defined and presented directly as musculoskeletal and general disorder adverse events that occurred within 3 days of each monthly dosing and lasted no more than 7 days. As expected, the incidence of the adverse events falling into this category was higher in the monthly ibandronate treatment regimen (6.8%) than in the weekly alendronate treatment regimen (3.0%). The most common events were influenza-like illness (2.4%) and myalgia (1.6%) in the ibandronate arm compared with 0.5% and 0.7% reported respectively, in the alendronate arm. Several features of this group of adverse events were observed: (1) they were usually reported during the first 2 months of treatment and infrequently reported during months 3 to 12; (2) the vast majority were mild or moderate in severity; (3) most were considered related to the study drug; and (4) all resolved without sequelae.

Treatment-related adverse events were slightly more frequently reported in the ibandronate arm (26.5%) than in the alendronate arm (20.5%). The difference between the two arms was likely due to an increase in the incidence of musculoskeletal and general disorder adverse events that occurred within 3 days of each monthly dosing and lasted no more than 7 days, as summarized in the previous paragraph.

Fewer patients experienced serious adverse events in the ibandronate arm (4.5%) than in the alendronate arm (6.4%). Specifically, the incidence of serious gastrointestinal disorders, serious nervous system disorders, and serious hepatobiliary disorders was lower in the ibandronate-treated patients. Furthermore, of the 6 patients with treatment-related serious adverse events, 5 were treated with alendronate. Specifically, three events, gastrointestinal hemorrhage, intestinal hemorrhage, and oesophagitis ulcerative, which were considered treatment-related serious adverse events by the investigator, all occurred in the alendronate arm.

The incidence of clinical fractures during the trial was balanced in the two groups (ibandronate 3.1% vs alendronate 2.7%) as was the incidence of clinical osteoporotic fractures (2.1% in the ibandronate group vs 2.0% in the alendronate group). The incidence was also balanced in the two arms for clinical osteoporotic vertebral fractures (0.6% in each arm) and non-vertebral fractures (1.6% with ibandronate and 1.4% with alendronate), suggesting that both treatments could have similar clinical efficacy for clinical osteoporotic fractures.

There were 6 deaths reported during the trial (4 in the alendronate arm and 2 in the ibandronate arm), which were mainly caused by cardiovascular disorders, common in the population studied. One death case in the ibandronate group (cause unknown) was not confirmed and the information on possible death was received after the patient failed to return to the regular visit.

No clinically relevant laboratory test value abnormalities were seen. The marked laboratory test value abnormalities were rare. In particular, there was no evidence suggesting that the monthly ibandronate treatment regimen led to clinically significant changes in renal or hepatic functions or serum electrolyte concentrations as compared with the weekly alendronate treatment regimen.

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CONCLUSIONS:

The monthly 150-mg ibandronate treatment regimen was non-inferior to the weekly 70-mg alendronate treatment regimen in improving the lumbar spine and total hip BMD following 12 months of therapy in women with postmenopausal osteoporosis. BMD increases at other proximal hip sites as well as reductions in bone turnover markers were similar with both treatments.

The safety profile including incidence of clinical fractures was comparable between monthly 150-mg ibandronate and weekly 70-mg alendronate treatment regimens. No new safety signals of clinical significance were identified.