SYNOPSIS (PROTOCOL ML19913)

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

TITLE OF THE STUDY / DATE OF REPORT	Abbreviated Clinical Study Report – ML19913: A randomised, open-label, multi-national study to investigate the impact of bone marker feedback (at 2 months) on adherence to once-monthly ibandronate treatment for post-menopausal osteoporosis (PMO). 26 March 2008		
CENTERS AND COUNTRIES (PLANNED AND ACTUAL)	**Planned:** 100 European centres in Austria, Belgium, Greece, Ireland, Luxemburg and Portugal. **Actual:** 77 European centres in Austria, Belgium, Greece, Ireland and Luxemburg. **Analysed:** 76 European centres in Austria, Belgium, Greece, Ireland and Luxemburg.		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	15 March 2006 to 13 November 2007	CLINICAL PHASE	IV
OBJECTIVES	**Primary objective:** To assess the impact of bone marker feedback (BMF) using serum Type 1 crosslinked C-Telopeptide (CTx) on adherence to once-monthly ibandronate in women with PMO. **Secondary Objectives:** • To evaluate patient satisfaction of treatment with once-monthly ibandronate derived from the treatment experience score of the Osteoporosis Patient Satisfaction Questionnaire (OPSAT-Q) administered at the final visit. • To evaluate patient satisfaction of treatment with once-monthly ibandronate in different patient categories based on baseline variables (age, previous bisphosphonate treatment if any), measured by the OPSAT-Q. • To evaluate patient satisfaction with regimen (drug treatment and physician handling) by the OPPS (Osteoporosis Patient Perception Survey) administered at the final visit. • To evaluate the difference in patient satisfaction with regimen (drug treatment and physician handling) between the two study arms by the OPPS. • To evaluate patient satisfaction (BMF group only) with the BMF method as reported in additional BMF section of the OPPS. • To evaluate physician satisfaction with a method of assessment of bone marker quantification (Physician Feedback Questionnaire). • To evaluate the safety and tolerability of a once-monthly tablet		

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	of ibandronate
STUDY DESIGN	This was a 6-month randomised, prospective, open-label, multi-national, 2-arm study, where post-menopausal women with osteoporosis who were either naïve to bisphosphonate treatment or lapsed bisphosphonate users (last bisphosphonate intake >6 months prior to study entry), were randomised to one of two arms at baseline: one to receive BMF and the other not to receive BMF.
NUMBER OF PATIENTS (PLANNED AND ANALYZED)	**Planned:** Originally, 400 evaluable patients per study arm were planned. This was reduced to 290 planned per study arm due to the loss of one country (Portugal) and delays in recruitment in other countries (Greece and Ireland). **Analysed:** A total of 585 patients were randomised. However, with the exclusion of the following patients from all analyses, only data from 575 patients were analysed: • all patients from Centre [redacted] (seven patients) • two patients who were included into the study without their consent (and subsequently withdrew from the study after being randomised) • one patient ([redacted]) gave informed consent, but was randomised in error and was not assigned to either treatment group, only 575 patients were included in the planned analyses.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION / EXCLUSION	The patients enrolled in the study were ambulatory, post-menopausal women with osteoporosis, who were either naïve to bisphosphonates or lapsed bisphosphonate users (last bisphosphonate intake >6 months prior to study entry).
INVESTIGATIONAL PRODUCT / (BATCH) No.	Ibandronate (RO 200-5450)
DOSE / ROUTE / REGIMEN / DURATION	The study drug was administered orally as a once-monthly tablet of ibandronate 150 mg. The first dose was taken either at the first clinic visit or the morning after the first visit, under fasting conditions. Subsequent dosing was once-monthly for 5 additional months. The duration of the study was 6 months.
STANDARD CARE REGIMENS	N/A
DOSE / ROUTE / REGIMEN / DURATION	N/A
CRITERIA FOR EVALUATION	
EFFICACY:	The following primary variable was assessed:

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	• A binary variable indicating that adherence to study treatment was at least 83%, corresponding to at least 5 of 6 monthly ibandronate doses taken within -3 to 21 days of the monthly osteoporosis treatment date. Secondary variables assessed were: • Patient satisfaction derived from the OPSAT-Q administered at the final visit. • Patient satisfaction with the regimen derived from items 1 to 6 of the OPPS questionnaire administered at the final visit. • Satisfaction with the BMF method, assessed by the patients of the BMF group only. The assessment was derived from the OPPS questionnaire (items 7 to 18) administered at the final visit. • Physician satisfaction with the BMF method as assessed by the physician by means of the Bone Marker Feedback Physician (BMFP) questionnaire administered at the final visit. • Serum bone resorption marker CTx. Serum CTx was determined for the patients of the BMF group only at baseline and after 6 weeks of treatment. Note that serum CTx was assessed at a central laboratory.
SAFETY:	The following variables were assessed: • Duration of exposure to study drug. • Incidence of adverse events, including serious adverse events. • All abnormal laboratory variables.
STATISTICAL METHODS	All efficacy analyses were performed on the intent-to-treat (ITT) population. Frequency counts and percentages were used to summarise categorical data. Descriptive statistics (N, mean, SD, median and range) were presented for continuous data (including domain scores and composite scores). Adherence to study treatment: Cochran-Mantel-Haenszel test, stratified by centre was performed. The following sensitivity analyses were performed: • Analysis repeated using the Per-Protocol (PP) population • Analysis repeated, stratified by country • Subgroup analyses stratified by country: Age (<70 years and ≥70 years); Previous use of bisphosphonates (yes/no)

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OPSAT-Q and OPPS Questions 1 to 6: For each domain score and for the composite satisfaction score, an analysis of variance (ANOVA) was performed with treatment and country as factors; p-value was assessed at the 5% significance level. A separate ANOVA including terms for treatment, country and treatment-by-country interaction was also performed; the p-value for the interaction term was assessed at the 10% level. For OPPS Item 6, the Cochran-Mantel-Haenszel test stratified by country was applied; the general association statistic was used.

OPPS Questions 7 to 18 and BMFP Questionnaire: Descriptive statistics were presented for each domain score and composite score. Frequency counts and percentages were presented for OPPS Items 15 to 18, and BMFP Item 11.

Serum Bone Resorption Marker CTx: Descriptive statistics were presented for the serum CTx concentration at each visit, the change from baseline, and the percentage change from baseline. The number and percentage of patients with a percentage change from baseline in serum CTx greater than 30% was also summarised.

METHODOLOGY:

Patients were randomised to one of two arms at baseline: one to receive BMF and the other not to receive BMF. In the BMF arm, patients had serum CTx testing performed at baseline (visit 1) and at Month 1.5 (visit 2). BMF was given by phone 1-2 weeks after visit 2. Patients in the BMF arm were told whether or not their result fell within or outside the desired range. A "BMF-form" was provided to the physician to allow communication of the bone marker result to the patient in an easy to understand way. The targeted suppression was defined as being greater than the least significant change which is a 30% drop in CTx from baseline.

Patients in both arms were given comparable adherence advice at Month 1.5 (visit 2) as per good clinical practice (GCP). This advice contained the following information:

- A reminder to patients of the importance of treating osteoporosis and that this reduces fracture risk;
- A reminder to patients that good adherence was required for a good result;
- A reminder to patients of ibandronate dosing instructions.

At the Month 6 final visit, all patients were assessed for adherence and received an OPSAT-Q and OPPS. Patients who were in the BMF arm completed an additional section of the OPPS. Physicians were asked to complete a BMFP questionnaire at study close out. A follow-up call was scheduled 15 to 30 days after the last intake of study medication to assure collection of additional safety information. With regards to the questionnaires, only OPSAT-Q was validated for the English version. The country translations were not validated. The other questionnaires were not validated. Therefore, overall, the analyses of questionnaire data were performed using non-validated questionnaires.

EFFICACY RESULTS:

Adherence to study treatment was slightly lower for the ibandronate with BMF group, (65.7% patients

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adhered to study treatment compared with 70.2% patients in the ibandronate without BMF group; however, no statistically significant difference was observed between the treatment groups for the ITT population stratified by centre (p=0.164). The results of the sensitivity analysis for the PP population were consistent with those for the primary analysis, i.e., no statistically significant difference in adherence was demonstrated between the two treatment groups. Similarly, the results of the sensitivity analyses which were stratified by country, including the subgroup analyses, showed no statistically significant differences in adherence between the two treatment groups.

Overall, adherence to study treatment was lower than expected in the ibandronate with BMF group. Although 85.7% patients took at least five tablets, only 65.7% of these patients had at least five tablets fall within the -3 to 21 days intake window. In terms of assessing therapeutic adherence using the medication possession ratio (MPR), again the mean value for the MPR was 4.8% lower for the ibandronate with BMF group (mean=89.0%), compared with the ibandronate without BMF group (mean=93.8%). For Greece, adherence to study treatment was much lower compared with other the countries; 40.6% of ITT patients in the ibandronate with BMF group and 34.4% in the ibandronate without BMF group adhered to study treatment, compared with at least 60.0% across treatment groups in other countries.

No statistically significant differences between the treatment groups were observed for any of the domain and composite scores for the OPSAT-Q. Statistically significant treatment by country interactions were observed for quality of life, overall satisfaction, and composite satisfaction scores, suggesting that the differences between treatment groups could be in opposite directions among countries. Countries with a larger number of patients generally showed negative treatment differences as reflected in the overall results. The countries with a smaller number of patients generally showed positive treatment differences; favouring the ibandronate with BMF group.

Statistically significant differences of at least 3.8% between treatment groups were observed for all domain and composite scores for the OPPS Questionnaire, with the exception of the motivation domain, favouring the ibandronate with BMF group ($p \leq 0.021$). No statistically significant treatment by country interactions were observed for the OPPS domains and composite scores.

A higher proportion (70.6%) of patients in the ibandronate with BMF group replied positively to the question "Would you recommend the study medication to other women with osteoporosis?", compared with the ibandronate without BMF group (66.8%), but no significant difference between the treatment groups was observed (p=0.537). From the OPPS domain scores (questions 7 to 18), patients felt a high degree of motivation in taking their medication, confident that their osteoporosis condition was under control, satisfied with the feedback from the blood test and did not find the BMF inconvenient. Based on the BMF, 78.0% of patients indicated their osteoporosis had either improved or stabilized (Item 15).

Overall, investigators found the BMF valuable, were interested in continuing to give BMF, and found the patients were not inconvenienced by the BMF. All but one of the investigators who completed the questionnaire felt it was worth having the BMF, however, there was no overall consensus of when the BMF should be given.

A mean reduction of 53.6% from baseline in serum CTx was observed. Based on the serum CTx results provided to the investigators, 72.4% of patients in the ibandronate with BMF group were informed that their percentage reduction lay within the target suppression zone, i.e., that their osteoporosis condition was improving. However, from the study database calculation for these patients, the percentage reduction for three of these patients was actually outside the zone. Thus, 71.3% of patients were actually given the

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correct feedback that their percentage reduction lay within the target suppression zone.

SAFETY RESULTS:

Mean persistence (length of study treatment) was 169.2 days for the ibandronate with BMF group, compared with 175.4 days for the ibandronate without BMF group.

Although approximately 60% patients experienced adverse events, most of these events were mild or moderate in severity. There were 29 treatment-emergent adverse events that were classified as severe in the ibandronate with BMF group and 48 adverse events classified as severe in the ibandronate without BMF group. There were two life-threatening events in each group, which were both considered unrelated to study drug, and two deaths were reported during this study, one in each group; neither death was considered related to study drug. In total, 43 serious adverse events were reported for 35 patients, and only three of these serious events were considered related to study drug. Overall, 35 patients withdrew from the study due to treatment-emergent adverse events: 19 in the ibandronate with BMF group and 16 in the ibandronate without BMF group. The most common treatment-emergent adverse events were gastrointestinal disorders, followed by musculoskeletal and connective tissue disorders and infections and infestations. The observed adverse events profile was consistent with the reported effects for this compound.

CONCLUSIONS:

In conclusion, the results of this study indicate that although adherence to study treatment was slightly lower for those patients who received BMF, patient satisfaction, feeling informed and confidence derived from the OPPS questionnaire, was significantly higher. In general, the physicians were in favour of the BMF, although a consensus was not reached on the most appropriate time this should be given. The BMF method was not validated in this study.

The most commonly reported adverse effects for ibandronate are back pain, pain in the arms or legs, abdominal pain, and diarrhoea. The most commonly reported adverse events in this study were: upper abdominal pain, nausea, arthralgia, diarrhoea and back pain. Therefore, this study indicates that ibandronate is generally well tolerated and the safety profile is similar to that previously reported.