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PROTOCOL TITLE/NO.: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Persistence of the Effect of Monthly Ibandronate on Bone Resorption in Postmenopausal Women with Osteoporosis (MK-0217-908)

AMENDMENT: Statistical Study Report Synopsis MK-0217-908AM1 (2012-MAY-11)

UNIQUE IDENTIFIER: NCT00092053

SPONSOR: Merck Inc.

INVESTIGATOR(S)/STUDY CENTER(S): Multi-center

CLINICAL PHASE: II

DURATION OF TREATMENT: A 3-month treatment period

OBJECTIVE(S):

Primary Objective: In postmenopausal women with osteoporosis, to evaluate and compare with placebo the persistence of the effect of oral monthly ibandronate, 100 mg and 150 mg, on percent change from baseline in the biochemical marker of bone resorption, serum carboxyterminal crosslinked telopeptide of Type I collagen (CTxI), during the third month of treatment (four weeks post dose compared to one week post dose).

Secondary Objectives: In postmenopausal women with osteoporosis:

1. To evaluate and compare with placebo the persistence of the effect of oral monthly ibandronate, 100 mg and 150 mg, on percent change from baseline in the biochemical marker of bone resorption, serum CTxI, during the third month of treatment at three weeks and two weeks post dose compared to one week post dose.
2. To evaluate and compare with placebo the persistence of the effect of oral monthly ibandronate, 100 mg and 150 mg, on percent change from baseline in the biochemical marker of bone resorption, urinary aminoterminal crosslinked telopeptide of Type I collagen corrected for creatinine (NTx/Cr) during the third month of treatment.
3. To evaluate the effect of oral monthly ibandronate, 100 mg and 150 mg, on the proportion of patients with a percentage change from baseline in the biochemical markers of bone resorption (serum CTxI and urinary NTx/Cr) above the pre-specified reference levels of -40%, -50% and -60% during the third month of treatment.
4. To evaluate the effect of oral monthly ibandronate, 100 mg and 150 mg, on the proportion of patients with absolute value in the biochemical markers of bone resorption (serum CTxI and urinary NTx/Cr) above the 90% percentile for normal premenopausal women [3] during the third month of treatment.
5. To evaluate and compare with placebo the persistence of the effect of oral monthly ibandronate, 100 mg and 150 mg, on percent change from baseline in the biochemical markers of bone resorption (serum CTxI and urinary NTx/Cr), during the first and second month of treatment.
6. To evaluate the effect of oral monthly ibandronate, 100 mg and 150 mg, on biochemical markers of bone resorption (serum CTxI and urinary NTx/Cr) during three months of treatment.
7. To evaluate the safety and tolerability of oral monthly ibandronate, 100 mg and 150 mg, and placebo.

STUDY DESIGN: Multi-center, double-blind, placebo-controlled, randomized study.

PATIENT ACCOUNTING:

Table 1. Patient Accounting

	Ibandronate 150 mg	Ibandronate 100 mg	Placebo	Total
Patients Randomized	68	68	67	203
Age (years)	65.7	63.9	65.1	64.9
Age range (years)	51 to 87	50 to 87	50 to 85	50 to 87
Patients Completed Study	64 (94.1%)	65 (95.6%)	65 (97.0%)	194 (95.6%)
Patients Discontinued	4 (5.9%)	3 (4.4%)	2 (3.0%)	9 (4.4%)
Clinical Adverse Experience	2 (2.9%)	0	1 (1.5%)	3 (1.5%)
Withdrew consent	1 (1.5%)	1 (1.5%)	0	2 (1.0%)
Other reason	1 (1.5%)	2 (2.9%)	1 (1.5%)	4 (2.0%)

DOSAGE/FORMULATION.: 3x50 mg oral ibandronate acid (as ibandronate sodium) tablet monthly, or 2x50 mg ibandronate acid plus 1 placebo tablet monthly, or 3 placebo tablets monthly. Doses were administered at the Randomization Visit, and at the end of Weeks 4 and 8.

DIAGNOSIS/INCLUSION CRITERIA: Post-menopausal women with osteoporosis

EVALUATION CRITERIA: *Primary efficacy endpoint:* Change from Week 9 (one week post dose) at Week 12 (four weeks post dose) in serum CTxI log-transformed fraction from baseline.

Secondary Efficacy Endpoints:

Change from Week 9 in log-transformed fraction from baseline in serum CTxI at Weeks 10 and 11.

Change from Week 9 in log-transformed fraction from baseline in urinary NTx/Cr at Weeks 10, 11, and 12.

Percentage of patients with a percent change from baseline in biochemical markers (CTxI and NTx/Cr) above the pre-specified reference levels of -40%, -50%, -60% at Week 9, 10, 11, or 12.

Percentage of patients with absolute value in biochemical markers (CTxI and NTx/Cr) above the 90% percentile for normal premenopausal women [3] at Week 9, 10, 11, or 12.

Change from Week 5 in log-transformed fraction from baseline in serum CTxI and urine NTx/Cr at Week 8.

Change from Week 1 in log-transformed fraction from baseline in serum CTxI and urine NTx/Cr at Week 4.

Log-transformed fraction from baseline in biochemical markers (CTxI and NTx/Cr) at Weeks 1 through 12.

Safety Endpoints

The percentage of patients with adverse experiences (AEs), gastrointestinal (GI) AEs and with acute phase reaction-related (APR) AEs during the 3-month double-blind treatment period was summarized. Percentage of patients with AEs for the above specified categories during the 7 days after the first dose of treatment, during the 7 days after the second dose of treatment, during the 7 days after the third dose of treatment, and in the 7 days after any of the 3 intakes of treatment were also summarized.

STATISTICAL METHODS:

The analysis of biochemical markers was based on a per-protocol approach, including all patients randomized in the study with a baseline and a follow-up measurement, who had taken at least one dose of double-blind study medication. All randomized patients who took at least one dose of study medication were included in the safety analyses.

The change from Week 9 in log-transformed fraction from baseline (calculated by dividing the on-treatment value by the baseline value and then applying the natural log) in CTxI at Weeks 12 (primary analysis), 11, and 10 were analyzed. The 2 doses of ibandronate were compared to placebo by means of an analysis of variance (ANOVA) model with factors for treatment and study center. The Hochberg procedure was used for the primary analysis to allow for multiple comparisons due to multiple doses. Similar analyses were provided for the change from Week 5 at Week 8 and for the change from Week 1 at Week 4.

Number (%) of patients with a percent change from baseline in serum CTxI above -40%, above -50% and above -60% at least once at Week 9, 10, 11, or 12 was summarized for each of the 3 treatment groups. The number (%) of patients with serum CTxI above the 90% percentile for normal premenopausal women at Week 9, 10, 11, or 12 were summarized for each of the 3 treatment groups. Similar analyses were conducted for urinary NTx/Cr. Serum CTxI and urinary NTx/Cr measurements were summarized at Weeks 0 (before first treatment intake), 1, 4 (before second treatment intake), 5, 8 (before third treatment intake), 9, 10, 11 and 12 together with the geometric mean percent change from baseline at each during-treatment time point.

Assuming a geometric mean percent decrease from baseline of 75% at Week 9 and 55% at Week 12 and a standard deviation on the change in log-transformed fraction from baseline of 0.80, a sample of 49 patients per treatment group would provide 95% power to detect the difference between each ibandronate dose compared to placebo at a 0.050 significance level. If one of the doses did not reach significance at 0.050, the other dose would be tested at α=0.025; affording 91% power to detect a treatment difference of (α=0.025).

RESULTS:

Efficacy: Ibandronate 150 mg and 100 mg monthly did not maintain their lowering effect on serum CTxI and urinary NTx/Cr ratio 4 weeks after dosage. (Table 2)

Safety: No important differences were seen between the safety profiles of ibandronate 150 mg and 100 mg compared to placebo. (Table 3)

Table 2. Biochemical Markers of Bone Resorption at Week 12

Endpoint	N	Geometric Mean Percent Change from Week 9[†] Mean[‡]	95% CI	Comparison with Placebo Adjusted Mean[§]	95% CI	p-Value
Serum C-Terminal Telopeptide Collagen I (ng/mL)						
Ibandronate 150 mg	59	117.2***	(82.1,159.1)	115.5	(87.0, 144.0)	<0.001
Ibandronate 100 mg	58	78.3***	(56.6,103.0)	82.1	(57.0, 107.2)	<0.001
Placebo	58	-1.4	(-8.2,5.9)			
Urine N-Telopeptide/Creatinine Ratio (nmol/mmol[creatinine])						
Ibandronate 150 mg	60	26.9***	(12.8,42.8)	34.3	(18.5, 50.0)	<0.001
Ibandronate 100 mg	58	27.1***	(15.4,40.0)	34.6	(18.7, 50.6)	<0.001
Placebo	59	-6.9	(-13.9,0.7)			

[†] Back-transformed from log-transformed fraction from Week 9.

[‡] Within-treatment test of mean=0: ***:p≤0.001, **:p≤0.010, *:p≤0.050.

[§] Back-transformed from LS mean difference in ln(fraction from Week 9) - Ibandronate minus Placebo.

Table 3. Clinical, Gastrointestinal (GI) and Acute Phase Reaction (APR) Adverse Experience (AE) Summary

	Ibandronate 150 mg (N=68)		Ibandronate 100 mg (N=68)		Placebo (N=67)	
	n	(%)	n	(%)	n	(%)
With one or more AEs	39	(57.4)	34	(50.0)	30	(44.8)
With drug-related AEs†	12	(17.6)	10	(14.7)	4	(6.0)
With serious AEs	2	(2.9)	0		0	
With serious drug-related AEs†	0		0		0	
Who died	0		0		0	
Discontinued due to AE(s)	2	(2.9)	0		1	(1.5)
With one or more GI AE(s)	12	(17.6)	8	(11.8)	5	(7.5)
With drug-related GI AE †	8	(11.8)	5	(7.4)	2	(3.0)
With serious GI AE	0		0		0	
Discontinued due to GI AE	0		0		0	
With one or more APR AE(s)	9	(13.2)	12	(17.6)	6	(9.0)
With drug-related APR AE †	3	(4.4)	5	(7.4)	1	(1.5)
With serious APR AE	0		0		0	
Discontinued due to APR AE	0		0		0	

† Determined by the investigator to be possibly, probably or definitely drug related.

CONCLUSIONS:

Efficacy:

In postmenopausal women with osteoporosis, oral monthly ibandronate, at doses of 100 mg and 150 mg, does not achieve persistence in reduction of bone resorption throughout the monthly dosing interval, as demonstrated by a larger change in:

- serum CTxI log-transformed fraction from baseline four weeks post dose compared to one week post dose, during the third month of treatment, in patients taking ibandronate compared to those participants taking placebo.
- serum CTxI log-transformed fraction from baseline two and three weeks post dose compared to one week post dose, during the third month of treatment, in the patients taking ibandronate compared to those participants taking placebo.
- serum NTx/Cr log-transformed fraction from baseline two, three and four weeks post dose compared to one week post dose, during the third month of treatment, in the patients taking ibandronate compared to those participants taking placebo.

Safety:

The safety of ibandronate (150 mg and 100 mg once-monthly) was consistent with the established safety profile of monthly ibandronate 150 mg tablets.

Date of Report: 2012 May 31