2. Synopsis of Final Study Report

NAME OF COMPANY **Teva Pharmaceutical Industries Ltd.** **NAME OF FINISHED PRODUCT:** **Alendronate/cholecalciferol (Teva Pharmaceutical Industries Ltd.)** **NAME OF ACTIVE INGREDIENT(S):** **alendronate sodium/cholecalciferol**	**INDIVIDUAL STUDY TABLE REFERRING TO CLINICAL DOCUMENTATION OF THE DOSSIER:** **Volume:** **Page:**	*(FOR NATIONAL AUTHORITY USE ONLY)*

Title of the study:

A-15 week, double-blind, randomized, active-controlled, multicenter study to evaluate the efficacy and safety of Alendronate plus Vitamin D3 in women with osteoporosis

Investigator(s):

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Center 11_RO:	Assoc. Prof. Mihaela Popoviciu, MD, PhD
Center 12_RO:	Luminita Stamoran, MD, PhD

BG: Bulgaria; PL: Poland; RO: Romania

Active study centers:

n=35

14 centers in Bulgaria, 11 centers in Poland, 10 centers in Romania

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Studied period: date of first enrolment: 10-Oct-2011 date of last completion: 02-Aug-2012	**Phase of development:** Phase III

Objectives:

The main objective of the present trial was to estimate the proportion of patients with 25-hydroxy vitamin D insufficiency (<15 ng/ml) after 15 weeks of treatment with two oral test products containing alendronate sodium/cholecalciferol 70 mg/0.07 mg or 70 mg/0.14 mg (Alendronate/cholecalciferol (Teva Pharmaceutical Industries Ltd.)) as compared to alendronate alone (Fosamax®).

The secondary objectives of the present trial were:

- To evaluate the efficacy of both test products as compared to Fosamax® alone in reducing the proportion of patients with 25-hydroxy vitamin D deficiency (<9 ng/ml) after 15 weeks of treatment.
- To assess the difference in the mean serum 25-hydroxy vitamin D between both test products and the reference product after 15 weeks of treatment.
- To assess the percent change from baseline in the serum concentrations of intact serum parathyroid hormone (iPTH) between both test products and the reference product after 15 weeks of treatment.
- To evaluate the changes from baseline in the rate of bone turnover as assessed by biochemical markers [bone-specific alkaline phosphatase (BSAP) and urine N-telopeptides of type 1 collagen corrected for creatinine (NTx/Cr)].

The safety objectives of the present trial were:

- Incidence of adverse events and serious adverse events;
- Changes from baseline in the results of clinical examination and vital signs;
- Changes from baseline in serum calcium (albumin-adjusted);
- Changes from baseline in serum phosphate;
- % of subjects with hypercalciuria, defined as one of the following:
  - calcium excreted in urine larger than 300mg/24 hours or
  - increase of calcium excreted in urine larger than 25% of the baseline;
- Changes from baseline in safety laboratory parameters (hematology and biochemistry).

Study design:

- Prospective
- Double-blind
- Randomized
- Verum-controlled
- Multicentric
- Multiple-dose
- Three parallel groups of patients
- Phase III
- International
- 420 patients (three groups of 140 patients each) planned for randomization

Subjects (planned and analyzed):	planned for screening:	630
	screened:	1045
	planned for randomization:	420
	randomized (total):	476
	– stratum 1[1]:	144
	– stratum 2[2]:	332
	drop-outs after randomization:	82
	evaluated:	
	– safety population:	476
	– full analysis set:	431
	– per protocol set:	366

[1] baseline levels for serum 25-hydroxy vitamin D: ≥9 and <15 ng/ml
[2] baseline levels for serum 25-hydroxy vitamin D: ≥15 ng/ml

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Diagnosis and criteria for selection:

Inclusion criteria:

[1] 18 years and older
[2] Patients in good general health, according to the investigator's judgment
[3] Serum 25-hydroxy vitamin D ≥9 ng/ml
[4] Normal (within reference range) iPTH and BSAP for patients with serum 25-hydroxy vitamin D ≥9 ng/ml and <15 ng/ml
[5] Postmenopausal women defined as one of the following:
- more than 6 months amenorrhea in patients ≥55 years OR
- more than 18 months amenorrhea in patients <55 years OR
- baseline serum FSH >35 IU/l in patients <55 years and less than 18 months amenorrhea OR
- surgical menopause since more than 4 weeks.

[6] Recent (within the last 6 months) bone mineral density (BMD) T-score determined by dual energy X-ray absorptiometry (DEXA) of either lumbar spine or hip of ≤ -2.5 (≥2.5 standard deviations below the mean for normal premenopausal women)
[7] Patient agrees to apply sunscreen and limit sunlight-exposure to 1 hour per day during the study
[8] Patient agrees to avoid tanning beds/UV therapy within 14 days of study start, and during the study
[9] Patients with ability to follow study instructions and likely to attend and complete all required visits
[10] Written informed consent of the patient.

Exclusion:

[1] Hypersensitivity to the active substances or to any of the excipients, or to any related drug
[2] Bone fractures within 3 months prior to screening
[3] Inability to stand or sit upright for at least 30 minutes
[4] Inability to take the study drugs as recommended: after getting up for the day with a full glass of water (not less than 200 ml)
[5] Active upper gastrointestinal problems, such as dysphagia, esophageal disease, gastritis, duodenitis, ulcers
[6] Recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty
[7] Known Barrett's esophagus
[8] Malabsorption
[9] Hypocalcemia: serum calcium <2.1 mmol/l (9 mg/dl)
[10] Concomitant malignancy except carcinoma in situ not needing other than local therapy
[11] History of solid tumors not curatively treated or showing a recurrence within the last 5 years
[12] Concomitant untreated severe periodontal disease
[13] Renal impairment (glomerular filtration rate less than 35 ml/min)
[14] Presence of bone or mineral metabolism disorders, other than idiopathic osteoporosis (e.g. hyperparathyroidism, hyperthyroidism, osteomalacia of other origin, Paget's disease of bone, glucocorticoid-induced osteoporosis)
[15] Diseases associated with unregulated overproduction of calcitriol (e.g. leukemia, lymphoma, sarcoidosis)
[16] Previous or concomitant intake of drugs and/or food additives restricted by the protocol (for a complete list please see chapter 8.6.6 of study protocol, page 38)
[17] Pregnancy or lactation
[18] Simultaneous participation in another clinical study or participation in any clinical study involving an investigational drug within 3 months prior to start of the present study
[19] Severe physical or mental concomitant diseases that might hamper the realization of the trial according to protocol
[20] History of alcohol or drug addiction
[21] Legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the study
[22] Unreliability or lack of cooperation.

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Test 1 product, dose and mode of administration, batch number:	Name:	Alendronate/cholecalciferol (Teva Pharmaceutical Industries Ltd.)
	(Name according CoA):	ALENDRONATE/CHOLECALCIFEROL 70/0.07 mg TABLETS, EU
	Active ingredient:	alendronate sodium/cholecalciferol
	Dosage form:	tablet
	Strength:	70 mg/0.07 mg per tablet
	Route of administration:	oral
	Regimen:	3 tablets as single dose per week (1 tablet with active compound and 2 placebos/dummies) with tap water only (not mineral water or other fluid) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day
	Manufacturer:	Teva Pharmaceutical Industries Ltd.
	Batch no.:	K-43326
	Blinded batch no.:	E07086-010L
	Blinded re-test date:	04/2012 (10/2012)[3]
Test 2 product, dose and mode of administration, batch number:	Name:	Alendronate/cholecalciferol (Teva Pharmaceutical Industries Ltd.)
	(Name according CoA):	ALENDRONATE/CHOLECALCIFEROL 70/0.14 mg TABLETS, EU
	Active ingredient:	alendronate sodium/cholecalciferol
	Dosage form:	tablet
	Strength:	70 mg/0.14 mg per tablet
	Route of administration:	oral
	Regimen:	3 tablets as single dose per week (1 tablet with active compound and 2 placebos/dummies) with tap water only (not mineral water or other fluid) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day
	Manufacturer:	Teva Pharmaceutical Industries Ltd.
	Batch no.:	K-43213
	Blinded batch no.:	E07086-010L
	Blinded re-test date:	04/2012 (10/2012)[3]

[3] original re-test date was 04/2012; new re-test date was 10/2012

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Reference product, dose and mode of administration, batch number:	Name:	Fosamax®
	(Name according CoA):	ALENDRONATE SODIUM TABLETS
	Active ingredient:	alendronate sodium
	Dosage form:	tablet
	Strength:	70 mg per tablet
	Route of administration:	oral
	Regimen:	3 tablets as single dose per week (1 tablet with active compound and 2 placebos/dummies) with tap water only (not mineral water or other fluid) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day
	Company responsible for placing the product on the market:	MSD Sharp & Dohme GmbH, Germany
	Lot no.:	1100705
	Blinded batch no.:	E07086-010L
	Blinded re-test date:	04/2012 (10/2012)[3]

Duration of treatment:

The study consisted of 2 periods with a total duration of up to 17 weeks:

- a up to 2-week screening period;
- a 15-week double-blind treatment period with the test and the reference products (15 weekly doses plus 6 days follow-up)

Criteria for evaluation:

Efficacy:

Primary endpoint:

- proportion of patients with 25-hydroxy vitamin D insufficiency (<15 ng/ml) after 15 weeks of treatment

Secondary endpoints:

- proportion of patients with 25-hydroxy vitamin D deficiency (<9 ng/ml) after 15 weeks of treatment,
- mean serum concentration of 25-hydroxy vitamin D after 15 weeks of treatment,
- percent change from baseline in intact serum parathyroid hormone (iPTH) after 15 weeks of treatment,
- changes from baseline in the rate of bone turnover as assessed by biochemical markers [bone-specific alkaline phosphatase (BSAP) and urine N-telopeptides of type 1 collagen corrected for creatinine (NTx/Cr)].

Safety:

Safety endpoints:

- incidence of adverse events and serious adverse events,
- changes from baseline in the results of clinical examination and vital signs,
- changes from baseline in serum calcium (albumin-adjusted),
- changes from baseline in serum phosphate,
- % of subjects with hypercalciuria, defined as one of the following:
  - calcium excreted in urine larger than 300mg/24 hours or
  - increase of calcium excreted in urine larger than 25% of the baseline,
- changes from baseline in safety laboratory parameters (hematology and biochemistry).

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Statistical methods:

The statistical aim of the present trial was to prove the superiority of each of both test products as compared to the reference formulation (Fosamax®) regarding the primary endpoint (proportion of patients with 25-hydroxy vitamin D insufficiency (<15 ng/ml) after 15 weeks of treatment).

Test procedure: A two-sided test procedure was used.

Statistical test and test strategy: The comparison of the primary endpoint was performed using the Cochran-Mantel-Haenszel test adjusted for baseline vitamin D stratum. The test assessed the relative reduction in the proportion of patients with 25-hydroxy vitamin D insufficiency (<15 ng/ml) after 15 weeks of treatment in both test groups as compared to the reference group.

Two statistical hypotheses were tested in the present trial. The decision about rejecting or accepting the null-hypotheses H_{0i}, i=1,2 was made with the stepwise-rejecting-multiple-test procedure for a priori ordered hypotheses (hierarchical test strategy). As a first step the higher strength of the test product was tested vs. the reference. In case that superiority can be shown the result is regarded as successful for this strength. As a second step the lower strength of the test product was tested vs. the reference. In case that superiority can be shown the result is regarded as successful for this strength too.

$$H_{01}: \pi_{AlCh\ 70/0.14} = \pi_{Al70}\ vs.\ H_{A1}: \pi_{AlCh\ 70/0.14} \neq \pi_{Al70}$$
$$H_{02}: \pi_{AlCh\ 70/0.07} = \pi_{Al70}\ vs.\ H_{A2}: \pi_{AlCh\ 70/0.07} \neq \pi_{Al70}$$

The procedure stops, if at step one the corresponding null-hypothesis cannot be rejected. In this case, the null-hypothesis of the following step is not rejected either. If a local type I error level α is applied in each step, this test procedure also guarantees control of the experiment-wise error rate α which means that no adjustment of α is needed.

The secondary endpoints:
a) proportion of patients with 25-hydroxy vitamin D deficiency (<9 ng/ml) after 15 weeks of treatment,
b) mean serum concentration of 25-hydroxy vitamin D after 15 weeks of treatment,
c) percent change from baseline in intact serum parathyroid hormone (iPTH) after 15 weeks of treatment,
d) changes from baseline in the rate of bone turnover as assessed by biochemical markers (bone-specific alkaline phosphatase (BSAP) and urine N-telopeptides of type 1 collagen corrected for creatinine (NTx/Cr)) were analyzed comparatively as follows:

- in a similar way as the primary endpoint for a) or
- by means of 95% confidence intervals calculated by an appropriate ANOVA for b), c), and d).

These tests were not be confirmative in nature. Further evaluations of the demographic parameters and safety endpoints were performed according to the type of distribution of the respective parameter. A Chi-square test was applied for parameters with discrete distribution. ANOVA was applied for continuously distributed parameters. These analyses were descriptive or exploratory in nature.

The statistical analysis was performed on three different patient populations:

- Safety population (all randomized patients who received at least one dose of double-blind study medication).
- Full analysis set (all randomized patients who received study medication at least once and had at least one post-baseline value for 25-hydroxy vitamin D) (primary type of statistical evaluation).
- Per protocol population (all patients of the full analysis set, excluding cases of drop-outs and major protocol deviations) (supportive evaluation).

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RESULTS

Disposition of patients:

A total number of 1045 postmenopausal female patients with osteoporosis at risk of vitamin D insufficiency were informed about the aim of the study and were screened after giving their consent in written form. A total number of 569 of the 1045 enrolled patients were excluded from the safety population, because they were not treated with study medication. Four hundred and seventy eight patients were randomized and 476 patients received study medication. One hundred and fifty seven patients were allocated to the test 1 medication, 161 patients to the test 2 drug and 158 patients to the reference product. Forty-five patients (21 treated with test 1, and each 12 treated with test 2 and reference, respectively) were excluded from the full analysis set which thus consists of 431 patients. Further 65 patients were excluded from the per protocol set due to major protocol deviations. Therefore, the per protocol set consists of 366 patients.

Efficacy:

Primary endpoints (results presented for the full analysis set)

The proportion of patients with 25-hydroxy vitamin D insufficiency after 15 weeks of treatment is given in text table TT 1 and as a graphic in text figure TF 1 (full analysis set, FAS). After 15 weeks of treatment only 8.8% of patients in the test 1 group (alendronate sodium/cholecalciferol, 70 mg/0.07 mg) and 4.7% of patients in the test 2 group (alendronate sodium/cholecalciferol, 70 mg/0.14 mg) had 25-hydroxy vitamin D values below 15 ng/ml, whereas in the reference group (alendronate sodium, Fosamax®) 37% of patients had vitamin D insufficiency. This differences are statistically significant.

The statistical aim of the present trial was to prove the superiority of each of both test products as compared to the reference formulation (Fosamax®) regarding the primary endpoint (proportion of patients with 25-hydroxy vitamin D insufficiency (<15 ng/ml) after 15 weeks of treatment).

As a first step the higher strength of the test product (Test 2) was tested vs. the reference with the result that alendronate sodium/cholecalciferol, 70 mg/0.14 mg per tablet reduced the risk for vitamin D insufficiency by 87.44% [relative risk vs. reference was 0.1256 (p < 0.0001; 95% CI: 0.0599 - 0.2635)].

The lower strength of the test product (Test 1, alendronate sodium/cholecalciferol, 70 mg/0.07 mg per tablet) reduced the risk for vitamin D insufficiency by 75.06% [relative risk vs. reference was 0.2494 (p <0.0001; 95% CI: 0.1452 - 0.4283)].

The results obtained for the per protocol set are similar to the results of the full analysis set.

TT 1 Proportion of patients with 25-hydroxy vitamin D insufficiency after 15 weeks of treatment, last-value-carried-forward, full analysis set

Insufficiency [< 15 ng/ml]	Test 1		Test 2		Reference	
	n	%	n	%	n	%
Yes	12	8.8	7	4.7	54	37.0
No	124	91.2	142	95.3	92	63.0

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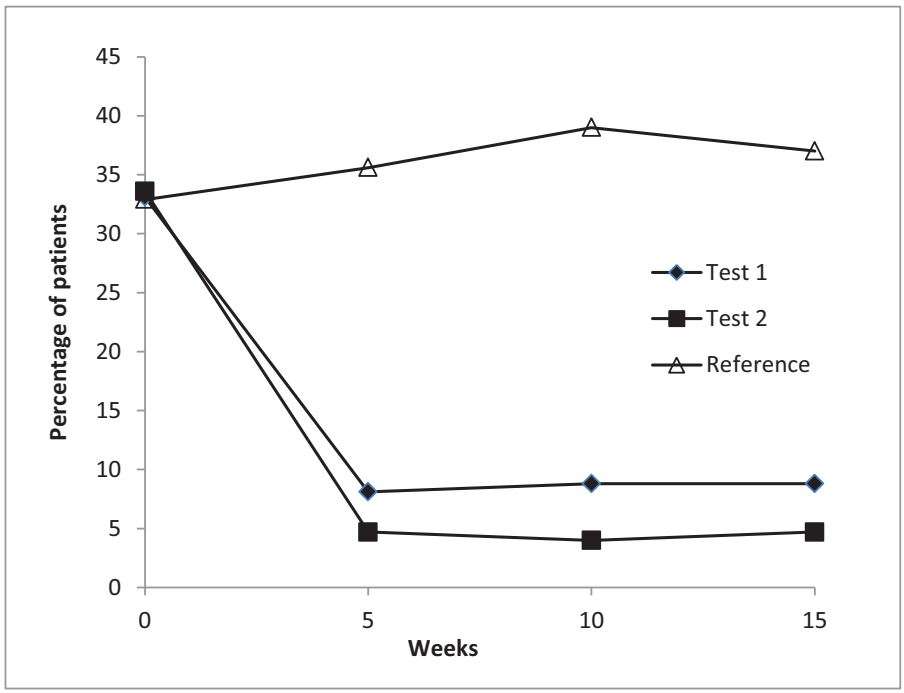

TF 1 Proportion of patients with 25-hydroxy vitamin D level < 15 ng/ml (insufficiency), full analysis set

Secondary endpoints (results presented for the full analysis set)

Proportion of patients with 25-hydroxy vitamin D deficiency (<9 ng/ml) after 15 weeks of treatment:

After 15 weeks of treatment only 5.1% of patients in the test 1 group (alendronate sodium/cholecalciferol, 70 mg/0.07 mg per tablet) and 2.7% of patients in the test 2 group (alendronate sodium/cholecalciferol, 70 mg/0.14 mg per tablet) had 25-hydroxy vitamin D values < 9 ng/ml, whereas in the reference group (alendronate sodium, Fosamax®) 15.1% of patients had vitamin D deficiency. These differences are statistically significant.

The higher strength of the test product (alendronate sodium/cholecalciferol, 70 mg/0.14 mg per tablet) reduced the risk for vitamin D deficiency by 82.57% [relative risk vs. reference was 0.1743 (p < 0.0001; 95% CI: 0.0645 - 0.4714)].

The lower strength of the test product (alendronate sodium/cholecalciferol, 70 mg/0.07 mg per tablet) reduced the risk for vitamin D deficiency by 63.44% [relative risk vs. reference was 0.3656 (p = 0.0043; 95% CI: 0.1733 - 0.7709)].

Mean serum concentration of 25-hydroxy vitamin D after 15 weeks of treatment:

The mean serum concentration of 25-hydroxy vitamin D after 15 weeks of treatment (secondary endpoint) was significantly higher in both test groups compared with the reference group.

Percent change from baseline in intact serum parathyroid hormone (iPTH) after 15 weeks of treatment:

The reference group (Fosamax®) had a significantly greater increase in iPTH from baseline at week 15 (secondary endpoint) compared to both test groups (Alendronate / cholecalciferol (Teva Pharmaceutical Industries Ltd.).

Changes from baseline in the rate of bone turnover as assessed by biochemical markers [bone-specific alkaline phosphatase (BSAP) and urine N-telopeptides of type 1 collagen corrected for creatinine (NTx/Cr)]:

In all treatment groups BSAP decreased in the course of the trial to approximately -20% at week 15. There were no statistically significant differences between the treatment groups. In all treatment groups the NTx/Cr decreased obviously during the trial (test 1: -29.42%; test 2: -29.57%; reference: -24.92%). There were no statistically significant differences between the treatment groups.

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Safety:

Safety endpoints

Incidence of adverse events and serious adverse events:

A total number of 134 patients experienced 322 treatment emergent adverse events in the course of the trial. One hundred and seventeen AEs were reported by 49 (31.2%) patients in the test 1 group, 105 AEs by 40 (24.8%) patients in the test 2 group and 100 AEs by 45 (28.5%) in the reference group. Eleven adverse events in 8 patients were judged as serious (6 SAEs in 4 patients treated with test 1, 2 SAEs in 1 patient treated with test 2, and 3 SAEs in 3 patients treated with reference). Two SAEs (oesophageal ulcer and gastrointestinal hemorrhage) in one patient had a possible relationship to study drug treatment; all other SAEs were were judged as not study drug related. Seventeen patients were withdrawn from the trial due to adverse events.

A total number of 67 non-treatment emergent adverse events were observed in 50 patients before receiving any medication. Two of theses AEs in patient no. 2062 were assessed as serious (ischemic stroke and thrombocytopenia).

One fatal outcome was reported for patient no. 1183 treated with test 1 drug. This 80 years old patient suffered from pneumonia. There was no causal relationship between the event and the study drug administration (alendronate as well as vitamin D).

Changes from baseline in the results of clinical examination and vital signs:

There were no significant changes from baseline in the results of clinical examination and vital signs.

Changes from baseline in serum calcium (albumin-adjusted):

Only marginal changes from baseline in serum calcium (albumin-adjusted) were observed in all treatment groups with no significant differences between the groups.

Changes from baseline in serum phosphate:

No significant differences between the three treatment groups could be observed, and only minor changes from baseline in serum phosphate were registered within the groups.

Percent of subjects with hypercalciuria (defined as one of the following: calcium excreted in urine larger than 300mg/24 hours or increase of calcium excreted in urine larger than 25% of the baseline):

At the end of the trial after 15 weeks of treatment 41.5% of patients treated with test 1, 40.0% of patients treated with test 2, and 27.6% of patients in the reference group experienced hypercalciuria when hypercalciuria is defined as either an increase of the amount of calcium excreted into urine larger than 25% over baseline OR total amount excreted larger than 300mg/24 hours. If hypercalciuria is defined as a combination of both components (both have to be simultaneously fulfilled), which is in fact the clinically relevant definition, a very small number of patients can be defined as hypercalciuric: 6 patients (5.0%) treated with test 1, 4 patients (3.1%) treated with test 2, and 5 patients (4.0%) treated with reference. No statistically significant difference could be registered between any of both test groups and the reference group regarding hypercalciuria.

Changes from baseline in safety laboratory parameters (hematology and biochemistry):

There were no conspicuous values in any of the laboratory parameters indicating any significant pre-post change.

The comparison of vital signs, ECG, physical and clinical examination revealed no indication for adverse events or poor tolerability.

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CONCLUSIONS

The statistical evaluation of the primary endpoint demonstrated the superiority of both strengths of the test product (Alendronate/cholecalciferol (Teva Pharmaceutical Industries Ltd.); 70 mg/0.07 mg and 70 mg/0.14 mg per tablet) over the reference product (Fosamax®, alendronate sodium, 70 mg per tablet) in reducing the proportion of patients with with 25-hydroxy vitamin D insufficiency. The analysis of the secondary endpoints supports this conclusion and also demonstrates the superiority of both test products over alendronate regarding a lower increase in iPTH combined with no differences in markers of bone turnover (bone-specific alkaline phosphatase (BSAP) and urine N-telopeptides of type 1 collagen corrected for creatinine (NTx/Cr).

The evaluation of safety parameters [incidence of adverse events and serious adverse events, changes from baseline in the results of clinical examination and vital signs, changes from baseline in serum calcium (albumin-adjusted), changes from baseline in serum phosphate, % of subjects with hypercalciuria, changes from baseline in safety laboratory parameters (hematology and biochemistry)] provides no evidence for any safety concern.

Both test products are significantly superior to the reference drug (alendronate) in reducing the relative risk for vitamin D insufficiency while providing no indication for safety concerns.

Date of Study Report (Final Version 1.0): 07-Dec-2012