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Sponsor / Company : Sanofi **Drug Substance :** Risedronate Sodium		**Study Identifier :** NCT00460733 **Study Code :** RISED_L_01930
Title of the study:	National study, multicenter, opened, comparative, randomized, with parallel groups, in post menopausal women with Colles'fracture, of the Risedronate Sodium usage in the consolidation and in the callus of the Colles'fracture.	
Study center(s):	7 Brazilian active sites	
Study period: Date first **patient** enrolled: 07-Mar-2007 Date last **patient** completed: 14-Sep-2011		**Phase of development:** Clinical phase IV
Objectives:	Primary: Evaluate the efficacy in BMD (Bone Mineral Density) preservation provided by risedronate sodium 35mg in the forearm proximal region (namely ROI 33%) after 90 days of treatment according to the difference between the treatments risedronate sodium plus calcium and vitamin D or calcium and vitamin D isolated. Secondary: - Evaluate the efficacy in BMD preservation provided by risedronate sodium 35mg in the forearm proximal region (namely ROI 33%) at 180 days of treatment; - Evaluate differences in ultradistal BMD between the two treatments based on differences in callus formation at 90 and 180 days; - Evaluate the radiologic identification of the callus; - Evaluate adverse events.	
Methodology:	This was a multicenter, randomized (1:1), open label, parallel-group, stratified (1:1) by age (<65 years and ≥ 65 years), comparative study in post-menopausal women for at least 2 years, with confirmed Colles' fracture occurred in the previous 7 days of the patient enrollment, with T-score ≤ -2.0 standard deviation at lumbar spine (L1-L4 and/or L2-L4) and/or femoral neck and/or total femur and/or radius 33%.	

Methodology (continuation):	The study consisted of 7 visits: - V0: Screening visit - within 7 days after Colles'fracture; - VR: Randomization visit (D0) – within 7 days after V0; - V1 (D15±3); - V2 (D30±3); - V3 (D45±3); - V4 (D90±3); - V5 (D180±3); The patients eligible for the study were randomized at VR to receive during 180 days: - Risedronate sodium + Calcium and vitamin D **Group (RS+Ca+Vit D):** 35mg of risedronate sodium (once a week) plus 1000mg of calcium and 400UI of vitamin D (daily – except in the day of risedronate intake), 6 days per week. or - Calcium and vitamin D **Group (Ca+Vit D):** 1000mg of calcium and 400UI of vitamin D (daily), 7 days per week.		
Number of patients:	Planned: 140 (70 per arm)	Randomized: 141 71 (Risedronate Sodium + Calcium and vitamin D Group) 70 (Calcium and vitamin D Group))	Treated: 137 70 (Risedronate sodium + Calcium and vitamin D Group) 67 (Calcium and vitamin D Group)
Evaluated:	Efficacy : 137	Safety: 141	Pharmacokinetics: NA
Diagnosis and criteria for inclusion/exclusion:	Inclusion criteria: - Post-menopausal women for at least 2 years; - Confirmed Colles'fracture occurred in the previous 7 days of the patient enrollment; - T-score ≤ -2.0 standard deviation at lumbar spine (L1-L4 and/or L2-L4) and/or femoral neck and/or total femur and/or radius 33%. Exclusion criteria: - Previous fracture(s) in the same wrist or forearm; - Fractures that, according to the evaluation of the orthopedist/responsible, present exclusively surgical indication; - Distal radius fracture or fracture of the contralateral forearm bones, previous or simultaneous, which prevent the comparative densitometric evaluations under the study; - Use of concomitant drugs that can affect the calcium metabolism; - Previous treatment with bisphosphonates for more than 12 months in the last 36 months; - Use of bisphosphonates for any period of time in the last 3 months; - Use of bisphosphonates cumulatively for more than 36 months at any time; - Rheumatoid arthritis or other joint diseases involving the wrist; - Unstable hyper or hypothyroidism known, treated or not; - Hipocalcemia, hepatic diseases, renal insufficiency and rheumatic diseases.		

Investigational product: Dose: Administration:	Sodium Risedronate + Calcium and vitamin D Sodium risedronate: 35mg once a week 1000mg calcium plus 400UI vitamin D daily (except in the day of risedronate administration) Oral	
Duration of treatment: 180 days		**Duration of observation:** About 7 days + 180 days
Reference therapy: Dose: Administration:	Calcium and vitamin D 1000mg calcium plus 400UI vitamin D, daily Oral	
Criteria for evaluation:		
Efficacy:	Changes from Visit V0 to visits V4 and V5 in T-score of the forearm proximal region (33% radius region), expressed in percentage, for both fractured and non-fractured side: Difference (expressed in percentage) between T-Score at V4 minus T-Score at V0, divided by T-score at V0. The correspondent calculation was also made for T-Score difference between V5 and V0. T-score mean of the forearm proximal region (33% radius region) along to the visits (V0, V4 and V5) in both fractured and non-fractured side. Radiological identification of the callus in the X-Ray.	
Safety:	Adverse events reported by the patient or noted by the investigator.	
Statistical methods:	All randomized patients who had used at least one dose of the study drugs were considered in the Intent-to-treat (ITT) population. From this total, the patients without any major protocol violation were considered in the Per-Protocol (PP) population. Major protocol violations were defined independently of the identification of the treatment, however, took part of the PP population only the patients who achieved at least one densitometric evaluation of the forearm proximal region (33% radius region) for fractured side at V0 and V4. The efficacy and safety analyses were conducted based on the ITT population and the analysis involving the primary objective were also performed based on PP population. The demographic variables of continuous nature were described separately for the two treatment groups by the mean, standard deviation and range and the comparison of the treatment groups was indicated by the p-value of the t-Student Test. The discrete demographic variables were summarized in frequency tables and the comparison of the treatment groups was based on the p-value of the Chi-square or Fisher's test, depending on the frequency of the events. All tests applied were performed using SAS v9.1 and it was adopted a statistical significance level of 5%.	

Statistical methods (continuation):	Primary analysis It was applied the U-Mann-Whitney Test (independent observations) for the comparison of the Treatments groups on the T-Score changes (%) from Visit V0 to visit V4 and from Visit V0 to visit V5. It was applied the Wilcoxon-Signed Rank test (dependent observations) for compare the Visits (V4 and V5) on the T-Score changes (%), in each treatment group. Secondary analysis - To compare treatments groups across visits concerning T-Score mean it was applied an Analysis of Variance (ANOVA) model, with the factors Group of Treatment ("Sodium Risedronate + Calcium and vitamin D" and "Calcium and vitamin D"), Visits (V0, V4 and V5) and the respective interaction between them. - To compare the treatments groups concerning the radiological identification of the callus it was applied the Chi-Square or F-Fisher's Test, according to the frequency of the events. Sample size definition The total number of patients recruited should be of 140 patients (70 per group).The calculation was based in the comparison of the groups with respect to the mean, expressed in percentage, of the BMD change after 90 days of treatment. It was adopted a power of 80%, a significance level of 5% and a drop-out rate of 10%. It was assumed a standard deviation of 0.08, and a difference of interest of 4% between the groups (mean percentage of BMD change after 90 days of treatment).

Summary:	Patients enrollment Between 07-Mar-2007 and 22-Feb-2011, 180 patients were enrolled to the study. From this total, 141 patients were randomized to the study treatments: 71 (50.4%) to the *Risedronate sodium + Calcium and vitamin D Group* and 70 (49.6%) to the *Calcium and vitamin D Group*. Demographic data The age of the patients at time of inclusion ranged from 44 to 90 years, with a mean age of 67.1 (SD=10.9) years for *Risedronate sodium + Calcium and vitamin D Group* and from 44 to 92 years, with a mean age of 64.9 (SD=10.4) years for the *Calcium and vitamin D Group*. There was no statistically significant difference between them (p-value=0.224). In the *Risedronate sodium + Calcium and vitamin D Group*, 38/71 (53.5%) patients presented age ≥ 65 years and in the *Calcium and vitamin D Group*, 36/70 (51.4%) patients. In both treatments groups the most of women were Caucasian (70.4% in *Risedronate sodium + Calcium and vitamin D Group* and 81.4% in *Calcium and vitamin D Group*), with a p-value of 0.439. In the *Risedronate sodium + Calcium and vitamin D Group,* the women were in menopause from 3 to 55 years, with a mean of 19.8 (SD=12.1) years and in the *Calcium and vitamin D Group* between 2 and 43 years, with a mean of 18.3 (SD=9.8) years. There was no statistically significant difference between groups (p-value=0.439). Colles'fracture The elapsed mean time between the occurrence of Colles'fracture and Visit V0 was 3.5 (SD=1.7) days and 3.4 (SD=1.8) days for *Risedronate sodium + Calcium and vitamin D* and *Calcium and vitamin D* groups, respectively (p-value=0.580). There was no statistically significant difference between the treatment groups about the side of the fracture (p-value=0.670): 36/71 (50.7%) patients and 38/70 patients (54.3%) had the Colles'fracture in the left side in the *Risedronate sodium + Calcium and vitamin D* and in the *Calcium and vitamin D group*, respectively. For the most of patients the universal classification of the Colles'fracture was I or II/IIa: 15/71 (21.1%) patients and 46/71 (64.8%) respectively, for *Risedronate sodium + Calcium and vitamin D* group and 16/70 (22.9%) patients and 43/70 (61.4%) patients respectively, for *Calcium and vitamin D* Group (p-value=0,917).

Summary (continuation):

T-Score results at Visit V0

There was no statistically significant difference between the treatment groups about Bone Mineral Density evaluated by T-Score at Visit V0, in the fractured and non-fractured forearm, lumbar spine, femoral neck and femoral total (Table 1).

Table 1. T-score results at visit V0.

	RS+Ca+VitD N=71	Ca+VitD N=70	p-value
Non-fractured fore arm			
n (%)	71 (100.0%)	69 (98.6%)	
mean (SD)	-2.8 (1.4)	-2.7 (1.5)	0.542
min ; max	-6.0 ; 0.3	-6.6 ; 1.1	
n (%) ≤ - 2	55 (77.5%)	53 (75.7%)	0.927
lumbar spine			
n (%)	71 (100.0%)	70 (100.0%)	
mean (SD)	-2.9 (0.9)	-2.8 (1.0)	0.533
min ; max	-5.4 ; -0.1	-5.8 ; -0.2	
n (%) ≤ - 2	64 (90.1%)	58 (82.9%)	0.205
femoral neck			
n (%)	71 (100.0%)	70 (100.0%)	
mean (SD)	-2.2 (0.9)	-2.0 (1.1)	0.277
min ; max	-3.8 ; -0.4	-4.6 ; 0.4	
n (%) ≤ - 2	44 (62.0%)	41 (58.6%)	0.680
femoral total			
n (%)	71 (100.0%)	70 (100.0%)	
mean (SD)	-1.8 (0.9)	-1.7 (1.1)	0.515
min ; max	-3.8 ; 0.2	-4.1 ; 0.4	
n (%) ≤ - 2	31 (43.7%)	26 (37.1%)	0.430
Fractured fore arm			
n (%)	68 (95.8%)	66 (94.3%)	
mean (SD)	-2.6 (1.4)	-2.4 (1.5)	0.594
min ; max	-6.0 ; 0.4	-6.4 ; 0.9	
n (%) ≤ - 2	44 (62.0%)	43 (61.4%)	0.957

Treatment adherence

The most of patients in both groups had used at least 80% of the total number of tablets planned per visit (Table 2).

Table 2. Usage of at least 80% of the number of tablets planned.

Visits	V1	V2	V3	V4	V5
Actonel					
RS+Ca+VitD					
N	70	69	68	63	59
n (%)	68 (97.1)	69 (100)	68 (100)	62 (98.4)	58 (98.3)
Oscal					
Ca+VitD					
N	70	69	68	63	59
n (%)	68 (97.1)	68 (98.6)	67 (98.5)	62 (98.4)	59 (100)
Oscal Group					
N	67	65	63	60	56
n (%)	67 (100)	64 (98.5)	62 (98.4)	58 (96.7)	53 (94.6)

Efficacy results:

Changes in T-score of the forearm proximal region (33% radius region), expressed in percentage, at 90 and 180 days of treatment.

For fractured side, about the changes in T-score (%) from V0 to visits V4 and V5, it was possible to observe that the BMD (evaluated by T-score) decreased from V0 to Visit V4 (D90) and to Visit V5 (D180) in both treatment groups, with decreases ranging from 20.8% to 32.8% (Table 3).

It was also possible to note a tendency of a greater decrease in BMD (evaluated by T-score) for the patients treated only with *Calcium and vitamin D* (V4: -31.9%; V5: -32.8%) than in the patients treated with *Risedronate sodium + Calcium and vitamin D* (V4: -25.7%; V5: -20.8%). However, there was not a statistically significant difference between groups in both visits: (V4: p-value=0.352 and V5: p-value=0.069) (Table 3).

Comparing the visits V4 and V5 for T-score changes, in each group, there was not a statistically significant difference between them, for both treatment groups: (*Risedronate sodium + Calcium and vitamin D*: p-value=0.727; *Calcium and vitamin D*: p-value=0.769) (Table 3).

Table 3. Changes in T-score of the forearm proximal region (33% radius region), expressed in percentage – fractured side – ITT population.

	Visit V4	Visit V5	p-value[1] (Visits)
RS+Ca+VitD			
N° patients	N = 59	N = 59	
mean (SD)	-25.7%(40.7%)	-20.8% (39.5%)	
min./med./max.	-200% / -15.2% / 27.8%	-200% / -9.1% / 15.4%	0.727
Ca+VitD			
N° patients	N = 57	N = 56	
mean (SD)	-31.9% (62.5%)	-32.8% (68.0%)	
min./med./max.	-400% / -21.4% / 75%	-366.7% / -18.9% / 90%	0.769
p-value (Groups)	0.352	0.069	

[1]: Wilcoxon signed rank Test; [2]: U-Mann-Whitney Test

It is showed below the primary analysis for the PP population. It was excluded the patients with Visit V4 out of the defined timeline window (90±3 days), patients with non adherence to the study at visit V4 (< 80% of the planned treatment medication was used) and T-Score performed out of the defined timeline window (21 days after Colles'fracture) (Table 4).

It was observed a greater BMD decreases (evaluated by T-score) in the *Calcium and vitamin D* group than in the *Risedronate sodium + Calcium and vitamin D* group, however there was not a statistically significant difference between them (p-value=0.110) (Table 4).

Table 4. Changes in T-score of the forearm proximal region (33% radius region), expressed in percentage – fractured side – PP population

	Visit V4
RS+Ca+VitD	
N° patients	N = 45
mean (SD)	-24.6% (41.9%)
min./med./max.	-200% / -15.2% / 27.8%
Ca+VitD	
N° patients	N = 46
mean (SD)	-27.4% (30.8%)
min./med./max.	-166.7% / -23.0% / 20%
p-value [2] (Groups)	0.110

[2]: U-Mann-Whitney Test

For non-fractured side, about the changes in T-score (%) from V0 to visits V4 and V5, it was possible to observe that the BMD (evaluated by T-score) ranged from 4.2% (increase from V0 to Visit V4-D90) to -6.0% (decrease V0 to Visit V5-D180) (Table 5).

At visit V4 there was observed a greater BMD increase (evaluated by T-score) in the *Calcium and vitamin D* group (4.2%) than in the Risedronate sodium + Calcium and vitamin D group (1.9%) and, at visit V5, there was a BMD decrease (evaluated by T-score) for both groups, greater in *Calcium and vitamin D* group (-5.7%) than in the *Risedronate sodium + Calcium and vitamin D* group (-2.2%) (Table 5).

There was not a statistically significant difference between groups in both visits: (V4: p-value=0.438 and V5: p-value=0.861) and neither between visits for both treatment groups (*Risedronate sodium + Calcium and vitamin D*: p-value=0.223; *Calcium and vitamin D*: p-value=0.128) (Table 5).

Table 5. Changes in T-score of the forearm proximal region (33% radius region), expressed in percentage – non-fractured side – ITT population.

	Visit V4	Visit V5	p-value [1] (Visits)
RS+Ca+VitD			
N° patients	N = 59	N = 59	
mean (SD)	1.9% (17.4%)	-2.2% (28.2%)	
min./med./max.	-36.4% / 0% / 79.2%	-133.3% / 0% / 75.5%	0.223
Ca+VitD			
N° patients	N = 57	N = 56	
mean (SD)	4.2% (37.4%)	-5.7% (29.8%)	
min./med./max.	-142.9% / 3.8% / 150%	-142.9% / 0% / 34.6%	0.128
p-value [2] (Groups)	0.438	0.861	

[1]: Wilcoxon signed rank Test; [2]: U-Mann-Whitney Test

T-score mean of the forearm proximal region (33% radius region) along to the visits (V0, V4 and V5).

Between V0 and V4 (D90), in the fractured side, it was observed that the most of the patients, in both treatment groups, had a loss of BMD (worsening of T-score at V4): 46/63 (73.0%) patients in the *Risedronate sodium + Calcium and vitamin D* group and 46/60 (76.7%) patients in the *Calcium and vitamin D* group. The mean (SD) of the BMD loss between V0 and V4 was -0.5 (0.4) for the *Risedronate sodium + Calcium and vitamin D* group and -0.7 (0.4) for the *Calcium and vitamin D* group. On the other hand, in the non-fractured side, about 30% of the patients in both groups had a loss of BMD between Visits V0 and V4 (D90) (Table 6).

About the proportion of patients with BMD loss at V4, there was a statistically significant difference between sides fractured and non-fractured for both treatment groups (*Risedronate sodium + Calcium and vitamin D*: p-value<0.0001; Calcium and vitamin D: p-value<0.0001) (Table 6) This different pattern observed between forearm sides it was probably related to the immobilization of the fractured side.

Comparing V0 and V5 (D180), In the fractured side, there was observed a loss of BMD (worsening of T-score at V5) for 39/59 (66.1%) patients in *the Risedronate sodium + Calcium and vitamin D* group and for 43/56 (76.8%) patients in the *Calcium and vitamin D* group. The mean (SD) of the BMD difference between V5 and V0 was -0.5 (0.4) for the *Risedronate sodium + Calcium and vitamin D* group and -0.7 (0.4) for the *Calcium and vitamin D* group. In the non-fractured side, about 42% of the patients, in both groups, had a loss of BMD between Visits V0 and V5 (D180) (Table 7).

About the proportion of patients with BMD loss at V5, there was a statistically significant difference between sides fractured and non-fractured for both treatment groups (*Risedronate sodium + Calcium and vitamin D*: p-value=0.010; Calcium and vitamin D: p-value=0.0003) (Table 7) This different pattern observed between groups it was probably related to the immobilization of the fractured side (Table 7).

Table 6. BMD loss in the forearm proximal region (33% radius region) between visits V0 and V4 (D90) – ITT population.

	RS+Ca+VitD	*Ca+VitD*
fractured		
n	63	60
BMD loss	46 (73.0%)	46 (76.7%)
mean (SD)	-0.5 (0.4)	-0.7 (0.4)
non-fractured		
n	63	60
BMD loss	19 (30.2%)	20 (33.3%)
mean (SD)	-0.3(0.3)	-0.4 (0.3)
p-value [1]	<0.0001	<0.0001

[1]: Chi-square Test;

Table 7. BMD loss in the forearm proximal region (33% radius region) between visits V0 and V5 (D180) – ITT population.

	RS+Ca+VitD	*Ca+VitD*
fractured		
n	59	56
BMD loss	39 (66.1%)	43 (76.8%)
mean (SD)	-0.5 (0.4)	-0.7 (0.4)
non-fractured		
n	59	56
BMD loss	25 (42.4%)	24 (42.9%)
mean (SD)	-0.3(0.3)	-0.3 (0.2)
p-value [1]	0.022	0.001

[1]: Chi-square Test;

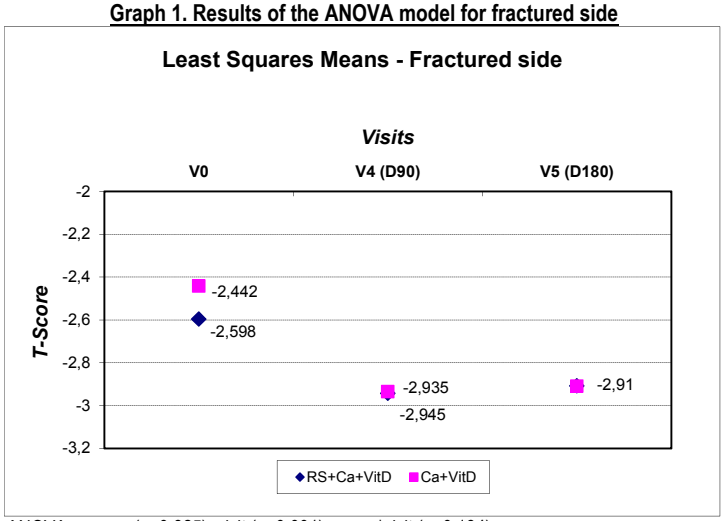
To compare treatments groups across visits concerning T-Score mean it was applied an Analysis of Variance (ANOVA), with the factors Group of Treatment (*Risedronate sodium + Calcium and vitamin D* and *Calcium and vitamin D*), Visits (V0, V4 and V5) and the respective interaction between them in the model.

The result of that analysis showed that there was not evidence of a significant interaction between factors "group" and "visit" for fractured side (p = 0.134) neither for non-fractured side (p = 0.982), indicating that the two treatment groups had a similar pattern across time (visits) (Graphs 1 and 2).

For the fractured side it was observed a statistically significant difference among visits, the mean value of T-scores at V4 and at V5 were significantly lower than the mean score at V0 (p <0.001). There was not an evidence of a significant difference between treatment groups (p-value=0.825) (Graph 1).

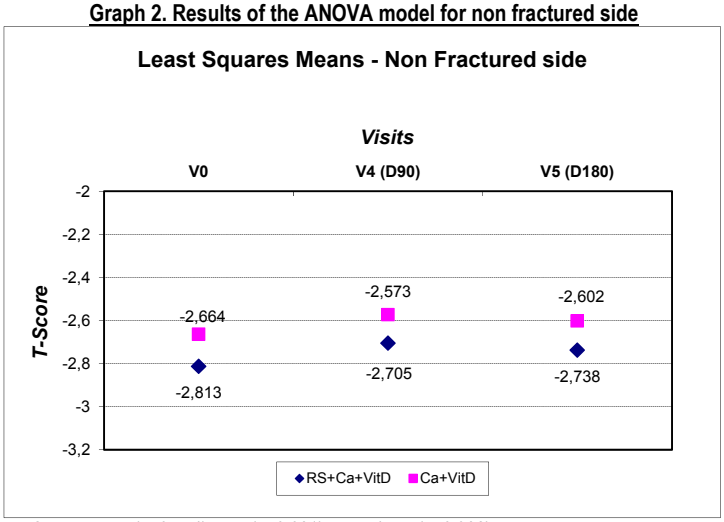
For the non-fractured side it was not observed an evidence of statistically significant difference between groups (p = 0.554) neither between visits (p = 0.081) (Graph 2).

Graph 1. Results of the ANOVA model for fractured side



ANOVA – group (p=0.825); visit (p<0.001); group*visit (p=0.134)

Graph 2. Results of the ANOVA model for non fractured side



ANOVA – group (p=0.554); visit (p=0.081); group*visit (p=0.982)

	Radiological identification of the callus In the Table 8 below is showed the results by visit of the radiological identification of the callus. There was not an evidence of a significant difference between treatment groups at visits V1 (p-value=0.674), V2 (p-value=0.755) and V3 (p-value=0.749) in the proportion of patients for which the callus was identified at the X-Ray. At the other visits, V4 and V5, the callus identification in the X-Ray occurred for almost all patients, in both groups, and thus no statistical comparison was made. **Table 8. Radiological identification of the callus by X-Ray – ITT population.** **Visits** | **V1** | **V2** | **V3** | **V4** | **V5** **RS+Ca+VitD** N | 70 | 69 | 68 | 63 | 59 n (%) | 2 (2.9%) | 20 (29.0%) | 62 (91.2%) | 62 (98.4) | 58 (98.3) **Ca+VitD** N | 67 | 65 | 63 | 60 | 56 n (%) | 3 (4.5%) | 17 (26.2%) | 56 (93.3%) | 60 (100%) | 54 (96.4)
Safety results:	From the 71 patients randomized to the *Risedronate sodium + Calcium and vitamin D* Group, 23 (32.4%) patients had reported at least one adverse event (AE) during the study period, totalizing 34 events. From the 70 patients randomized to the *Calcium and vitamin D* Group, 23 (32.9%) patients had reported adverse event (AE) during the study period, totalizing 41 events. Three events were considered by the investigator as serious (SAE): - Re-fracture of left wrist – moderate intensity; required hospitalization and surgery for external fixation; patient recovered; *Risedronate sodium + Calcium and vitamin D* Group. - Hypoechoic collection in the right calf – moderate intensity; required hospitalization; patient was recovering at the time of reporting (July 27th 2011); *Calcium and vitamin D* Group. - Cardiorespiratory arrest at home – severe intensity; caused the patient death; *Calcium and vitamin D* Group. None of the three SAEs were considered by the investigator as related to the study medication. In the *Calcium and vitamin D* Group, both SAEs lead to the treatment interruption. For the patient in the *Risedronate sodium + Calcium and vitamin D* Group, the medication was not immediately interrupted due to the SAE, but the event was the cause of study withdrawal (Table 9). A total of 3 patients presented treatment withdrawal due to an adverse event related to the study treatment: 1/71 patient (1.4%) in the *Risedronate sodium + Calcium and vitamin D* Group had Acute Gastritis and in the *Calcium and vitamin D* Group, one patient (1.4%) had heartburn and gastric discomfort and another one (1.4%) reported epigastralgia. Another two patients were treatment withdrawal unrelated to the study medication: in *Calcium and vitamin D* Group, for one patient was reported cardiorespiratory arrest and for another one psychotic outbreak and Hypoechoic collection in the right calf (Table 9).

	Table 9. Patients reporting any Adverse Event

Adverse Event	Risedronate sodium + Calcium and vitamin D ® Group		Calcium and vitamin D ® Group	
	Patients N=71 (%)	Nº of Events	Patients N=70 (%)	Nº of Events
Any	23 (32.4)	34	23 (32.9)	41
Related to study medication: *Risedronate sodium*	4 (5.6)	4		
Related to study medication: *Calcium and vitamin D*	1 (1.4)	1	4 (5.7)	7
Serious	1 (1.4)	1	2 (2.9)	2
Serious and related to study medication	-	-	-	-
Outcome: causing death[1]	-	-	1 (1.4)	1
Related and causing death	-	-	-	-
Leading to treatment withdrawal: *Risedronate sodium*	1 (1.4)	1		
Leading to treatment withdrawal: *Calcium and vitamin D*	-	-	4 (5.7)	6
Related and leading to treatment withdrawal: *Risedronate sodium*	1 (1.4)	1		
Related and leading to treatment withdrawal: *Calcium and vitamin D*	-	-	2 (2.9)	3

[1] Cardiorespiratory arrest at home (patient in *Calcium and vitamin D* Group).

Date of issue:	15 October 2012