Clinical trial results:
A 24 months, prospective, randomised, double-blind study to assess the effect of daily oral administration of 2 g of strontium ranelate versus placebo on bone mineral density in postmenopausal osteoporotic women previously treated with bisphosphonates (following Amendment No. 4, instead of oral bisphosphonates initially planned in the study protocol).

Summary

EudraCT number	2011-000708-17
Trial protocol	DE AT BE HU
Global end of trial date	26 June 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CL3-12911-038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2014
Global end of trial reached?	Yes
Global end of trial date	26 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effect of daily oral administration of 2 g of strontium ranelate versus placebo over 24 months of treatment on the lumbar areal bone mineral density in postmenopausal women with osteoporosis previously treated with bisphosphonates (instead of "oral bisphosphonates", as per Amendment No. 4).

Protection of trial subjects:

The study was to be prematurely discontinued for a patient for one of the following reasons: adverse events (considered or not as related to the study drug or to the study procedures and which could modify the benefice/risk ratio for the patient according to the investigator's opinion, as added by Amendment No. 1), protocol deviation, non-medical reason, lost to follow-up.
The study was to be imperatively discontinued (as specified by Amendment No. 1) for a patient in case of lack of efficacy being defined as BMD decrease ≥ 5% (relative change versus baseline) at one or more sites (lumbar L1-L4, femoral neck or total hip), with a T-score at baseline ≤ -2.0 SD as added by Amendment No. 5, or two or more new osteoporotic non-traumatic major fractures (vertebral, hip or humerus).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	France: 1
Worldwide total number of subjects	83
EEA total number of subjects	83

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	65
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

In all, 9 centres located in 6 countries, 83 postmenopausal women with osteoporosis previously treated with bisphosphonates (instead of "oral bisphosphonates" as per Amendment No.4)

Pre-assignment

Screening details:

Planned: 160 patients, 80 in the strontium ranelate (SrRan) group and 80 in the placebo group.
Included: 83 patients, 39 in the SrRan group and 44 in the placebo group.
Due to difficulties in patient's recruitment, the number of included patients was much lower than initially planned.
Run-in period: 1-4 weeks from selection to inclusion visit.

Period 1

Period 1 title	Double blind treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SrRan 2 g

Arm description:

All patients received strontium ranelate 2 g

Arm type	Test drug
Investigational medicinal product name	Strontium ranelate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Patients had to take one sachet of granules containing 2 g of strontium ranelate once daily in the evening at bedtime, preferably at least 2 hours after eating.
The sachet must not be taken with food, milk and derivate products, and medicinal products containing calcium. The powder was to be placed into the glass first, and the tap water added thereafter, stirring at the same time. The suspension was to be taken immediately and patients should not wait longer than 24 hours before drinking the suspension. If a delay between the preparation and consumption occurred, the suspension had to be stirred again.

Arm title	Placebo

Arm description:

Patients recieved Placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Patients had to take one sachet of granules containing placebo once daily in the evening at bedtime, preferably at least 2 hours after eating.
The sachet must not be taken with food, milk and derivate products, and medicinal products containing calcium. The powder was to be placed into the glass first, and the tap water added thereafter, stirring at the same time. The suspension was to be taken immediately and patients should not wait longer than

24 hours before drinking the suspension. If a delay between the preparation and consumption occurred, the suspension had to be stirred again.

Number of subjects in period 1	SrRan 2 g	Placebo
Started	39	44
Completed	7	3
Not completed	32	41
non-medical reason	2	3
Adverse event, non-fatal	6	-
Study termination	18	25
Lack of efficacy	1	9
Protocol deviation	5	4

Baseline characteristics

Reporting groups	
Reporting group title	SrRan 2 g
Reporting group description:	
All patients received strontium ranelate 2 g	
Reporting group title	Placebo
Reporting group description:	
Patients recieved Placebo.	

Reporting group values	SrRan 2 g	Placebo	Total
Number of subjects	39	44	83
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	11	16
From 65-84 years	33	32	65
85 years and over	1	1	2
Gender categorical Units: Subjects			
Female	39	44	83
Male	0	0	0

End points

End points reporting groups

Reporting group title	SrRan 2 g
Reporting group description:	
All patients received strontium ranelate 2 g	
Reporting group title	Placebo
Reporting group description:	
Patients recieved Placebo.	
Subject analysis set title	Randomised set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All included patients to whom a therapeutic unit was randomly assigned at M0.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
This set corresponded to patients who had taken at least one dose of study treatment.	

Primary: Lumbar areal BMD (L1-L4)

End point title	Lumbar areal BMD (L1-L4)[1]
End point description:	
The main criterion was the lumbar areal BMD (L1-L4) (g/cm²) assessed by DXA over 24 months of treatment, expressed as value at each visit.	
End point type	Primary
End point timeframe:	
Mean value at baseline and at each post-baseline visit of lumbar L1-L4 BMD.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Efficacy analysis was carried out on the Randomised Set. Due to the premature stop of the study, only descriptive statistics at each visit was performed for the primary criteria.

End point values	SrRan 2 g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	44		
Units: g/cm²				
arithmetic mean (standard deviation)	0.8225 (± 0.0965)	0.8343 (± 0.0997)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Over the course of the study (M0-M24)

Adverse event reporting additional description:

Before starting treatment and at regular intervals, patients were to be evaluated with respect to cardiovascular risk. Patients with significant risk factors for cardiovascular events were to be closely monitored, and initiation and continuation of the treatment had to be carefully assessed based on the individual patient's overall risks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	SrRan 2 g
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	SrRan 2 g	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 39 (28.21%)	8 / 44 (18.18%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye operation complication			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iris operation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval warts removal			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Restless legs syndrome			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			

subjects affected / exposed	1 / 39 (2.56%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iris cyst			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterovaginal prolapse			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 39 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis membranous			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bartholin's abscess			
subjects affected / exposed	1 / 39 (2.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SrRan 2 g	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)	30 / 44 (68.18%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 39 (12.82%)	7 / 44 (15.91%)	
occurrences (all)	5	7	
Contusion			
subjects affected / exposed	4 / 39 (10.26%)	6 / 44 (13.64%)	
occurrences (all)	4	6	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 39 (7.69%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	2 / 39 (5.13%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 39 (7.69%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 39 (7.69%)	2 / 44 (4.55%)	
occurrences (all)	3	3	
Abdominal pain upper			
subjects affected / exposed	2 / 39 (5.13%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
Abdominal distension			
subjects affected / exposed	2 / 39 (5.13%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Depression			
subjects affected / exposed	2 / 39 (5.13%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 39 (5.13%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 39 (15.38%)	4 / 44 (9.09%)	
occurrences (all)	7	4	
Arthralgia			
subjects affected / exposed	2 / 39 (5.13%)	4 / 44 (9.09%)	
occurrences (all)	2	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 39 (25.64%)	10 / 44 (22.73%)	
occurrences (all)	12	12	
Bronchitis			
subjects affected / exposed	5 / 39 (12.82%)	4 / 44 (9.09%)	
occurrences (all)	5	4	
Upper respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)	1 / 44 (2.27%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2011	Amendment N°1: The non-selection criterion "Participant belonging to any of the following categories: incarcerated persons, subjects in an emergency situation, patients with severe mental disorders, patients legally incapacitated" has been completed by the mention "patients who are placed in an institution following official or judicial order". This has been added in the corresponding section of the protocol. The criterion for the discontinuation of the study has been detailed by adding that the study can be prematurely interrupted in case of any new findings, which can modify the benefit/risk ratio in patients. The withdrawal criteria have been detailed by adding that the study may be prematurely discontinued for a participant for one of the following reasons: adverse events, considered or not as related to the study drug or to the study procedures and which could modify the benefice/risk ratio for the patient according to the investigator's opinion, protocol deviation, non medical reason, lost to follow-up. The study must imperatively be discontinued for a participant in case of: Lack of efficacy being defined as BMD decrease ≥5% (e.g relative change vs.baseline) at one or more sites (lumbar L1-L4, femoral neck or total hip) or two or more new osteoporotic non traumatic major fractures (vertebral, hip or humerus). Information about the packaging and the numbering of the supplementation (Calcimagon®500 and Vigantoletten®1000) has been updated. The originally planned pack size of the supplementation was changed, the number of boxes of Calcimagon®500 and Vigantoletten®1000 given to the patient has been updated consequently. For a clear identification of the supplementation, it will now be numbered. A 6 digits number independent of the patient number will identify this supplementation.
15 February 2012	Amendment N°2: The selection criteria have been modified to select patients with "Osteoporosis with previous bisphosphonate therapy for at least 36 continuous months* before study entry with oral alendronate (70 mg once weekly or 10 mg daily), oral risedronate (35mg once weekly or 5mg daily), or oral ibandronate (150mg once monthly) and last bisphosphonate intake within 2 months before study entry". *An adaequate previous bisphosphonate treatment requires an estimated overall medication posession ratio (MPR) of at least 80% for the last 36 months of bisphosphonate treatment, in general, as well as an estimated recent MPR of at least 80% for the last 12 months before study entry, in particular. The pQCT exams will be performed at M012 in duplicate. The total irradiation for the whole study is 27 µSv with a maximal total irradiation in case of 3 scans per site at each visit is 97 µSv, since repeated measurements might be needed due to movement artifacts or mandatory relocation of a scan. Following the BfS (Bundesamt für Strahlenschutz) approval, the irradiation dose for the hr-QCT measurement is estimated at 5.1 mSv. The investigator has to evaluate and confirm patients' data by documenting them directly in the patient's medical file. Moreover the recruitment process and the documentation of the data used for clinical assessment is described in the internal procedure of the site. The conditions of sampling for the safety biological parameters have been changed, fasting condition is not necessary anymore. Blood samples should be collected before 10:00 am on the morning of the visit. Only CK-MB isoenzyme will be measured in case of CK above upper limit of the reference range. The Sponsors address is modified to 50 rue Carnot, 92284 Suresnes cedex, France in the Protocol.

16 April 2012	Amendment N°3: The non-selection criteria have been updated in the study summary sheet and in the protocol. The non-selection criteria concerning venous thrombotic events has been rephrased as follows: "Current or previous venous thromboembolic events, including deep vein thrombosis and pulmonary embolism, or patients at high risk of venous thromboembolism". A new non-selection criteria was introduced: "Temporary or permanent immobilization due to e.g. post-surgical recovery or prolonged bed rest" The following treatment withdrawal criteria have been added in the Protocol: Treatment should be temporarily or permanently discontinued as soon as possible in the event of an illness or a condition leading to immobilization (for example post-surgical recovery or prolonged best rest). Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. Treatment should also be immediately and permanently discontinued in the following cases: a) venous thromboembolic events; b) presence of symptoms or signs of Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN; e.g. progressive skin rash often with blisters or mucosal lesions) or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS; e.g. rash, fever,eosinophilia and systemic involvement [e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease]). The following precision concerning management of cases of severe hypersensitivity reaction has been added in the protocol, under paragraph 12 "Safety assessments": In all participants experiencing severe hypersensitivity reaction type DRESS, TEN or SJS, the investigator in charge of the patient will receive a letter from the Sponsor with recommendation for additional investigations. A careful monitoring of these events will have to be performed.
20 August 2012	Amendment N°4: The title of the study has been modified to "A 24 months, prospective, randomized, double-blind study to assess the effect of daily oral administration of 2 g of strontium ranelate versus placebo on bone mineral density in postmenopausal osteoporotic women previously treated with bisphosphonates". The recruitment period has been extended by 9 months. Thus, the Study completion date (LVLP) has been postponed to September 2015 in the Study Summary Sheet. The selection criteria have been modified to select patients with "Osteoporosis with previous bisphosphonate therapy before study entry for at least 30 months among the last 5 years, and last bisphosphonate intake within 6 months before study entry. Bisphosphonate therapy includes oral alendronate (70 mg once weekly or 10 mg daily), oral risedronate (35 mg once weekly or 5 mg daily), oral ibandronate (150 mg once monthly) or intravenous ibandronate (3 mg/3 months). *An adequate previous bisphosphonate treatment requires an estimated recent medication possession ratio (MPR) of at least 75% in the last year of bisphosphonate treatment.

18 December 2012	Amendment N°5: The study is now a multicentric study. The wording has been adapted within the all protocol (i.e. "the center" became "each center"). The following sections have been updated: Study summary sheet: Coordinator(s), Study centre(s), Methodology and Statistical methods. Administrative structure of the study: International Coordinator, National Coordinators and Structure responsible for local management of the study. Procedure for an event requiring immediate notification: Persons to be contacted in ICTR. Measures to minimize bias. Statistical analysis. Hr-QCT and p-QCT will not be performed in new countries. Hr-QCT will be performed only in the International Coordinator's centre and p-QCT will be performed only in Germany. Thus, the following sections have been updated: Study summary sheet: Secondary objectives, Main non-selection/non-inclusion criteria and Secondary efficacy criteria. Investigational schedule. Medical and therapeutic criteria. Assessment of bone geometry and bone strength by p-QCT: Method of investigation and measurement time. Hr-QCT Th12 (spiral CT): Method of investigation. Statistical analysis concerning p-QCT and Hr-QCT. BMD and VFA assessment will be performed by a Lunar® or a Hologic® device. Thus, the following sections have been updated: Assessment of BMD measurement by DXA. Vertebral Fracture Assessment. Local specificities of the International Coordinator's centre have been implemented with general information to take into account all additional centres. Thus, the following sections have been updated: Study summary sheet: Main non-selection/non-inclusion criteria. Non sponsor parties. Investigational schedule. Products administered. Treatment management. Previous bisphosphonate therapy. Participant information and informed consent. Other modifications: The criteria and procedure for patient withdrawal have been precised, typing error regarding the composition of the placebo has been deleted. Administrative sponsor updated.
17 May 2013	Amendment N°6: Selection criteria have been updated in order to specify that selected patients should have a high risk of fracture. The non-selection criteria have been also updated. The non-selection criterion concerning cardiac ischaemic events has been introduced: "Current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease". Patients with not adequately controlled hypertension were already not selected in the study. The following treatment withdrawal criteria have been added: "Treatment should be permanently discontinued as soon as possible in the event of uncontrolled hypertension, or in the event of the treatment is considered as no longer appropriate by the investigator e.g. in case of significant cardiovascular risk factors.", "Treatment should be immediately and permanently discontinued in the case of current or past ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease." Before starting treatment and at regular intervals, patients should be evaluated with respect to cardiovascular risk. Patients with significant risk factors for cardiovascular events will be closely monitored, and initiation and continuation of the treatment will be carefully assessed based on the individual patient's overall risks. For this reason, additional safety measurements have been added to the protocol: additional blood pressure measurements at M003, M006 and M018 visits, and blood biological parameters (HDL and LDL cholesterol, triglycerides, glycaemia, under fasting conditions) at the selection, M006, M012, M018 and M024 visits. Thus, the following sections have been updated: Investigational schedule, Safety measurements, Clinical safety, Biological safety, Safety. The procedure to be followed in case of premature discontinuation of the study has been adapted. The last visit last patient date, list of investigation and administrative sponsor(s) parties have been updated.

05 July 2013	Amendment N°7: only for BEL, DEU, FRA , HUN and POL. Calicmagon®500 is replaced by Orocal®500, 60 tablets per box. Thus, the following sections have been updated: - Study summary sheet: Precaution with supplementations. - Products administered (Paragraph 8.4.1.). - Treatment management (Paragraph 8.4.2.). - Treatments administered (Paragraph 10.1.). - Previous and concomitant treatments (Paragraph 10.3.). Paragraph 8.4.1. (Products administered) has also been updated regarding the number of tablets in each box of Vigantoletten®1000. The last visit last patient date has been updated in the study summary sheet. Paragraph 12.2.2. has been updated to inform that results of all biological safety parameters are reported in the e-CRF by the investigator. A typing error has been corrected in Paragraph 8.3..
05 July 2013	Amendment N°8: only for AUT. The selection criteria have been updated in order to specify that selected patients should have taken bisphosphonate therapy for at least 60 months before their participation in the study. Calicmagon®500 is replaced by Orocal®500, 60 tablets per box. Thus, the following sections have been updated: - Study summary sheet: Precaution with supplementations. - Products administered (Paragraph 8.4.1.). - Treatment management (Paragraph 8.4.2.). - Treatments administered (Paragraph 10.1.). - Previous and concomitant treatments (Paragraph 10.3.). Paragraph 8.4.1. (Products administered) has also been updated regarding the number of tablets in each box of Vigantoletten®1000. The last visit last patient date has been updated in the study summary sheet. Paragraph 12.2.2. has been updated to inform that results of all biological safety parameters are reported in the e-CRF by the investigator. A typing error has been corrected in Paragraph 8.3..

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 March 2014	The study was prematurely discontinued, due to difficulties in patients' recruitment. Thus, the study lasted at maximum 2 years, with a mean of about one year.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report.

Notes: