Clinical trial results:
Effect of active vitamin D treatment on arterial stiffness and albuminuria in patients with type 2 diabetes and stage 3 chronic kidney disease

Summary

EudraCT number	2010-018285-23
Trial protocol	GB
Global end of trial date	01 April 2018

Results information

Result version number	v1 (current)
This version publication date	02 June 2019
First version publication date	02 June 2019
Summary attachment (see zip file)	Summary report (Summary Report.pdf)

Trial information

Trial identification

Sponsor protocol code	18102009

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Diabetes Research, King's College London, 0044 02078484413, luigi.gnudi@kcl.ac.uk
Scientific contact	Diabetes Research, King's College London, 0044 02078484413, luigi.gnudi@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Dr Luigi Gnudi, Guy's and St Thomas' NHS Foundation Trust, 0044 02078484413, luigi.gnudi@kcl.ac.uk
Scientific contact	Dr Luigi Gnudi, Guy's and St Thomas' NHS Foundation Trust, 0044 02078484413, luigi.gnudi@kcl.ac.uk

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	01 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2018
Global end of trial reached?	Yes
Global end of trial date	01 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main research question is to evaluate the effect of Calcitriol treatment as compared to placebo on arterial stiffness in patients with type 2 diabetes and chronic kidney disease. Arterial stiffness is a marker and predictor of cardiovascular disease risk. Arterial stiffness will be assessed by aortic pulse wave velocity (Ao-PWV) which is a measure of arterial stiffness. Ao-PWV measures the the speed of transmission of the pulse wave along the aorta the largest blood vessel in the body. The greater the speed the greater the arterial stiffness. Interventions that recuce arterial stiffness may prevent cardiovascular disease.
Currently it is not known if treatment with Calcitriol can affect arterial stiffness in patients with diabetes and kidney disease. We wish to study the effect of Calcitriol or placebo as add on treatment to existing medical treatments on arterial stiffness in a placebo controlled double blind study. Patients will continue with other medical treatments for their

Protection of trial subjects:

Subjects will be provided with a Patient Information Sheet (PIS) and time to consider the contents of this document. They will have the opportunity to discuss alternative treatment options and possible enrolment in the study with the Investigator, prior to providing written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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)	55
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be recruited from outpatient clinics at Guy’s and St Thomas Hospital. Patients referred from primary care or other regional hospitals will be reviewed in the above clinics and recruited if suitable.

Pre-assignment

Screening details:

Patients were eligible to participate if they were diagnosed with Type 2 diabetes and had stage 3 chronic kidney disease.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Calcitriol

Arm description:

0.25 mcg od of calcitriol for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Rocaltrol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.25 µg microgram(s) per day

Arm title	Placebo

Arm description:

Placebo for 48 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule per day

Number of subjects in period 1	Calcitriol	Placebo
Started	72	68
Completed	64	63
Not completed	8	5
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	2
Bereavement	1	-
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial Period

Reporting group description: -

Reporting group values	Overall Trial Period	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
Adults (18-64 years)	55	55	
From 65-84 years	85	85	
Gender categorical Units: Subjects			
Female	40	40	
Male	100	100	

End points

End points reporting groups

Reporting group title	Calcitriol
Reporting group description:	
0.25 mcg od of calcitriol for 48 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo for 48 weeks	

Primary: Change in pulse wave velocity

End point title	Change in pulse wave velocity[1]
End point description:	

End point type	Primary
End point timeframe:	
The mean change from baseline to endpoint. Endpoint will be defined as the last available post-baseline measurement up to and including 48 weeks post randomisation.	

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: Please see attached summary results.

End point values	Calcitriol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: m/s				
arithmetic mean (full range (min-max))	0.05 (-0.68 to 0.78)	0.23 (-0.46 to 0.93)		

Attachments (see zip file)	Summary Report/Summary Report.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from 2 weeks prior to randomisation to 60 weeks post randomisation

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	CALCITRIOL GROUP

Reporting group description:

Subjects randomised to receive calcitriol

Reporting group title	PLACEBO GROUP

Reporting group description: -

Serious adverse events	CALCITRIOL GROUP	PLACEBO GROUP	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 64 (15.63%)	20 / 63 (31.75%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Inferior cerebellar infarction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute infarction of right hemi-pons			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left anterothalamic infarct			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral vascular accident			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis	Additional description: Collapse due to aortic stenosis		
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic heart disease			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical chest pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath with chest pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hyponatraemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear and labyrinth disorders			
Otitis externa	Additional description: Left necrotising externa		
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gall stones			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision hernia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic bowel			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (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			
Bronchogenic cyst	Additional description: Collapse due to bronchogenic cyst		
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Foot infection			

subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
removal of basal cell carcinoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot ulcer			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex virus			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Cellulitis	Additional description: Right foot, debridement of 5th toe		
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right breast infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CALCITRIOL GROUP	PLACEBO GROUP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 64 (73.44%)	45 / 63 (71.43%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Surgical and medical procedures			

Cataract operation			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	2	
Vitrectomy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Insect bite			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Gout			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Hayfever			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Cough			

subjects affected / exposed	5 / 64 (7.81%)	4 / 63 (6.35%)	
occurrences (all)	7	4	
Shortness of breath			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Swelling			
subjects affected / exposed	2 / 64 (3.13%)	4 / 63 (6.35%)	
occurrences (all)	2	4	
Atrial fibrillation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
bilateral peripheral oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Bell's phenomenon			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Loss of consciousness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Dizziness			

subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Faint			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Shaking legs			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Dizzy spells			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Colour vision disturbance			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Laser therapy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Photocoagulation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 64 (3.13%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
heart burn			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Irreducible hernia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Loose stools			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Loss of appetite			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 64 (1.56%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Rectal bleeding			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blister			
subjects affected / exposed	0 / 64 (0.00%)	4 / 63 (6.35%)	
occurrences (all)	0	4	
Cracked skin			

subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Intertrigo			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Lipohypertrophy			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Skin abrasion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Skin rash			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Itchy skin			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
increased urinary frequency			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Nephritis interstitial			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Urethra prolapse			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Renal function deterioration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blood in urine			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Back stiffness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Pain			
subjects affected / exposed	17 / 64 (26.56%)	7 / 63 (11.11%)	
occurrences (all)	17	7	
Painful extemities			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Muscle stiffness			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Fracture			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Muscle cramps			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
trapetiumectomy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infection			
subjects affected / exposed	8 / 64 (12.50%)	9 / 63 (14.29%)	
occurrences (all)	8	9	
Cold			
subjects affected / exposed	5 / 64 (7.81%)	1 / 63 (1.59%)	
occurrences (all)	5	1	
Conjunctivitis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Flu like symptoms			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Influenza			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Ulcer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Nasal infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	2 / 64 (3.13%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
Cellulitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 64 (3.13%)	5 / 63 (7.94%)	
occurrences (all)	2	5	
Urinary tract infection			
subjects affected / exposed	1 / 64 (1.56%)	4 / 63 (6.35%)	
occurrences (all)	1	4	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	

Hypoglycaemia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Hypokalaemia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Testosterone low			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2010	IMP labels amended
21 December 2011	1) Change to Inclusion criteria to add a history of a raised intact parathyroid hormone level between 65 pg/ml and 200pg/ml in the 3 months preceding screening visit (or at screening as previously stated). 2) Clarification of the open label phase of the trial 3) Clarification of the deviation from annex 13 compliant labelling.
18 June 2014	Inclusion criteria amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported