Clinical trial results:
A PROSPECTIVE, RANDOMIZED, CROSS-OVER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE ANTIPROTEINURIC EFFECT OF SELECTIVE VITAMIN D RECEPTOR ACTIVATION BY PARICALCITOL IN TYPE 2 DIABETES PATIENTS ON LOW OR HIGH SODIUM DIET AND STABLE RAS INHIBITOR THERAPY

Summary

EudraCT number	2011-001713-14
Trial protocol	IT
Global end of trial date	29 May 2015
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)	Paper Lancet Diabetes Endocrinol 2017 (Proceed_Paper_2017.pdf) Supplementary appendix (Proceed supplementary.pdf)

Trial information

Trial identification	
Sponsor protocol code	PROCEED
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01393808
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	via G. La Masa 19, Milano MI, Italy, 20156
Public contact	Laboratorio attività regolatorie relative agli studi clinici, Centro di Ricerche Cliniche per le Malattie Rare Aldo e Cele Daccò, 0039 035 453531, paola.boccardo@marionegri.it
Scientific contact	Laboratorio attività regolatorie relative agli studi clinici, Centro di Ricerche Cliniche per le Malattie Rare Aldo e Cele Daccò, 0039 035 453531, paola.boccardo@marionegri.it

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	07 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2015
Global end of trial reached?	Yes
Global end of trial date	29 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The broad aim of this study was to evaluate the interaction between paricalcitol therapy and sodium intake in type 2 diabetes patients with proteinuric kidney disease on stable background RAS inhibitor therapy.
The primary aim was to compare changes in Urinary Albumin Excretion (UAE) rate achieved by one month paricalcitol therapy vs placebo in patients on stable Renin-Angiotensin System (RAS) inhibitor therapy on high (>200 mEq/day) or low (<100 mEq/day) sodium intake.

Protection of trial subjects:

This study was conducted in conformance with Declaration of Helsinki, Good Clinical Practice standards and applicable country regulations regarding ethical committee review, informed consent, protection of human subjects participating in biomedical research and privacy.
We assessed by monitoring of vital signs, physical examination, (BP and heart rate), laboratory tests, adverse event data and documentation of additional medication use, assessed at baseline and at the end of each monthly visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 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	Italy: 115
Worldwide total number of subjects	115
EEA total number of subjects	115

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	56
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All participating centers in Italy were activated between September and October 2011. The recruitment started on October 13, 2011 and concluded on December 18, 2014.

Pre-assignment

Screening details:

195 subjects were screened for inclusion in the study. 115 subjects were randomized. Of those not randomised , 55 did not meet inclusion criteria, 1 was lost to follow up, 22 declined to participate and 2 were excluded for concomitant diseases.

Period 1

Period 1 title	Treatment Period 1 (1 month)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A - Stratum Low Sodium Diet Paricalcitol

Arm description:

Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during Treatment period 1 and received Placebo tablets twice daily for 1 month during Treatment period 3.

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Group B - Stratum Low Sodium Diet Placebo

Arm description:

Participants received placebo tablets twice daily for 1 month during Treatment period 1 and received Paricalcitol 1 micrograms tablets twice daily for 1 month during Treatment period 3. There is one-month wash-out period between Treatment periods 1 and 3

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Arm title	Group C - Stratum High Sodium Diet Paricalcitol

Arm description:

Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 1 and received Placebo twice daily for 1 month during treatment period 3.

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Group D - Stratum High Sodium Diet Placebo

Arm description:

Participants received placebo tablets twice daily for 1 month during treatment period 1 and received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3.

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Number of subjects in period 1	Group A - Stratum Low Sodium Diet Paricalcitol	Group B - Stratum Low Sodium Diet Placebo	Group C - Stratum High Sodium Diet Paricalcitol
Started	28	29	29
Completed	28	28	28
Not completed	0	1	1
Consent withdrawn by subject	-	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	Group D - Stratum High Sodium Diet Placebo
Started	29
Completed	27
Not completed	2
Consent withdrawn by subject	1
Protocol deviation	1

Period 2	
Period 2 title	Treatment period 2 (1 month - washout)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	No
Arm title	Group A - Stratum Low Sodium Diet placebo

Arm description:

Participants received Placebo tablets orally twice daily for 1 month (for patients that were on Paricalcitol during previous period)

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Group B - Stratum Low Sodium Diet placebo

Arm description:

Participants received Placebo tablets orally twice daily for 1 month (for patients that were on Placebo during previous period)

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Group C - Stratum High Sodium Diet placebo

Arm description:

Participants received Placebo tablets (for patients that were on Paricalcitol during previous period)

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Group D - Stratum High Sodium Diet placebo

Arm description:

Participants received Placebo tablets twice daily for 1 month (for patients that were on Placebo during previous period)

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Number of subjects in period 2	Group A - Stratum Low Sodium Diet placebo	Group B - Stratum Low Sodium Diet placebo	Group C - Stratum High Sodium Diet placebo
Started	28	28	28
Completed	27	28	28
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

Number of subjects in period 2	Group D - Stratum High Sodium Diet placebo
Started	27
Completed	27
Not completed	0
Consent withdrawn by subject	-

Period 3

Period 3 title	Treatment period 3 (1 month)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A - Stratum Low Sodium Diet Placebo

Arm description:

Participants received placebo tablets twice daily for 1 month during treatment period 3 and received Paricalcitol 1 microgram tablets twice daily for 1 month during tratment period 1.

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Arm title	Group B - Stratum Low Sodium Diet Paricalcitol

Arm description:

Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3 and received placebo tablets twice daily for 1 month during treatment period 1.

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Group C - Stratum High Sodium Diet Placebo

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Arm title	Group D - Stratum Low Sodium Diet Paricalcitol

Arm description:

Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3 and received Placebo tablets twice daily for 1 month during treatment period 1.

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Number of subjects in period 3	Group A - Stratum Low Sodium Diet Placebo	Group B - Stratum Low Sodium Diet Paricalcitol	Group C - Stratum High Sodium Diet Placebo
Started	27	28	28
Completed	27	26	28
Not completed	0	2	0
Lost to follow-up	-	2	-

Number of subjects in period 3	Group D - Stratum Low Sodium Diet Paricalcitol
Started	27
Completed	27
Not completed	0

Lost to follow-up	-

Period 4

Period 4 title	Stratification and Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Low Sodium Diet

Arm description:

Participants stratified for Low sodium diet (Paricalcitol and Placebo)

Arm type	Diet

No investigational medicinal product assigned in this arm

Arm title	High Sodium Diet

Arm description:

Participants stratified for High sodium diet (Paricalcitol and Placebo)

Arm type	Diet

No investigational medicinal product assigned in this arm

Arm title	Paricalcitol in High Sodium Diet

Arm description:

Participants stratified for High sodium diet who took in Paricalcitol regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Arm title	Placebo in High Sodium Diet

Arm description:

Participants stratified for High sodium diet who took in Placebo regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Arm title	Paricalcitol in Low Sodium diet

Arm description:

Participants stratified for Low sodium diet who took in Paricalcitol regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	
Other name	Zemplar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paricalcitol 1 microgram tablets orally twice daily for 1 month.

Arm title	Placebo in Low Sodium Diet

Arm description:

Participants stratified for Low sodium diet who took in Placebo regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

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

Dosage and administration details:

Placebo tablets orally twice daily for 1 month.

Number of subjects in period 4	Low Sodium Diet	High Sodium Diet	Paricalcitol in High Sodium Diet
Started	57	58	58
Completed	53	55	55
Not completed	4	3	3
Consent withdrawn by subject	2	2	2
Lost to follow-up	2	-	-
Protocol deviation	-	1	1

Number of subjects in period 4	Placebo in High Sodium Diet	Paricalcitol in Low Sodium diet	Placebo in Low Sodium Diet
Started	58	57	57
Completed	55	53	53
Not completed	3	4	4
Consent withdrawn by subject	2	2	2
Lost to follow-up	-	2	2
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A - Stratum Low Sodium Diet Paricalcitol
Reporting group description:	
Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during Treatment period 1 and received Placebo tablets twice daily for 1 month during Treatment period 3.	
Reporting group title	Group B - Stratum Low Sodium Diet Placebo
Reporting group description:	
Participants received placebo tablets twice daily for 1 month during Treatment period 1 and received Paricalcitol 1 micrograms tablets twice daily for 1 month during Treatment period 3. There is one-month wash-out period between Treatment periods 1 and 3	
Reporting group title	Group C - Stratum High Sodium Diet Paricalcitol
Reporting group description:	
Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 1 and received Placebo twice daily for 1 month during treatment period 3.	
Reporting group title	Group D - Stratum High Sodium Diet Placebo
Reporting group description:	
Participants received placebo tablets twice daily for 1 month during treatment period 1 and received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3.	

Reporting group values	Group A - Stratum Low Sodium Diet Paricalcitol	Group B - Stratum Low Sodium Diet Placebo	Group C - Stratum High Sodium Diet Paricalcitol
Number of subjects	28	29	29
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)	11	16	14
From 65-84 years	17	13	15
85 years and over	0	0	0
age	0	0	0
Age continuous			
Units: years			
arithmetic mean	65.0	64.2	64.2
standard deviation	± 6.3	± 8.2	± 10.8
Gender categorical			
Units: Subjects			
Female	0	3	6
Male	28	26	23
Patients taking Losartan alone			
Units: Subjects			
Monotherapy	2	6	4
No monotherapy	26	23	25
Smoke			

Units: Subjects			
Never	6	3	4
Current	7	12	10
Former	15	14	15
Body Mass Index			
Units: kg/m2			
arithmetic mean	31.2	31.4	29.1
standard deviation	± 3.5	± 5.0	± 4.0
Weight			
Units: kg			
arithmetic mean	90.7	91.5	81.1
standard deviation	± 13.7	± 16.7	± 14.6
Systolic Blood Pressure			
Units: mm HG			
arithmetic mean	147.6	148.2	146.3
standard deviation	± 12.0	± 14.1	± 11.4
Diastolic Blood Pressure			
Units: mm Hg			
arithmetic mean	81.1	79.0	79.8
standard deviation	± 5.4	± 7.0	± 5.9
Mean Blood Pressure			
Units: mm Hg			
arithmetic mean	102.9	102.5	101.6
standard deviation	± 6.8	± 7.8	± 6.5
Serum calcium			
Units: mg/dL			
arithmetic mean	9.1	9.1	9.3
standard deviation	± 0.3	± 0.4	± 0.3
Serum Phosphorus			
Units: mg/dL			
arithmetic mean	3.3	3.3	3.5
standard deviation	± 0.4	± 0.6	± 0.5
Serum iPTH			
Units: pg/mL			
arithmetic mean	50.0	50.0	42.1
standard deviation	± 22.4	± 20.0	± 22.1
Serum 25OH vit D			
Units: ng/mL			
arithmetic mean	12.25	12.1	10.6
standard deviation	± 5.7	± 6.4	± 4.6
Serum Glucose			
Units: mg/dL			
arithmetic mean	148.7	149.6	163.8
standard deviation	± 41.4	± 47.9	± 65.0
HbA1C			
Units: Percentual			
arithmetic mean	7.7	7.4	7.8
standard deviation	± 3.4	± 3.2	± 3.7
Serum potassium			
Units: meq/L			
arithmetic mean	4.0	4.2	4.2
standard deviation	± 0.5	± 0.6	± 0.6

Total cholesterol			
Units: mg/dL			
arithmetic mean	166.9	171.9	174.7
standard deviation	± 48.3	± 32.7	± 40.7
HDL cholesterol			
Units: mg/dL			
arithmetic mean	42.5	41	47.5
standard deviation	± 12.1	± 9.6	± 14.2
LDL cholesterol			
Units: mg/dL			
arithmetic mean	94.7	105.4	107.2
standard deviation	± 37.2	± 32.0	± 36.2
Triglycerides			
Units: mg/dL			
arithmetic mean	177.7	164.6	134.8
standard deviation	± 140.5	± 71.1	± 78.5
Hemoglobin			
Units: mg/dL			
arithmetic mean	13.8	13.7	13.5
standard deviation	± 1.4	± 1.5	± 1.5
24 h urinary calcium excretion			
Units: mg			
median	82.7	90.6	76.3
inter-quartile range (Q1-Q3)	43.9 to 123.3	41.1 to 149.7	45.0 to 116.2
Glomerular Filtration Rate			
Units: mL/min/1.73m2			
arithmetic mean	87.33	94.22	81.51
standard deviation	± 21.14	± 33.08	± 26.27
24 h urinary phosphorus excretion			
Units: mg			
median	617.7	763.1	634.3
inter-quartile range (Q1-Q3)	542.7 to 828.5	546.0 to 986.2	429.2 to 860.8
24 h urinary albumin excretion			
Units: mg			
median	749	724	750
inter-quartile range (Q1-Q3)	402 to 1493	449 to 1198	505 to 1338
24 h albumin-to-creatinine ratio			
Units: mg/g			
median	447.0	548.5	604.3
inter-quartile range (Q1-Q3)	355.9 to 1070.9	254.1 to 693.9	421.8 to 806.9
Urinary Sodium Excretion			
Units: mEq/24h			
median	184.4	203.1	200.2
inter-quartile range (Q1-Q3)	157.4 to 229.6	173.5 to 223.4	151.3 to 226.5

Reporting group values	Group D - Stratum High Sodium Diet Placebo	Total	
Number of subjects	29	115	
Age categorical			
Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	15	56	
From 65-84 years	14	59	
85 years and over	0	0	
age	0	0	
Age continuous			
Units: years			
arithmetic mean	64.1		
standard deviation	± 9.1	-	
Gender categorical			
Units: Subjects			
Female	4	13	
Male	25	102	
Patients taking Losartan alone			
Units: Subjects			
Monotherapy	7	19	
No monotherapy	22	96	
Smoke			
Units: Subjects			
Never	11	24	
Current	6	35	
Former	12	56	
Body Mass Index			
Units: kg/m2			
arithmetic mean	31.7		
standard deviation	± 6.1	-	
Weight			
Units: kg			
arithmetic mean	88.7		
standard deviation	± 18.8	-	
Systolic Blood Pressure			
Units: mm HG			
arithmetic mean	143.1		
standard deviation	± 12.6	-	
Diastolic Blood Pressure			
Units: mm Hg			
arithmetic mean	77.9		
standard deviation	± 5.2	-	
Mean Blood Pressure			
Units: mm Hg			
arithmetic mean	99.3		
standard deviation	± 6.4	-	
Serum calcium			
Units: mg/dL			
arithmetic mean	9.2		
standard deviation	± 0.3	-	

Serum Phosphorus			
Units: mg/dL			
arithmetic mean	3.4		
standard deviation	± 0.5	-	
Serum iPTH			
Units: pg/mL			
arithmetic mean	48.2		
standard deviation	± 23.2	-	
Serum 25OH vit D			
Units: ng/mL			
arithmetic mean	12.8		
standard deviation	± 6.6	-	
Serum Glucose			
Units: mg/dL			
arithmetic mean	151.3		
standard deviation	± 56.3	-	
HbA1C			
Units: Percentual			
arithmetic mean	7.0		
standard deviation	± 3.4	-	
Serum potassium			
Units: meq/L			
arithmetic mean	4.1		
standard deviation	± 0.4	-	
Total cholesterol			
Units: mg/dL			
arithmetic mean	176.9		
standard deviation	± 34.4	-	
HDL cholesterol			
Units: mg/dL			
arithmetic mean	43		
standard deviation	± 13.3	-	
LDL cholesterol			
Units: mg/dL			
arithmetic mean	105.1		
standard deviation	± 24.4	-	
Triglycerides			
Units: mg/dL			
arithmetic mean	178.5		
standard deviation	± 125.3	-	
Hemoglobin			
Units: mg/dL			
arithmetic mean	13.1		
standard deviation	± 1.8	-	
24 h urinary calcium excretion			
Units: mg			
median	67.6		
inter-quartile range (Q1-Q3)	55.0 to 136.2	-	
Glomerular Filtration Rate			
Units: mL/min/1.73m2			
arithmetic mean	86.37		
standard deviation	± 34.51	-	

24 h urinary phosphorus excretion Units: mg median inter-quartile range (Q1-Q3)	 779.3 539.1 to 914.5	 -	
24 h urinary albumin excretion Units: mg median inter-quartile range (Q1-Q3)	 658 389 to 1058	 -	
24 h albumin-to-creatinine ratio Units: mg/g median inter-quartile range (Q1-Q3)	 458.5 240.7 to 683.3	 -	
Urinary Sodium Excretion Units: mEq/24h median inter-quartile range (Q1-Q3)	 181.8 144.4 to 223.5	 -	

End points

End points reporting groups

Reporting group title	Group A - Stratum Low Sodium Diet Paricalcitol
Reporting group description:	
Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during Treatment period 1 and received Placebo tablets twice daily for 1 month during Treatment period 3.	
Reporting group title	Group B - Stratum Low Sodium Diet Placebo
Reporting group description:	
Participants received placebo tablets twice daily for 1 month during Treatment period 1 and received Paricalcitol 1 micrograms tablets twice daily for 1 month during Treatment period 3. There is one-month wash-out period between Treatment periods 1 and 3	
Reporting group title	Group C - Stratum High Sodium Diet Paricalcitol
Reporting group description:	
Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 1 and received Placebo twice daily for 1 month during treatment period 3.	
Reporting group title	Group D - Stratum High Sodium Diet Placebo
Reporting group description:	
Participants received placebo tablets twice daily for 1 month during treatment period 1 and received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3.	
Reporting group title	Group A - Stratum Low Sodium Diet placebo
Reporting group description:	
Participants received Placebo tablets orally twice daily for 1 month (for patients that were on Paricalcitol during previous period)	
Reporting group title	Group B - Stratum Low Sodium Diet placebo
Reporting group description:	
Participants received Placebo tablets orally twice daily for 1 month (for patients that were on Placebo during previous period)	
Reporting group title	Group C - Stratum High Sodium Diet placebo
Reporting group description:	
Participants received Placebo tablets (for patients that were on Paricalcitol during previous period)	
Reporting group title	Group D - Stratum High Sodium Diet placebo
Reporting group description:	
Participants received Placebo tablets twice daily for 1 month (for patients that were on Placebo during previous period)	
Reporting group title	Group A - Stratum Low Sodium Diet Placebo
Reporting group description:	
Participants received placebo tablets twice daily for 1 month during treatment period 3 and received Paricalcitol 1 microgram tablets twice daily for 1 month during tratment period 1.	
Reporting group title	Group B - Stratum Low Sodium Diet Paricalcitol
Reporting group description:	
Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3 and received placebo tablets twice daily for 1 month during treatment period 1.	
Reporting group title	Group C - Stratum High Sodium Diet Placebo
Reporting group description: -	
Reporting group title	Group D - Stratum Low Sodium Diet Paricalcitol
Reporting group description:	
Participants received Paricalcitol 1 microgram tablets twice daily for 1 month during treatment period 3 and received Placebo tablets twice daily for 1 month during treatment period 1.	
Reporting group title	Low Sodium Diet
Reporting group description:	
Participants stratified for Low sodium diet (Paricalcitol and Placebo)	
Reporting group title	High Sodium Diet

Reporting group description:

Participants stratified for High sodium diet (Paricalcitol and Placebo)

Reporting group title	Paricalcitol in High Sodium Diet

Reporting group description:

Participants stratified for High sodium diet who took in Paricalcitol regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

Reporting group title	Placebo in High Sodium Diet

Reporting group description:

Participants stratified for High sodium diet who took in Placebo regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

Reporting group title	Paricalcitol in Low Sodium diet

Reporting group description:

Participants stratified for Low sodium diet who took in Paricalcitol regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

Reporting group title	Placebo in Low Sodium Diet

Reporting group description:

Participants stratified for Low sodium diet who took in Placebo regardless of the IMP randomization sequence (Paricalcitol/Placebo or Placebo/Paricalcitol)

Primary: Changes in UAE rate between patients on paricalcitol and placebo on high (>200 mEq/day) or low (<100 mEq/day) sodium intake.

End point title	Changes in UAE rate between patients on paricalcitol and placebo on high (>200 mEq/day) or low (<100 mEq/day) sodium intake.

End point description:

24 h urinary albumin excretion absolute change

End point type	Primary

End point timeframe:

Baseline is at the start of treatment and after treatment is after the 1 month of Paricalcitol or Placebo treatment

End point values	Low Sodium Diet	High Sodium Diet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: mg/24h				
median (inter-quartile range (Q1-Q3))	-33.1 (-128.2 to 56.2)	-108.0 (-273.6 to -24.5)		

Statistical analyses

Statistical analysis title	Changes in UAE

Statistical analysis description:

Changes in UAE between paricalcitol and placebo period, over sodium intake

Comparison groups	Low Sodium Diet v High Sodium Diet

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [1]
Method	ANCOVA

Notes:

[1] - The report p-value is referred to overall patients changes in UAE between paricalcitol and placebo periods.
Changes in patients on High Sodium Diet reported a p-value of 0.09, while changes in patients on Low Sodium Diet reported a p-value of 0.55.

Post-hoc: Changes in UAE at the end of the treatment period 1 (1 month) as compared to baseline in patients on Stratum Low Sodium orHigh Sodium independently of treatment allocation to Placebo or Paricalcitol

End point title	Changes in UAE at the end of the treatment period 1 (1 month) as compared to baseline in patients on Stratum Low Sodium orHigh Sodium independently of treatment allocation to Placebo or Paricalcitol

End point description:

End point type	Post-hoc

End point timeframe:

Baseline to the end of first month of treatment.

End point values	Low Sodium Diet	High Sodium Diet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[2]	55[3]		
Units: mg				
median (inter-quartile range (Q1-Q3))	-144 (-217.4 to -102.2)	-49 (-201.6 to 21.6)		

Notes:

[2] - 1 withdrew consent

[3] - 2 withdrew consent and 1 violated protocol

Statistical analyses

No statistical analyses for this end point

Post-hoc: Changes in UAE at the end of the washout period (1 month) as compared to baseline in patients on Stratum Low Sodium orHigh Sodium independently of treatment allocation to Placebo or Paricalcitol

End point title	Changes in UAE at the end of the washout period (1 month) as compared to baseline in patients on Stratum Low Sodium orHigh Sodium independently of treatment allocation to Placebo or Paricalcitol

End point description:

End point type	Post-hoc

End point timeframe:

Baseline to the second month of treatment.

End point values	Low Sodium Diet	High Sodium Diet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[4]	55[5]		
Units: mg				
median (inter-quartile range (Q1-Q3))	-106.6 (-181.4 to -69.1)	-13 (-115.2 to 116.6)		

Notes:

[4] - 1 withdrew consent during the washout period

[5] - 2 withdtrew consent and 1 violated protocol during the period 1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Changes in UAE at the end of the treatment period 3 (1 month) as compared to baseline in patients on Stratum Low Sodium orHigh Sodium independently of treatment allocation to Placebo or Paricalcitol

End point title	Changes in UAE at the end of the treatment period 3 (1 month) as compared to baseline in patients on Stratum Low Sodium orHigh Sodium independently of treatment allocation to Placebo or Paricalcitol

End point description:

End point type	Post-hoc

End point timeframe:

Baseline to end of third month of treatment.

End point values	Low Sodium Diet	High Sodium Diet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[6]	55		
Units: mg				
median (inter-quartile range (Q1-Q3))	-273.6 (-385.9 to -151.2)	20.2 (-128.2 to 93.6)		

Notes:

[6] - 2 lost to follow-up during the third period

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The adverse events will be reported during whole study up to 30 days after last dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients received Placebo tablets twice daily for 1 month, regardless of sequence.	
Reporting group title	Paricalcitol
Reporting group description:	
Patients received Paricalcitol 1 microgram tablets twice daily for 1 month, regardless of sequence.	

Serious adverse events	Placebo	Paricalcitol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 115 (0.00%)	2 / 115 (1.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Ischaemic heart disease			
subjects affected / exposed	0 / 115 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	0 / 115 (0.00%)	1 / 115 (0.87%)	
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: 0 %

Non-serious adverse events	Placebo	Paricalcitol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 115 (31.30%)	51 / 115 (44.35%)	
Vascular disorders			

Hypotension			
subjects affected / exposed	2 / 115 (1.74%)	0 / 115 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Tinnitus, hands tingling, or dizziness			
subjects affected / exposed	2 / 115 (1.74%)	1 / 115 (0.87%)	
occurrences (all)	2	1	
Fever or asthenia (unspecified)			
subjects affected / exposed	0 / 115 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Immune system disorders			
Allergic reactions, urticaria, or pruritus			
subjects affected / exposed	1 / 115 (0.87%)	1 / 115 (0.87%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Flu-like symptoms, cough, bronchitis, or synusitis			
subjects affected / exposed	2 / 115 (1.74%)	7 / 115 (6.09%)	
occurrences (all)	2	7	
Cardiac disorders			
Legs oedema			
subjects affected / exposed	0 / 115 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache or migraine			
subjects affected / exposed	1 / 115 (0.87%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Thrombocytopenia or anaemia			
subjects affected / exposed	2 / 115 (1.74%)	1 / 115 (0.87%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Gastroenteritis, diarrhoea, or abdominal pain			
subjects affected / exposed	1 / 115 (0.87%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Worsening symptoms of ulcerous colitis			

subjects affected / exposed	0 / 115 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hypophosphaturia			
subjects affected / exposed	2 / 115 (1.74%)	2 / 115 (1.74%)	
occurrences (all)	2	2	
Dermatitis and skin infection			
subjects affected / exposed	0 / 115 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Urinary tract infection or macrohaematuria			
subjects affected / exposed	2 / 115 (1.74%)	1 / 115 (0.87%)	
occurrences (all)	2	1	
Endocrine disorders			
Low serum iPTH concentration			
subjects affected / exposed	0 / 115 (0.00%)	3 / 115 (2.61%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Lumbar pain or cramps			
subjects affected / exposed	0 / 115 (0.00%)	2 / 115 (1.74%)	
occurrences (all)	0	2	
Osteoarthritis and trigger finger			
subjects affected / exposed	0 / 115 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	2	
Traumatic pain or tendon tear			
subjects affected / exposed	1 / 115 (0.87%)	1 / 115 (0.87%)	
occurrences (all)	1	1	
Infections and infestations			
Herpes zoster infection			
subjects affected / exposed	0 / 115 (0.00%)	1 / 115 (0.87%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypercalciuria			
subjects affected / exposed	1 / 115 (0.87%)	14 / 115 (12.17%)	
occurrences (all)	1	14	
Hypocalciuria			

subjects affected / exposed	11 / 115 (9.57%)	3 / 115 (2.61%)	
occurrences (all)	11	3	
Hyperphosphaturia			
subjects affected / exposed	6 / 115 (5.22%)	2 / 115 (1.74%)	
occurrences (all)	6	2	
Hypercalcaemia			
subjects affected / exposed	0 / 115 (0.00%)	6 / 115 (5.22%)	
occurrences (all)	0	6	
Hyperphosphataemia			
subjects affected / exposed	0 / 115 (0.00%)	5 / 115 (4.35%)	
occurrences (all)	0	5	
Hypokalaemia, hyperhomocysteinemia, or low bone alkaline phosphate concentration			
subjects affected / exposed	1 / 115 (0.87%)	2 / 115 (1.74%)	
occurrences (all)	1	2	
Hypocalcaemia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 115 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 115 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29104158