Clinical trial results:
A Prospective, Randomized, Open, Blinded Endpoint (PROBE), Clinical Trial to Assess The Renal and Humoral Effects of Sevelamer Carbonate in Patients with Chronic Kidney Disease and Residual Proteinuria Despite Best Available Treatment

Summary

EudraCT number	2012-005416-26
Trial protocol	IT
Global end of trial date	21 September 2015

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019
Summary attachment (see zip file)	Article (AJKD_The ANSWER Randomized Trial article.pdf)

Trial information

Trial identification

Sponsor protocol code	ANSWER

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02464891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	via G.B. Camozzi, 3, Ranica BG, Italy, 24020
Public contact	Dep. Renal Medicine, Clinical Research Center for Rare Disease "Aldo & Cele Daccò", 0039 03545351, piero.ruggenenti@marionegri.it
Scientific contact	Dep. Renal Medicine, Clinical Research Center for Rare Disease "Aldo & Cele Daccò", 0039 03545351, piero.ruggenenti@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	27 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2015
Global end of trial reached?	Yes
Global end of trial date	21 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 3-month Sevelamer carbonate therapy compared to standard therapy on 24 h urinary protein excretion in patients with Chronic Kidney Disease (CKD) and residual proteinuria despite optimized Renin Angiotensin System (RAS) inhibitor therapy:

Protection of trial subjects:

The study was conducted in conformance with Good Clinica Practice standards and applicable country regulations regarding ethical committee review, informed consent and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2013
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: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	36
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

2 Italian centers (Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Ranica, Bergamo, and Bianchi-Melacrino-Morelli Hospital, Nephrology Unit, Reggio Calabria) were activated rispectively between November 2013 and December 2014.

Pre-assignment

Screening details:

72 subjects were screened for inclusion in the study. 53 subjects were randomized. Of those not randomized, 9 did not meet inclusion criteria, 3 were lost to follow up and 7 declined to participate.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Renvela

Arm description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

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

Dosage and administration details:

1600 mg, 3 times per day during meals,

Arm title	No Renvela

Arm description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Renvela	No Renvela
Started	53	53
Completed	49	53
Not completed	4	0
Adverse event, non-fatal	4	-

Period 2

Period 2 title	Washout Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Washout Period

Arm description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Washout Period
Started	53
Completed	53

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	53	53	
Age categorical Units: Subjects			
Adults (18-64 years)	38	38	
From 65-84 years	15	15	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	55		
standard deviation	± 17	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	42	42	
Body mass Index Units: Kg/m2			
arithmetic mean	27		
standard deviation	± 4	-	
Systolic Blood Pressure Units: mm Hg			
arithmetic mean	128		
standard deviation	± 22	-	
Diastolic Blood Pressure Units: mm Hg			
arithmetic mean	73		
standard deviation	± 10	-	
Pulse Rate Units: Beats/min			
arithmetic mean	69		
standard deviation	± 11	-	
Creatinine Units: mg/dl			
median	1.6		
inter-quartile range (Q1-Q3)	1 to 2.3	-	
Phosphate Units: mg/dl			
arithmetic mean	3.8		
standard deviation	± 0.6	-	
Calcium Units: mg/dl			
arithmetic mean	9.2		
standard deviation	± 0.4	-	

PTH Units: pg/dL arithmetic mean standard deviation	 70 ± 33	 -	
Magnesium Units: mg/dL arithmetic mean standard deviation	 1.97 ± 0.22	 -	
Cholesterol Units: mg/dL arithmetic mean standard deviation	 181 ± 38	 -	
LDL cholestrol Units: mg/dL arithmetic mean standard deviation	 113 ± 33	 -	
Triglycerides Units: mg/dL median inter-quartile range (Q1-Q3)	 114 88 to 159	 -	
Albumin Units: g/dL arithmetic mean standard deviation	 3.6 ± 0.4	 -	
Hemoglobin Units: g/dL arithmetic mean standard deviation	 12.9 ± 1.8	 -	
Urine Protein Units: g/24 H median inter-quartile range (Q1-Q3)	 1.54 0.97 to 2.59	 -	
Urine Albumin Units: µg/min median inter-quartile range (Q1-Q3)	 829 481 to 1372	 -	
mGFR Units: mL/min/1.73m2 arithmetic mean standard deviation	 49.3 ± 23.5	 -	
Fractional Albumin clearance Units: absolute value x 1000000 median inter-quartile range (Q1-Q3)	 43 18 to 93	 -	

End points

End points reporting groups

Reporting group title	Renvela

Reporting group description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Reporting group title	No Renvela

Reporting group description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Reporting group title	Washout Period

Reporting group description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Primary: Urinary protein 24 H

End point title	Urinary protein 24 H

End point description:

End point type	Primary

End point timeframe:

Changes in 24-hour proteinuria at the end of the 2 treatment periods with sevelamer or without sevelamer compared to each pretreatment period. Three consecutive 24-hour proteinuria measurements were obtained at each visit and the mean of the 3 samples

End point values	Renvela	No Renvela		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: g/24 H				
median (inter-quartile range (Q1-Q3))	1.36 (0.77 to 2.6)	1.48 (0.81 to 2.77)		

Statistical analyses

Statistical analysis title	Change in Urine Proteine Excretion 24 H

Statistical analysis description:

changes in 24-hour proteinuria at the end of the 2 treatment periods with sevelamer or without sevelamer compared to each pretreatment period. Three consecutive 24-hour proteinuria measurements were obtained at each visit and the mean of the 3 samples was used.

Comparison groups	Renvela v No Renvela
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Wilcoxon signed rank test performed between pre-post treatment period.

[2] - P= 0.1 refered to Renvela vs non-Renvela period; differences between pre and post renvela treatment reported a p = 0.1; differences between pre and post non-renvela treatment reported a p = 0.5.

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	18.1

Reporting groups

Reporting group title	Renvela

Reporting group description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Reporting group title	No Renvela

Reporting group description:

Patients who met the selection criteria and were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or >4 mg/dL. Each group was then randomly assigned to 1 of 2 treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times per day during meals, followed by a 1- month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1,600 mg, 3 times daily.

Serious adverse events	Renvela	No Renvela	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	2 / 53 (3.77%)	
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)			
Colon adenoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Brain Hemorrage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (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			
Anal abscess			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
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	Renvela	No Renvela	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 53 (66.04%)	30 / 53 (56.60%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 53 (9.43%)	7 / 53 (13.21%)	
occurrences (all)	5	8	
Claudicatio intermittens			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
legs edema			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Worsening symptoms of prostatic hypertrophy			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Common cold, cough, pharyngitis or bronchitis			
subjects affected / exposed	5 / 53 (9.43%)	7 / 53 (13.21%)	
occurrences (all)	5	7	
Psychiatric disorders			
Dysphoria			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Investigations			
Increase of CPK levels			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Tendor tear, joint or traumatic pain			
subjects affected / exposed	1 / 53 (1.89%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Cardiac disorders			
Sinus bradicardia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Ventricular, Supraventricular extrasystoles			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Hypertensive cardiopathy			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Nervous system disorders			
Syncope or dizziness			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Leg paresthesia			

subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Ear and labyrinth disorders			
Otitis media			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Eye disorders			
Retinal exudates			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gatroenteritis, diarrhea, abdominal pain			
subjects affected / exposed	7 / 53 (13.21%)	2 / 53 (3.77%)	
occurrences (all)	9	2	
Constipation			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
lumbar pain or muscle pain			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Meteorism			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Pancreatic cyst			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis and eczema			

subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Urinary tract infection or dysuria			
subjects affected / exposed	3 / 53 (5.66%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Worsening of renal function			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Relapse of nephrotic syndrome			
subjects affected / exposed	0 / 53 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences (all)	1	1	
Infections and infestations			
Flulike syndrome or fever (unspecified)			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	4	
Dental infection, dental abscess or toothache			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Hyperphosphataemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Hypospermia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	

Hyperkalaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Dyslipidemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2014	The amendment makes the following changes without modifying the study design and without adding risk to patients: 1) possibility to include in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Short treatment duration, lower pretreatment proteinuria than expected

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31027883