Clinical trial results:
A prospective, randomized, open label blinded end point (PROBE) trial to evaluate whether, at comparable blood pressure control, combined therapy with the ACE inhibitor Benazepril and the angiotensin II receptor blocker ARB Valsartan reduces progression to ESRD more effectively than Benazepril or Valsartan alone in high risk patients with type 2 diabetes and overt nephropathy (VALID Study)

Summary

EudraCT number	2006-005951-14
Trial protocol	IT SI
Global end of trial date	15 April 2016

Results information

Result version number	v1 (current)
This version publication date	05 June 2019
First version publication date	05 June 2019
Summary attachment (see zip file)	Original article (Ruggenenti_et_al-2019-Diabetes,_Obesity_and_Metabolism.pdf)

Trial information

Trial identification

Sponsor protocol code	AIFA VALID

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00494715
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	V. G. B. Camozzi, 3, Ranica / Bergamo, Italy, 24020
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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	15 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2016
Global end of trial reached?	Yes
Global end of trial date	15 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether, at comparable blood pressure control, dual RAS blockade with combined therapy with halved doses of benazepril (10 mg/day) and valsartan (160 mg/day) reduces the incidence of ESRD more effectively than single drug RAS blockade by full doses of benazepril (20 mg/day) or valsartan (320 mg/day) given alone in high-risk patients with type 2 diabetes and overt nephropathy.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2007
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	Slovenia: 30
Country: Number of subjects enrolled	Italy: 73
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	51
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter trial. Patients were recruited in 12 Clinical sites. The recruitment was competitive. The first patient signed the informed consent on April 20th, 2009 and the last patient was recruited on February 19th, 2013.

Pre-assignment

Screening details:

Of the 158 patients assessed for eligibility, 38 did not fulfil the eligibility criteria, nine withdrew consent, seven were lost to follow-up and one died; thus, 103 patients were enrolled and randomized.

Pre-assignment period milestones

Number of subjects started	158[1]
Number of subjects completed	103

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 9
Reason: Number of subjects	Lost to followup: 7
Reason: Number of subjects	Adverse event, serious fatal: 1
Reason: Number of subjects	Not fulfil the eligibility criteria: 38

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 158 patient assessed for eligibility. 53 patient were not enrolled due to several causes

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Benazepril

Arm description:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Benazepril (10 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 20 mg

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

Dosage and administration details:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Benazepril (10 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 20 mg

Arm title	Valsartan

Arm description:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Valsartan (180 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 360 mg

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

Dosage and administration details:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Valsartan (180 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 360 mg

Arm title	Combination Benazepril/Valsartan

Arm description:

Participants were randomly given equivalent doses (one-quarter of the full doses of both agents in combination) of Valsartan (80 mg) and Benazepril (5 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatments were uptitrated to the one-half of the standard dose of both agents in combination (Valsartan 180 mg and Benazepril 10 mg)

Arm type	Experimental
Investigational medicinal product name	Benazepril/Valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were randomly given equivalent doses (one-quarter of the full doses of both agents in combination) of Valsartan (80 mg) and Benazepril (5 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatments were uptitrated to the one-half of the standard dose of both agents in combination (Valsartan 180 mg and Benazepril 10 mg)

Number of subjects in period 1	Benazepril	Valsartan	Combination Benazepril/Valsartan
Started	34	36	33
Completed	34	36	33

Baseline characteristics

Reporting groups	
Reporting group title	Benazepril
Reporting group description:	
Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Benazepril (10 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 20 mg	
Reporting group title	Valsartan
Reporting group description:	
Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Valsartan (180 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 360 mg	
Reporting group title	Combination Benazepril/Valsartan
Reporting group description:	
Participants were randomly given equivalent doses (one-quarter of the full doses of both agents in combination) of Valsartan (80 mg) and Benazepril (5 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatments were uptitrated to the one-half of the standard dose of both agents in combination (Valsartan 180 mg and Benazepril 10 mg)	

Reporting group values	Benazepril	Valsartan	Combination Benazepril/Valsartan
Number of subjects	34	36	33
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)	19	19	19
From 65-84 years	15	17	14
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	66.3	63.9	63.1
standard deviation	± 7.1	± 9.2	± 9
Gender categorical Units: Subjects			
Female	4	5	6
Male	30	31	27
Smoker Units: Subjects			
Never	12	18	12
Former	13	13	8
Current	9	5	13

BMI			
Units: Kg/m2			
median	31.7	32.6	30.8
standard deviation	± 5.4	± 6.5	± 6.3
Systolic BP			
Units: mm Hg			
arithmetic mean	143.8	149.2	149.6
standard deviation	± 16.6	± 21.2	± 22.2
Diastolic BP			
Units: mm Hg			
arithmetic mean	79.2	80.4	79.1
standard deviation	± 10.8	± 12.2	± 11.3
MAP			
Units: mm Hg			
arithmetic mean	100.7	103.3	102.6
standard deviation	± 9.9	± 12.6	± 12.5
HbA1c			
Units: mmol/mol			
arithmetic mean	72.1	71.9	70.5
standard deviation	± 12.1	± 16	± 17.8
Serum glucose			
Units: mg/dl			
arithmetic mean	160.9	167.6	169.5
standard deviation	± 60.2	± 80.9	± 73.3
Serum potassium			
Units: mg/dl			
arithmetic mean	4.36	4.52	4.57
standard deviation	± 0.54	± 0.80	± 0.64
haemoglobin			
Units: g/dl			
arithmetic mean	13.3	13.4	13.1
standard deviation	± 2.3	± 1.8	± 2
Total cholesterol			
Units: mmol/L			
arithmetic mean	4.72	4.76	4.63
standard deviation	± 1.14	± 1.13	± 1.18
HDL			
Units: mmol/L			
arithmetic mean	1.14	1.07	1.08
standard deviation	± 0.25	± 0.32	± 0.36
LDL			
Units: mmol/L			
arithmetic mean	2.53	2.72	2.36
standard deviation	± 0.71	± 0.98	± 0.98
Triglycerides			
Units: mmol/mol			
arithmetic mean	2.51	2.37	2.75
standard deviation	± 1.71	± 1.15	± 1.99
Serum creatinine			
Units: µmol/L			
arithmetic mean	203.3	185.6	212.2
standard deviation	± 70.7	± 53	± 70.7

Measured GFR			
Units: mL/min/1.73m2			
median	39.9	42	39.7
inter-quartile range (Q1-Q3)	29.7 to 47.5	34.4 to 69.1	31.9 to 49
24-hour proteinuria			
Units: gram			
median	3.01	2.98	4.17
inter-quartile range (Q1-Q3)	2.13 to 5.25	1.9 to 4.45	2.29 to 6.2
Known duration of diabetes			
Units: years			
arithmetic mean	19.5	17.7	18.1
standard deviation	± 0	± 0	± 0

Reporting group values	Total		
Number of subjects	103		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	57		
From 65-84 years	46		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	15		
Male	88		
Smoker			
Units: Subjects			
Never	42		
Former	34		
Current	27		
BMI			
Units: Kg/m2			
median			
standard deviation	-		
Systolic BP			
Units: mm Hg			
arithmetic mean			
standard deviation	-		
Diastolic BP			
Units: mm Hg			
arithmetic mean			

standard deviation	-		
MAP Units: mm Hg arithmetic mean standard deviation	-		
HbA1c Units: mmol/mol arithmetic mean standard deviation	-		
Serum glucose Units: mg/dl arithmetic mean standard deviation	-		
Serum potassium Units: mg/dl arithmetic mean standard deviation	-		
haemoglobin Units: g/dl arithmetic mean standard deviation	-		
Total cholesterol Units: mmol/L arithmetic mean standard deviation	-		
HDL Units: mmol/L arithmetic mean standard deviation	-		
LDL Units: mmol/L arithmetic mean standard deviation	-		
Triglycerides Units: mmol/mol arithmetic mean standard deviation	-		
Serum creatinine Units: µmol/L arithmetic mean standard deviation	-		
Measured GFR Units: mL/min/1.73m2 median inter-quartile range (Q1-Q3)	-		
24-hour proteinuria Units: gram median inter-quartile range (Q1-Q3)	-		
Known duration of diabetes Units: years arithmetic mean			

standard deviation	-		

End points

End points reporting groups

Reporting group title	Benazepril

Reporting group description:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Benazepril (10 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 20 mg

Reporting group title	Valsartan

Reporting group description:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Valsartan (180 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 360 mg

Reporting group title	Combination Benazepril/Valsartan

Reporting group description:

Participants were randomly given equivalent doses (one-quarter of the full doses of both agents in combination) of Valsartan (80 mg) and Benazepril (5 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatments were uptitrated to the one-half of the standard dose of both agents in combination (Valsartan 180 mg and Benazepril 10 mg)

Primary: Progression to End Stage Renal Disease

End point title	Progression to End Stage Renal Disease

End point description:

End point type	Primary

End point timeframe:

The Progression to End Stage Renal Disease defined as the need for chronic RRT by dialysis or kidney transplantation,during a median (IQR) follow-up of 41 (18-54)months

End point values	Benazepril	Valsartan	Combination Benazepril/Valsartan	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	36	33	
Units: Participant	12	5	9	

Statistical analyses

Statistical analysis title	Primary End Point

Statistical analysis description:

The Progression to End Stage Renal Disease defined as the need for chronic RRT by dialysis or kidney transplantation,during a median (IQR) follow-up of 41 (18-54)months

Comparison groups	Benazepril v Valsartan v Combination Benazepril/Valsartan

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [1]
Method	Regression, Cox

Notes:

[1] - Three comparisons were performed:
Valsartan vs Benazepril: p=0.018
Valsartan vs Combination: p=0.038
Benazepril vs Combination: NS

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

Reporting groups

Reporting group title	Benazepril

Reporting group description:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Benazepril (10 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 20 mg

Reporting group title	Valsartan

Reporting group description:

Participants were randomly given equivalent doses (half the full dose recommended by the manufacturer for blood pressure control) of Valsartan (180 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatment was uptitrated to the full dose of 360 mg

Reporting group title	Combination Benazepril/Valsartan

Reporting group description:

Participants were randomly given equivalent doses (one-quarter of the full doses of both agents in combination) of Valsartan (80 mg) and Benazepril (5 mg). After 1 week in participants without symptomatic hypotension, serum creatinine increase <30% and serum potassium < 5.5mEq/L, treatments were uptitrated to the one-half of the standard dose of both agents in combination (Valsartan 180 mg and Benazepril 10 mg)

Serious adverse events	Benazepril	Valsartan	Combination Benazepril/Valsartan
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 34 (52.94%)	15 / 36 (41.67%)	19 / 33 (57.58%)
number of deaths (all causes)	5	4	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Stomach cancer			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple Myeloma			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Melanoma			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate carcinoma			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocarcinoma			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Cancer			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Cerebral haemorrhage (trauma)			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Peripheral revascularisation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	3 / 33 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 34 (5.88%)	2 / 36 (5.56%)	5 / 33 (15.15%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Stroke			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Sudden cardiac death			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Heart failure			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Unstable angina/ revascularization			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary revascularisation			
subjects affected / exposed	0 / 34 (0.00%)	3 / 36 (8.33%)	3 / 33 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unstable angina			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hospitalization for heart failure			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitory ischaemic attack			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stable angina pectoris, coronary and peripheral artery disease without revascularization			
subjects affected / exposed	5 / 34 (14.71%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Other serious adverse events			
subjects affected / exposed	4 / 34 (11.76%)	4 / 36 (11.11%)	2 / 33 (6.06%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haemorrhagic gastroenteritis/duodenitis			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic duodenal ulcer			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute bronchitis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COPD reacutization			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Transient kidney function worsening			
subjects affected / exposed	5 / 34 (14.71%)	5 / 36 (13.89%)	6 / 33 (18.18%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-Anca vasculitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Othe infection			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	3 / 33 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Benazepril	Valsartan	Combination Benazepril/Valsartan
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 34 (82.35%)	32 / 36 (88.89%)	28 / 33 (84.85%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 34 (0.00%)	6 / 36 (16.67%)	2 / 33 (6.06%)
occurrences (all)	0	6	2
Calf swelling			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Peripheral artery disease			
subjects affected / exposed	0 / 34 (0.00%)	4 / 36 (11.11%)	7 / 33 (21.21%)
occurrences (all)	0	4	7
Hydrosaline retention			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	1 / 33 (3.03%)
occurrences (all)	1	2	1

Inferior limb varicose veins			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Diabetic foot			
subjects affected / exposed	4 / 34 (11.76%)	3 / 36 (8.33%)	3 / 33 (9.09%)
occurrences (all)	4	3	3
General disorders and administration site conditions			
Urticaria			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Other ocular, ear, oral, nasal events			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Impotence			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Pharyngitis, common cold, cough			
subjects affected / exposed	3 / 34 (8.82%)	1 / 36 (2.78%)	3 / 33 (9.09%)
occurrences (all)	3	1	3
Acute Bronchitis			
subjects affected / exposed	4 / 34 (11.76%)	3 / 36 (8.33%)	2 / 33 (6.06%)
occurrences (all)	4	3	2
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	1	1	1
Obstructive sleep apnea syndrome			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
COPD reacutization			

subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Epistaxis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Ischemic heart disease			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	3 / 33 (9.09%)
occurrences (all)	0	2	3
Atrial fibrillation			
subjects affected / exposed	0 / 34 (0.00%)	3 / 36 (8.33%)	3 / 33 (9.09%)
occurrences (all)	0	3	3
Atrial flutter			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Extrasystoles			
subjects affected / exposed	2 / 34 (5.88%)	5 / 36 (13.89%)	3 / 33 (9.09%)
occurrences (all)	2	5	3
Aortic stenosis, aortic insufficiency			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	3 / 33 (9.09%)
occurrences (all)	0	1	3
Mitral insufficiency			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Trycuspid insufficiency			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
First degree A-V block			

subjects affected / exposed	0 / 34 (0.00%)	3 / 36 (8.33%)	1 / 33 (3.03%)
occurrences (all)	0	3	1
Second degree A-V block			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Complete right bundle block			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Left ventricular hypertrophy			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	2 / 33 (6.06%)
occurrences (all)	1	0	2
Atrial enlargement			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Dilatative cardiopathy			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Sinus bradicardia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences (all)	2	1	2
Other non rilevant ECG alterations			
subjects affected / exposed	4 / 34 (11.76%)	2 / 36 (5.56%)	3 / 33 (9.09%)
occurrences (all)	4	2	3
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 34 (11.76%)	11 / 36 (30.56%)	11 / 33 (33.33%)
occurrences (all)	4	11	11
Thrombocytopenia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Splenomegaly			

subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
MGUS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Otitis media			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Vertigo			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Eye disorders			
Cataract			
subjects affected / exposed	3 / 34 (8.82%)	4 / 36 (11.11%)	1 / 33 (3.03%)
occurrences (all)	3	4	1
Glaucoma			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
conjuntivitis, chalazion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Diabetic retinopathy			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Retinal detachment			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Hemovitreous dexter			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences (all)	0	1	2
Gastritis, nausea, vomiting, abdominal pain			

subjects affected / exposed	5 / 34 (14.71%)	3 / 36 (8.33%)	3 / 33 (9.09%)
occurrences (all)	5	3	3
Cholelithiasis, Biliary colic			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	1	1	1
Liver steatosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Hiatus hernia, reflux esophagitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Duodenal ulcus			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Colon diverticulosis, colon polyps			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	3 / 33 (9.09%)
occurrences (all)	2	1	3
Constipation			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Hemorroids			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Other gastrointestinal events			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
High transaminases levels, high GGt levels			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	3 / 33 (9.09%)
occurrences (all)	1	2	3
Phlebitis			

subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Onychomycosis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Pruritic skin lesion			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Ring-like granuloma			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Other dermatologic events			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Transient renal function deteriration			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	3 / 33 (9.09%)
occurrences (all)	0	0	0
Acure renal failure			
subjects affected / exposed	8 / 34 (23.53%)	6 / 36 (16.67%)	8 / 33 (24.24%)
occurrences (all)	8	6	8
Urinary tract infection			
subjects affected / exposed	3 / 34 (8.82%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Renal colic			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Renal cyst ruptured			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Bening prostatic hyperplasia			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	2 / 33 (6.06%)
occurrences (all)	1	2	2
Other urologic events			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	0	1	1

Endocrine disorders			
Secondary hyperparathyroidism			
subjects affected / exposed	10 / 34 (29.41%)	12 / 36 (33.33%)	4 / 33 (12.12%)
occurrences (all)	10	12	4
Hypothyroidism			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Thyroid struma			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain, flank pain			
subjects affected / exposed	3 / 34 (8.82%)	3 / 36 (8.33%)	0 / 33 (0.00%)
occurrences (all)	3	3	0
Muscular pain, cramps			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	1	1	1
Fatigue			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Osteoarthritis, joint pain			
subjects affected / exposed	0 / 34 (0.00%)	5 / 36 (13.89%)	2 / 33 (6.06%)
occurrences (all)	0	5	2
Fracture, trauma, tendonitis, tendor tear			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Inguinal hernia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Foot arthritis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Other musculoskeletal events			
subjects affected / exposed	0 / 34 (0.00%)	3 / 36 (8.33%)	3 / 33 (9.09%)
occurrences (all)	0	3	3
Infections and infestations			

High CRP levels			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Flu like syndrome			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Fever unspecific			
subjects affected / exposed	1 / 34 (2.94%)	1 / 36 (2.78%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
herpes zoster			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Osteomyelitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	5 / 34 (14.71%)	11 / 36 (30.56%)	8 / 33 (24.24%)
occurrences (all)	5	11	8
Metabolic acidosis			
subjects affected / exposed	4 / 34 (11.76%)	4 / 36 (11.11%)	3 / 33 (9.09%)
occurrences (all)	4	4	3
Metabolic alkalosis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Hyperuricemia, Gout			
subjects affected / exposed	4 / 34 (11.76%)	9 / 36 (25.00%)	4 / 33 (12.12%)
occurrences (all)	4	9	4
Dyslipidemia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Hypoglicemia			
subjects affected / exposed	1 / 34 (2.94%)	3 / 36 (8.33%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Hypokalemia			

subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Hyperphosphatemia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Hypocalcemia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	1
Vitamin D deficiency, insufficiency			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
High CPK levels			
subjects affected / exposed	1 / 34 (2.94%)	2 / 36 (5.56%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Other metabolic events			
subjects affected / exposed	4 / 34 (11.76%)	1 / 36 (2.78%)	3 / 33 (9.09%)
occurrences (all)	4	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2008	The changes made aim to facilitate the recruitment of patients without change the philosophy of the general objective and the main objective of the project. Specifically, the selection criteria have been extended to include patients with a albuminuria/creatininuria (A/C) ratio > 1000 mg/g (instead of > 2000 mg/g). This approach leads to an increase in the pool of potentially eligible patients of around 63%. The model used to estimate the study sample consider the number of expected events in the various treatment groups. The number of expected events depends on the incidence of events over time (influenced by treatment) and the duration of follow-up. Originally it had been hypothesized a median follow-up of 3 years, equal to the duration of the treatment of the last patient randomized. In this amendment we specified that all randomized patients will come maintained in active follow-up until the last patient has completed the three years of treatment. Since the period initially envisaged for recruitment has been extended, it can be to predict that when the last randomized patient has completed three years of treatment provided, the median follow-up of patients will be at least 4.5 years.
23 April 2009	The protocol has been modified in order to allow the inclusion in the study of patients who for specific cardiovascular indications cannot suspend treatment with an ACE inhibitor or a sartan and who have an albumin/creatinine ratio in the urine spot of the same or higher morning at 500 mg/g. The changes made aim to facilitate the recruitment of patients without changing the general philosophy and the main objective of the project. The original version of the the protocol expected to be randomized patients who at the end of one month of washout from any previous treatment with ACE inhibitors and/or ARBs had an albumin/creatinine ratio in the urine spot of 1000 or more in the morning mg/g. In clinical practice, however, many of these patients are treated with ACE inhibitors and/or ARB for specific cardiovascular indications such as heart failure and/or ischemic heart disease. In these cases it may be unsafe to discontinue treatment with these drugs even for a month. Therefore, these patients cannot perform the wash-out and therefore cannot enter the study. This represents a significant obstacle to the finalization of the study when the vast majority of patients with type 2 diabetes and nephropathy have at least one cardiovascular indication for treatment with ACE inhibitors and / or sartans. With the proposed amendment also patients with specific cardiovascular indications for treatment with an ACE inhibitor or a sartan could be included. Therefore it was proposed to include in the study patients who have at least one month of treatment with an ACE inhibitor or a sartan and an albumin / creatinine ratio in the morning urine spot equal to or greater than 500 mg/g, without prejudice to the other inclusion and exclusion criteria already provided by the protocol.

Notes:

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/30793466