

**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 the incidence of microalbuminuria more effectively than Benazepril or Valsartan alone in hypertensive patients with type 2 diabetes and high-normal albuminuria VARIETY Study

Summary

EudraCT number	2006-005954-62
Trial protocol	IT
Global end of trial date	14 July 2021

Results information

Result version number	v1 (current)
This version publication date	14 August 2021
First version publication date	14 August 2021
Summary attachment (see zip file)	VARIETY article (Variety Paper.pdf)

Trial information**Trial identification**

Sponsor protocol code	AIFA MICRO
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00503152
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, 24010
Public contact	Dip. Renal Medicine, Clinical Research Center for Rare Diseases "Aldo & Cele Daccò", 0039 03545351, piero.ruggenenti@marionegri.it
Scientific contact	Dip. Renal Medicine, Clinical Research Center for Rare Diseases "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	14 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2021
Global end of trial reached?	Yes
Global end of trial date	14 July 2021
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 microalbuminuria 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, hypertension and high normal albuminuria.

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	13 July 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	Italy: 612
Worldwide total number of subjects	612
EEA total number of subjects	612

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)	280
From 65 to 84 years	331
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Type 2 diabetic patients with high-normal albuminuria included between July 2007 and April 2013 by the Istituto di Ricerche Farmacologiche Mario Negri IRCCS and 8 diabetology or nephrology units in Italy.

Pre-assignment

Screening details:

Patients were screened according to the inclusion/exclusion criteria. They referred to the Istituto di Ricerche Farmacologiche Mario Negri and to 8 diabetology or nephrology units, all in Italy. Eligibly patients who fulfilled the inclusion/exclusion criteria entered in 1 month of washout period and stratified before the randomization

Period 1

Period 1 title	Treatment period (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:

After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.

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

Dosage and administration details:

Benazepril 10 mg/day

Arm title	Valsartan
------------------	-----------

Arm description:

After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.

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

Dosage and administration details:

Valsartan 160 mg/day

Arm title	Combination
------------------	-------------

Arm description:

After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.

Arm type	Experimental
Investigational medicinal product name	Benazepril and Valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal film, Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Benazepril 5 mg/day and Valsartan 80 mg/day combination therapy. These doses correspond to half or one-fourth, respectively, of the full doses recommended by the manufacturer for BP control

Number of subjects in period 1	Benazepril	Valsartan	Combination
Started	209	201	202
Completed	203	201	196
Not completed	6	0	6
Protocol deviation	6	-	6

Baseline characteristics

Reporting groups

Reporting group title	Benazepril
Reporting group description:	
After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.	
Reporting group title	Valsartan
Reporting group description:	
After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.	
Reporting group title	Combination
Reporting group description:	
After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.	

Reporting group values	Benazepril	Valsartan	Combination
Number of subjects	209	201	202
Age categorical			
Units: Subjects			
Adults (18-64 years)	94	93	94
From 65-84 years	114	108	108
85 years and over	1	0	0
Age continuous			
Units: years			
arithmetic mean	64.7	64.3	65
standard deviation	± 7.7	± 7.9	± 7.1
Gender categorical			
Units: Subjects			
Female	63	62	56
Male	146	139	146
Smoking status			
Units: Subjects			
Never smoked	95	102	97
Former smoked	34	23	32
Current smoker	80	76	73
Known duration of diabetes			
Units: year			
arithmetic mean	11.5	11.7	12.2
standard deviation	± 7.1	± 6.9	± 7.1
BMI			
Units: kg/m2			
arithmetic mean	29.8	30.3	30.4
standard deviation	± 4.4	± 4.9	± 4.9
Systolic BP			
Units: mm Hg			
arithmetic mean	141.9	140.9	141.9
standard deviation	± 14.6	± 15.2	± 13.7

MAP Units: mm Hg arithmetic mean standard deviation	99.8 ± 8.8	99.7 ± 8	99.8 ± 8.6
HbA1c Units: mmol/mol arithmetic mean standard deviation	54.3 ± 14.2	54.3 ± 14.1	54.7 ± 12.9
Serum glucose Units: mg/dl arithmetic mean standard deviation	151.4 ± 44.8	151.1 ± 50.6	152.5 ± 41
Serum potassium Units: mg/dL arithmetic mean standard deviation	4.13 ± 0.42	4.11 ± 0.48	4.1 ± 0.46
Hemoglobin Units: g/dL arithmetic mean standard deviation	14 ± 1.3	14 ± 1.2	14.1 ± 1.2
Total Cholesterol Units: mg/dL arithmetic mean standard deviation	177.7 ± 33	178.4 ± 32.4	179.5 ± 34.6
LDL cholesterol Units: mg/dL arithmetic mean standard deviation	108 ± 28.2	108.4 ± 30.6	111.2 ± 32.3
HDL cholesterol Units: mg/dL arithmetic mean standard deviation	46.8 ± 12.2	48 ± 13.3	47.1 ± 11.5
Tryglycerides Units: mg/dL arithmetic mean standard deviation	128.5 ± 72.1	127.9 ± 79	132.7 ± 76.4
Serum creatinine Units: mg/dL arithmetic mean standard deviation	0.9 ± 0.19	0.88 ± 0.19	0.93 ± 0.2
eGFR Units: mL/min/1.73m ² arithmetic mean standard deviation	82.22 ± 15.28	84.19 ± 14.62	80.57 ± 15.99
mGFR Units: mL/min/1.73 m ² arithmetic mean standard deviation	85.93 ± 14.3	84.68 ± 20.85	83.04 ± 16.76
UAE Units: ug/min median inter-quartile range (Q1-Q3)	8.74 6.52 to 12.58	9.44 6.72 to 12.59	8.35 6.1 to 11.7

Reporting group values	Total		
Number of subjects	612		
Age categorical Units: Subjects			
Adults (18-64 years)	281		
From 65-84 years	330		
85 years and over	1		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	181		
Male	431		
Smoking status Units: Subjects			
Never smoked	294		
Former smoked	89		
Current smoker	229		
Known duration of diabetes Units: year arithmetic mean standard deviation	-		
BMI Units: kg/m ² arithmetic mean standard deviation	-		
Systolic 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	-		
Hemoglobin Units: g/dL			

arithmetic mean standard deviation	-		
Total Cholesterol Units: mg/dL arithmetic mean standard deviation	-		
LDL cholesterol Units: mg/dL arithmetic mean standard deviation	-		
HDL cholesterol Units: mg/dL arithmetic mean standard deviation	-		
Tryglycerides Units: mg/dL arithmetic mean standard deviation	-		
Serum creatinine Units: mg/dL arithmetic mean standard deviation	-		
eGFR Units: mL/min/1.73m ² arithmetic mean standard deviation	-		
mGFR Units: mL/min/1.73 m ² arithmetic mean standard deviation	-		
UAE Units: ug/min median inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Benazepril
Reporting group description: After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.	
Reporting group title	Valsartan
Reporting group description: After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.	
Reporting group title	Combination
Reporting group description: After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.	

Primary: Microalbuminuria

End point title	Microalbuminuria
End point description: The estimated acceleration factors were 1.410 (95% CI: 0.806 to 2.467, P = 0.229) for benazepril compared to combination therapy, 0.799 (95% CI: 0.422 to 1.514, P = 0.492) for benazepril compared to valsartan, and 1.665 (95% CI: 1.007 to 2.746, P = 0.047) for valsartan compared to combination therapy. After adjustment for predefined confounders, the estimated acceleration factors were 1.330 (95% CI: 0.784 to 2.255, P = 0.290) for benazepril compared to combination therapy, 1.051 (95% CI: 0.591 to 1.866, P = 0.866) for benazepril compared to valsartan, and 1.365 (95% CI: 0.873 to 2.132, P = 0.172) for valsartan compared to combination therapy. When using the Cox regression model, the hazard for new-onset microalbuminuria was similar with the 3 treatment regimens, even after adjustment for predefined features	
End point type	Primary
End point timeframe: During a median [IQR] follow-up of 66 [42 to 83] months, the primary endpoint of persistent microalbuminuria was reached by 57 (28.1%) patients on benazepril, 53 (27.0%) on combination therapy, and 64 (31.8%) on valsartan	

End point values	Benazepril	Valsartan	Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203	201	196	
Units: Person	57	64	53	

Statistical analyses

Statistical analysis title	Microalbuminuria
Comparison groups	Benazepril v Valsartan v Combination

Number of subjects included in analysis	600
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229 ^[1]
Method	accelerated failure time model

Notes:

[1] - Benazepril versus combination therapy

Valsartan versus combination therapy p value=0.047

Benazepril versus Valsartan p value= 0.492

Secondary: GFR decline

End point title	GFR decline
-----------------	-------------

End point description:

In the subgroup of patients in whom GFR was measured by iohexol plasma clearance, GFR declined by 1.78 [0.32 to 3.54] mL/min/1.73 m² per year. The annual rate of GFR decline did not differ significantly among the benazepril (1.73 [0.44 to 4.13] mL/min/1.73

m²), combination therapy (2.61 [0.77 to 3.59] mL/min/1.73 m²), or valsartan (1.45 [-0.94 to 2.92] mL/min/1.73 m²) groups.

End point type	Secondary
----------------	-----------

End point timeframe:

Annual rate of GFR decline

End point values	Benazepril	Valsartan	Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	25	24	
Units: mL/min/1.73 m ²				
median (inter-quartile range (Q1-Q3))	1.73 (0.44 to 4.13)	1.45 (-0.94 to 2.92)	2.61 (0.77 to 3.59)	

Statistical analyses

Statistical analysis title	GFR decline
Comparison groups	Benazepril v Valsartan v Combination
Number of subjects included in analysis	77
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2579 ^[2]
Method	Regression, Linear

Notes:

[2] - P value

Benazepril versus valsartan: 0.2579

Benazepril versus combination: 0.7620

Valsartan versus combination: 0.1416

Secondary: Composite cardiovascular endpoint

End point title	Composite cardiovascular endpoint
-----------------	-----------------------------------

End point description:

During the study period, 7 (3.3%) patients on benazepril, 9 (4.5%) on combination therapy, and 9 (4.5%) on valsartan reached the composite cardiovascular endpoint of sudden cardiac death and fatal and nonfatal acute myocardial infarction or stroke. The risk of progression to the combined endpoint was

similar between groups, even after adjusting for predefined confounders

End point type	Secondary
End point timeframe:	
During the study period	

End point values	Benazepril	Valsartan	Combination	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	201	202	
Units: Person	7	9	9	

Statistical analyses

Statistical analysis title	Composite cardiovascular endpoint
Comparison groups	Benazepril v Valsartan v Combination
Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.584 ^[3]
Method	Regression, Cox

Notes:

[3] - p-value

Benazepril versus combination: 0.584

Valsartan versus combination: 0.979

Benazepril versus valsartan: 0.567

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	21.0
--------------------	------

Reporting groups

Reporting group title	Benazepril
-----------------------	------------

Reporting group description:

After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.

Reporting group title	Valsartan
-----------------------	-----------

Reporting group description:

After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.

Reporting group title	Combination
-----------------------	-------------

Reporting group description:

After 1 month washout from any previous RAS blocking therapy (ACE inhibitor or ARB) and stratification by center, we randomly assigned included patients to treatment with benazepril, valsartan, or a combination of both medications on a 1:1:1 basis.

Serious adverse events	Benazepril	Valsartan	Combination
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 209 (30.14%)	52 / 201 (25.87%)	56 / 202 (27.72%)
number of deaths (all causes)	5	7	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasia events			
subjects affected / exposed	13 / 209 (6.22%)	13 / 201 (6.47%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 13	0 / 13	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 1
Injury, poisoning and procedural complications			
Traffic accident event			
subjects affected / exposed	1 / 209 (0.48%)	0 / 201 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			

Major cardiovascular events			
subjects affected / exposed	5 / 209 (2.39%)	8 / 201 (3.98%)	9 / 202 (4.46%)
occurrences causally related to treatment / all	0 / 5	0 / 8	0 / 9
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 3
Minor cardiovascular events			
subjects affected / exposed	19 / 209 (9.09%)	20 / 201 (9.95%)	26 / 202 (12.87%)
occurrences causally related to treatment / all	0 / 19	0 / 20	0 / 26
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neurological events			
subjects affected / exposed	1 / 209 (0.48%)	3 / 201 (1.49%)	7 / 202 (3.47%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal events			
subjects affected / exposed	6 / 209 (2.87%)	6 / 201 (2.99%)	11 / 202 (5.45%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Gynecological Events			
subjects affected / exposed	2 / 209 (0.96%)	0 / 201 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory events			
subjects affected / exposed	2 / 209 (0.96%)	2 / 201 (1.00%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Renal events			
subjects affected / exposed	6 / 209 (2.87%)	0 / 201 (0.00%)	3 / 202 (1.49%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urological events			

subjects affected / exposed	14 / 209 (6.70%)	7 / 201 (3.48%)	2 / 202 (0.99%)
occurrences causally related to treatment / all	0 / 14	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide event			
subjects affected / exposed	0 / 209 (0.00%)	1 / 201 (0.50%)	0 / 202 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal and trauma events			
subjects affected / exposed	11 / 209 (5.26%)	9 / 201 (4.48%)	21 / 202 (10.40%)
occurrences causally related to treatment / all	0 / 11	0 / 9	0 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection events			
subjects affected / exposed	4 / 209 (1.91%)	3 / 201 (1.49%)	6 / 202 (2.97%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Metabolic events			
subjects affected / exposed	5 / 209 (2.39%)	1 / 201 (0.50%)	6 / 202 (2.97%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Benazepril	Valsartan	Combination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 209 (88.04%)	181 / 201 (90.05%)	171 / 202 (84.65%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm benign, malignant and unspecified events			
subjects affected / exposed	5 / 209 (2.39%)	5 / 201 (2.49%)	3 / 202 (1.49%)
occurrences (all)	5	5	3
Vascular disorders			

Vascular disorder events subjects affected / exposed occurrences (all)	19 / 209 (9.09%) 19	31 / 201 (15.42%) 31	38 / 202 (18.81%) 38
Surgical and medical procedures Surgical and medical procedures events subjects affected / exposed occurrences (all)	3 / 209 (1.44%) 3	0 / 201 (0.00%) 0	1 / 202 (0.50%) 1
General disorders and administration site conditions General disorders and administration site conditions events subjects affected / exposed occurrences (all)	34 / 209 (16.27%) 34	35 / 201 (17.41%) 35	33 / 202 (16.34%) 33
Immune system disorders Immune system disorders events subjects affected / exposed occurrences (all)	5 / 209 (2.39%) 5	1 / 201 (0.50%) 1	0 / 202 (0.00%) 0
Reproductive system and breast disorders Reproductive system and breast disorders events subjects affected / exposed occurrences (all)	21 / 209 (10.05%) 21	21 / 201 (10.45%) 21	12 / 202 (5.94%) 12
Respiratory, thoracic and mediastinal disorders Respiratory thoracic and mediastinal disorders events subjects affected / exposed occurrences (all)	21 / 209 (10.05%) 21	13 / 201 (6.47%) 13	25 / 202 (12.38%) 25
Psychiatric disorders Psychiatric disorders events subjects affected / exposed occurrences (all)	10 / 209 (4.78%) 10	4 / 201 (1.99%) 4	8 / 202 (3.96%) 8
Investigations Investigations events subjects affected / exposed occurrences (all)	35 / 209 (16.75%) 35	27 / 201 (13.43%) 27	28 / 202 (13.86%) 28
Injury, poisoning and procedural complications Injury poisoning and procedural complications events			

subjects affected / exposed occurrences (all)	14 / 209 (6.70%) 14	10 / 201 (4.98%) 10	18 / 202 (8.91%) 18
Congenital, familial and genetic disorders Congenital familial and genetic disorders events subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1	3 / 201 (1.49%) 3	2 / 202 (0.99%) 2
Cardiac disorders Cardiac disorder events subjects affected / exposed occurrences (all)	51 / 209 (24.40%) 51	61 / 201 (30.35%) 61	55 / 202 (27.23%) 55
Nervous system disorders Nervous system disorders events subjects affected / exposed occurrences (all)	36 / 209 (17.22%) 36	27 / 201 (13.43%) 27	34 / 202 (16.83%) 34
Blood and lymphatic system disorders Blood and lymphatic system disorders events subjects affected / exposed occurrences (all)	22 / 209 (10.53%) 22	22 / 201 (10.95%) 22	23 / 202 (11.39%) 23
Ear and labyrinth disorders Ear and labyrinth disorder events subjects affected / exposed occurrences (all)	2 / 209 (0.96%) 2	2 / 201 (1.00%) 2	6 / 202 (2.97%) 6
Eye disorders Eye disorder events subjects affected / exposed occurrences (all)	28 / 209 (13.40%) 28	26 / 201 (12.94%) 26	28 / 202 (13.86%) 28
Gastrointestinal disorders Gastrointestinal disorders event subjects affected / exposed occurrences (all)	33 / 209 (15.79%) 33	35 / 201 (17.41%) 35	39 / 202 (19.31%) 39
Hepatobiliary disorders Hepatobiliary disorder events subjects affected / exposed occurrences (all)	16 / 209 (7.66%) 16	9 / 201 (4.48%) 9	11 / 202 (5.45%) 11
Skin and subcutaneous tissue disorders			

Skin and subcutaneous tissue disorders events subjects affected / exposed occurrences (all)	14 / 209 (6.70%) 14	7 / 201 (3.48%) 7	10 / 202 (4.95%) 10
Renal and urinary disorders Renal and urinary disorders events subjects affected / exposed occurrences (all)	17 / 209 (8.13%) 17	18 / 201 (8.96%) 18	23 / 202 (11.39%) 23
Endocrine disorders Endocrine disorders events subjects affected / exposed occurrences (all)	2 / 209 (0.96%) 2	2 / 201 (1.00%) 2	2 / 202 (0.99%) 2
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders events subjects affected / exposed occurrences (all)	42 / 209 (20.10%) 42	40 / 201 (19.90%) 40	44 / 202 (21.78%) 44
Infections and infestations Infection and infestation events subjects affected / exposed occurrences (all)	51 / 209 (24.40%) 51	56 / 201 (27.86%) 56	48 / 202 (23.76%) 48
Metabolism and nutrition disorders Metabolism and nutrition disorders events subjects affected / exposed occurrences (all)	47 / 209 (22.49%) 47	55 / 201 (27.36%) 55	53 / 202 (26.24%) 53

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 patient recruitment without changing the general philosophy and main objective of the project. Specifically, the selection criteria have been expanded to also include patients with albuminuria > 7 µg / min and <10 µg / min. In this way, patients are eligible for the study if they have albuminuria (including extremes) between 7 and 19.99 µg / min (instead of between 10 and 19.99 µg / min). This approach results in an increase in the pool of potentially eligible patients of approximately 60%. In this amendment we have specified that all randomized patients will be kept 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 expected that by the time the last randomized patient has completed the three years of planned treatment, the median follow-up of patients will be at least 4.5 years. With these new assumptions, the incidence of events expected per year in each treatment group is a little lower, but the follow up is longer. Therefore, the total number of expected events increases slightly and, consequently, the estimated numbers also decrease somewhat, from 1233 to 1020 randomized patients (17% reduction in number) .
22 May 2015	This amendment provides for a reduction in the number of patients with an extension of the follow-up duration compared to that established in the original version of the protocol. This change will not change the power of the analyzes to test the effect of the treatment on the main efficacy parameter of the study. In May 2015, 1060 patients were included in the study, of which 613 were randomized. The preliminary analyzes presented in the periodic report sent to AIFA, had highlighted an incidence of the main endpoint (microalbuminuria) over a 4.5-year period in the control group greater than assumed in the protocol (27.0% instead of 22.5%); a lower than expected incidence of premature exits from the study (5% vs 15%), which resulted in a substantial increase in patients available for final analyzes. These results were confirmed in the interim analysis provided for in the protocol, performed on 11/05/2015. In particular, the following were observed: an incidence of the main endpoint (microalbuminuria) over a time span of 4.5 years in the control group greater than that hypothesized in the than hypothesized in the protocol (27.6% instead of 22.5%); an incidence of premature exits from the study relative to patients not included in the main analyzes lower than expected (4.2% vs 15%). As of 31/12/2015, the median follow-up expected for the 613 patients currently randomized will be 69 months. Considering that, the current drop-out referred to patients who will not contribute to the main efficacy analysis is 4.2%, it can be estimated that at the time of reaching the third year of the last randomized patient, the power of the analyzes (80%) foreseen by the protocol to test the effect of the treatment on the main efficacy parameter will have already been achieved without the need to include additional patients.

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.

The lower-than-expected albuminuria in our study population at inclusion unavoidably reduced the power of the analyses to detect a treatment effect on the primary endpoint.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34260595>