Clinical trial results:
A PROSPECTIVE, RANDOMIZED, OPEN LABEL, BLINDED END-POINT (PROBE) TRIAL TO EVALUATE WHETHER, AT COMPARABLE BLOOD PRESSURE CONTROL, ACE INHIBITOR THERAPY MORE EFFECTIVELY THAN NON RAS INHIBITOR THERAPY REDUCES CARDIOVASCULAR MORBIDITY AND MORTALITY IN CHRONIC DIALYSIS PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY AND/OR ARTERIAL HYPERTENSION (ARCADIA Study)

Summary

EudraCT number	2008-003529-17
Trial protocol	IT
Global end of trial date	01 April 2016

Results information

Result version number	v1 (current)
This version publication date	20 March 2021
First version publication date	20 March 2021

Trial information

Trial identification

Sponsor protocol code	ARCADIA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00985322
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 035 45351, piero.ruggenenti@marionegri.it
Scientific contact	Dip. Renal Medicine, Clinical Research Center for Rare Diseases "Aldo &Cele Daccò", 0039 035 45351, 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	15 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2016
Global end of trial reached?	Yes
Global end of trial date	01 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether, at comparable BP control, ACE inhibitor as compared to non-RAS inhibitor therapy reduces the incidence of a combined end-point of CV death (including sudden cardiac death and cardiac arrest resuscitation) and myocardial infarction or non-fatal stroke.

Protection of trial subjects:

An independent Safety Committee periodically reviewed in an unblinded fashion Serious adverse events (SAEs) and non-SAEs.
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	01 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 269
Worldwide total number of subjects	269
EEA total number of subjects	269

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)	139
From 65 to 84 years	125
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Patients were included by 28 Italian Centers between July 2009 and February 2014. Of 314 patients assessed for eligibility, 45 were excluded because they did not meet the selection criteria. Of the remaining 269 patients who were included and centrally randomized.

Pre-assignment

Screening details:

One month wash-out period from previous RAS inhibitor therapy and stratification by center and presence or absence of diabetes, an independent investigator at the sponsoring institution allocated each participant by block-size randomization on a 1:1 basis to either ramipril or non-RAS inhibitor

Pre-assignment period milestones

Number of subjects started	314[1]
Number of subjects completed	269

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 9
Reason: Number of subjects	did not fulfil eligibility criteria: 24
Reason: Number of subjects	Unsatisfactory compliance: 3
Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	Adverse event, serious fatal: 4
Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	renal transplant: 2

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: Of 314 patients assessed for eligibility, 45 were excluded because they did not meet the selection criteria. Of the remaining 269 patients who were included and randomized

Period 1

Period 1 title	Ramipril/No-RAS inhibitor therapy (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramipril

Arm description:

Ramipril was started at 1.25 mg/day and was uptitrated to 2.5 mg/day, to 5 mg/day, and then to 10 mg/day, according to blood pressure control and tolerability.

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

Dosage and administration details:

Ramipril was started at 1.25 mg/day and was uptitrated to 2.5 mg/day, to 5 mg/day, and then to 10 mg/day, according to blood pressure control and tolerability.

Arm title	Non-RAS Inhibitor

Arm description:

Non-RAS Inhibitor therapy

Arm type	Experimental
Investigational medicinal product name	Non RAS inibithor therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage and the administration detail were according to the Centre clinical practice to achieve the blood pressure targets in patients randomized a non Ramipril therapy. All therapy were collected in the eCRF and described into the appendix.

Number of subjects in period 1	Ramipril	Non-RAS Inhibitor
Started	140	129
Completed	93	90
Not completed	47	39
Adverse event, serious fatal	13	9
Consent withdrawn by subject	7	7
Adverse event, non-fatal	1	1
Other	2	-
renal transplant	23	21
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Ramipril
Reporting group description:	
Ramipril was started at 1.25 mg/day and was uptitrated to 2.5 mg/day, to 5 mg/day, and then to 10 mg/day, according to blood pressure control and tolerability.	
Reporting group title	Non-RAS Inhibitor
Reporting group description:	
Non-RAS Inhibitor therapy	

Reporting group values	Ramipril	Non-RAS Inhibitor	Total
Number of subjects	140	129	269
Age categorical Units: Subjects			
Adults (18-64 years)	72	67	139
From 65-84 years	65	60	125
85 years and over	3	2	5
Age continuous Units: years			
arithmetic mean	64	62	
standard deviation	± 12	± 14	-
Gender categorical Units: Subjects			
Female	41	47	88
Male	99	82	181
Smoker Units: Subjects			
Current or former smoker	70	42	112
No smoker	70	87	157
Baseline stratification data arterial hypertension Units: Subjects			
Arterial Hypertension	140	128	268
No arterial hypertension	0	1	1
Prior to transplant Units: Subjects			
Prior to transplant	15	22	37
No prior to transplant	125	107	232
Dialysis type Units: Subjects			
Low-flux hemodialysis	47	39	86
High flux hemodialysis	41	33	74
Hemodiafiltration	51	54	105
Not available	1	3	4
Dialysis frequency Units: Subjects			
Twice week	21	15	36
Three tymes week	118	112	230

Not available	1	2	3
Vascular acces Units: Subjects			
Arteriovenous fistula	114	112	226
Arteriovenous graft	8	5	13
Central venous catheter	17	10	27
Not available	1	2	3
Previous cardiovascular history Units: Subjects			
Coronary	34	24	58
Cerebrovascular	11	11	22
Peripheral artery disease	27	21	48
Gastrointestinal ischemia	1	1	2
No cardiovascular event	67	72	139
Other antihypertensive agents - Diuretic therapies Units: Subjects			
Diuretics	74	54	128
No diuretic therapies	66	75	141
Lipid lowering agents Units: Subjects			
Statins	47	43	90
Omega-3 fatty acid	12	12	24
Fibrates	1	0	1
No therapy	80	74	154
Anti-platelet therapy/Anti-thrombotic agents Units: Subjects			
Anti-platelet therapy	89	74	163
No Therapy	51	55	106
Anti-thrombotic agents Units: Subjects			
Anti-thrombotic agents	23	30	53
No therapy	117	99	216
Baseline stratification data Left ventricular hypertrophy Units: Subjects			
Left ventricular hypertrophy	95	83	178
No Left ventricular hypertrophy	45	46	91
Baseline stratification data Diabetes mellitus Units: Subjects			
Diabetes mellitus	37	28	65
No Diabetes mellitus	103	101	204
Other antihypertensive agents - Calcium-channel blockers Units: Subjects			
Calcium-channel blockers	77	62	139
No Calcium-channel blockers therapies	63	67	130
Other antihypertensive agents - Beta Blockers Units: Subjects			

Beta Blockers	69	70	139
No Beta Blockers therapies	71	59	130

Pre-dialysis BMI			
Units: Kg/m2			
arithmetic mean	25.6	25	
standard deviation	± 4.4	± 4.2	-
SBP before dialysis			
Units: mmHg			
arithmetic mean	145	143	
standard deviation	± 19	± 20	-
DBP before dialysis			
Units: mmHg			
arithmetic mean	75	76	
standard deviation	± 13	± 13	-
SBP after dialysis			
Units: mmHg			
arithmetic mean	145	138	
standard deviation	± 22	± 22	-
DBP after dialysis			
Units: mmHg			
arithmetic mean	78	75	
standard deviation	± 16	± 14	-
Duration of dialysis			
Units: Months			
median	30	37	
inter-quartile range (Q1-Q3)	15 to 63	13 to 76	-
eKT/V			
Units: eKT/V			
arithmetic mean	1.1	1.1	
standard deviation	± 0.2	± 0.3	-
Interdialytic weight change			
Units: Kg			
arithmetic mean	2.6	2.5	
standard deviation	± 1.1	± 1	-
Total cholesterol			
Units: mg/dL			
median	148	159	
inter-quartile range (Q1-Q3)	129 to 181	132 to 188	-
Triglycerides			
Units: mg/dL			
median	133	153	
inter-quartile range (Q1-Q3)	104 to 185	112 to 196	-
Hemoglobin			
Units: g/dL			
arithmetic mean	11.3	11.1	
standard deviation	± 1.2	± 1.3	-
Hematocrit			
Units: percent			
arithmetic mean	34.9	34.9	
standard deviation	± 3.9	± 3.9	-

Serum potassium			
Units: mEq/L			
arithmetic mean	5.3	5.3	
standard deviation	± 0.8	± 0.8	-
C-reactive protein			
Units: mg/L			
median	1.05	0.6	
inter-quartile range (Q1-Q3)	0.29 to 2.63	0.2 to 3.2	-

End points

End points reporting groups

Reporting group title	Ramipril
Reporting group description:	
Ramipril was started at 1.25 mg/day and was uptitrated to 2.5 mg/day, to 5 mg/day, and then to 10 mg/day, according to blood pressure control and tolerability.	
Reporting group title	Non-RAS Inhibitor
Reporting group description:	
Non-RAS Inhibitor therapy	

Primary: Primary composite end point of major cardiovascular events

End point title	Primary composite end point of major cardiovascular events
End point description:	
To assess whether, at comparable BP control, ACE inhibitor as compared to non-RAS inhibitor therapy reduces the incidence of a combined end-point of CV death (including sudden cardiac death and cardiac arrest resuscitation) and myocardial infarction. Sudden cardiac death is a natural death due to cardiac causes, heralded by abrupt loss of consciousness and effective circulation within 1 hour of the onset of acute symptoms such as arrhythmias, hypotension, chest pain, dyspnea or lightheadedness and followed by failure of resuscitation or failure of electrical, mechanical, or CNS function after initial resuscitation. Preexisting heart disease may or may not have been known to be present, but the time and mode of death are unexpected.	
End point type	Primary
End point timeframe:	
During a median [IQR] follow-up of 33 [17-42] months,	

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Events	23	24		

Statistical analyses

Statistical analysis title	Primary End Point
Statistical analysis description:	
Reduction of the incidence of a combined end-point of CV death (including sudden cardiac death and cardiac arrest resuscitation) and myocardial infarction in patient with ACE inhibitor as compared to non-RAS inhibitor therapy	
Comparison groups	Ramipril v Non-RAS Inhibitor

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Secondary: Fatal cardiovascular event considered as a single endpoint

End point title	Fatal cardiovascular event considered as a single endpoint

End point description:

To compare the incidence of the single components of the combined end-point: Fatal cardiovascular event

End point type	Secondary

End point timeframe:

During the observation period

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Event	11	17		

Statistical analyses

No statistical analyses for this end point

Secondary: New-onset or recurrent atrial fibrillation as a single endpoint

End point title	New-onset or recurrent atrial fibrillation as a single endpoint

End point description:

To compare the incidence of the single components of the combined end-point: new onset of atrial fibrillation in one of its three forms (paroxysmal, persistent and permanent)
Atrial fibrillation is defined as paroxysmal in case of spontaneous resolution of the arrhythmia, persistent when pharmacological or electrical cardioversion was needed to interrupt it and permanent when it could not be interrupted either spontaneously, by using drugs or by cardioversion.

End point type	Secondary

End point timeframe:

During the observational period

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Event	10	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalization because of symptomatic fluid overload as a single endpoint

End point title	Hospitalization because of symptomatic fluid overload as a single endpoint

End point description:

To compare the incidence of the single components of the combined end-point: patients hospitalized during the study period because of symptomatic fluid overload.

End point type	Secondary

End point timeframe:

All study period

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Event	10	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Stenosis and thrombosis of the arteriovenous fistula as a single endpoint

End point title	Stenosis and thrombosis of the arteriovenous fistula as a single endpoint

End point description:

To compare the incidence of the single components of the combined end-point: Stenosis and thrombosis of the arteriovenous fistula.

End point type	Secondary

End point timeframe:

During the observational period

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Event	28	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Non-fatal stroke considered as a single endpoint

End point title	Non-fatal stroke considered as a single endpoint

End point description:

To compare the incidence of the single components of the combined end-point: non-fatal stroke event

End point type	Secondary

End point timeframe:

During the observational period

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Event	4	2		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Explorative composite endpoint

End point title	Explorative composite endpoint

End point description:

To comapre the incidence of progression to the explorative composite endpoint of cardiovascular death, myocardial infarction, unstable angina, stroke, coronary artery revascularization, hospitalization for fluid overload or resuscitated cardiac arrest

End point type	Post-hoc

End point timeframe:

During the observational period

End point values	Ramipril	Non-RAS Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	129		
Units: Event	34	43		

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.

Adverse event reporting additional description:

SAE: we indicated the number of events occuring for the first time in single patients
AE: we indicated the number of patient who at least one no-SAE and total number of AEs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Ramipril

Reporting group description:

Ramipril was started at 1.25 mg/day and was uptitrated to 2.5 mg/day, to 5 mg/day, and then to 10 mg/day, according to blood pressure control and tolerability.

Reporting group title	Non-RAS Inhibitor

Reporting group description:

Non-RAS Inhibitor therapy

Serious adverse events	Ramipril	Non-RAS Inhibitor	
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 140 (65.00%)	86 / 129 (66.67%)	
number of deaths (all causes)	26	30	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal cancer			
subjects affected / exposed	6 / 140 (4.29%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Any Cancer			
subjects affected / exposed	20 / 140 (14.29%)	9 / 129 (6.98%)	
occurrences causally related to treatment / all	0 / 20	0 / 9	
deaths causally related to treatment / all	0 / 7	0 / 1	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	54 / 140 (38.57%)	68 / 129 (52.71%)	
occurrences causally related to treatment / all	0 / 54	0 / 68	
deaths causally related to treatment / all	0 / 11	0 / 20	

Stroke/Myocardial Infarction			
subjects affected / exposed	13 / 140 (9.29%)	7 / 129 (5.43%)	
occurrences causally related to treatment / all	0 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unstable Angina			
subjects affected / exposed	4 / 140 (2.86%)	7 / 129 (5.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	12 / 140 (8.57%)	21 / 129 (16.28%)	
occurrences causally related to treatment / all	0 / 12	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 140 (2.14%)	7 / 129 (5.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary and peripheral artery revascularization			
subjects affected / exposed	16 / 140 (11.43%)	23 / 129 (17.83%)	
occurrences causally related to treatment / all	0 / 16	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
HD vascular acces thrombosis/interventions			
subjects affected / exposed	13 / 140 (9.29%)	17 / 129 (13.18%)	
occurrences causally related to treatment / all	0 / 13	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Any cardiovascular event			
subjects affected / exposed	54 / 140 (38.57%)	68 / 129 (52.71%)	
occurrences causally related to treatment / all	0 / 54	0 / 68	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Other fatal event			

subjects affected / exposed	5 / 140 (3.57%)	4 / 129 (3.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 4	
Other non fatal events			
subjects affected / exposed	21 / 140 (15.00%)	18 / 129 (13.95%)	
occurrences causally related to treatment / all	0 / 21	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Any events			
subjects affected / exposed	91 / 140 (65.00%)	86 / 129 (66.67%)	
occurrences causally related to treatment / all	0 / 91	0 / 86	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other non-fatal events			
subjects affected / exposed	21 / 140 (15.00%)	18 / 129 (13.95%)	
occurrences causally related to treatment / all	0 / 21	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and metabolic non fatal events			
subjects affected / exposed	5 / 140 (3.57%)	4 / 129 (3.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections			
subjects affected / exposed	38 / 140 (27.14%)	37 / 129 (28.68%)	
occurrences causally related to treatment / all	0 / 38	0 / 37	
deaths causally related to treatment / all	0 / 3	0 / 5	

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

Non-serious adverse events	Ramipril	Non-RAS Inhibitor	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 140 (100.00%)	129 / 129 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Neoplasm bening, malignant and unspecific			
subjects affected / exposed	4 / 140 (2.86%)	7 / 129 (5.43%)	
occurrences (all)	4	7	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	59 / 140 (42.14%)	23 / 129 (17.83%)	
occurrences (all)	94	41	
General disorders and administration site conditions			
General disorder and administration site conditions			
subjects affected / exposed	22 / 140 (15.71%)	17 / 129 (13.18%)	
occurrences (all)	34	25	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	2 / 140 (1.43%)	0 / 129 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Reproductive system and breast disorder			
subjects affected / exposed	10 / 140 (7.14%)	4 / 129 (3.10%)	
occurrences (all)	10	4	
Respiratory, thoracic and mediastinal disorders			
Respisratory, thoracic and mediastinal disorders			
subjects affected / exposed	36 / 140 (25.71%)	21 / 129 (16.28%)	
occurrences (all)	50	29	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	13 / 140 (9.29%)	10 / 129 (7.75%)	
occurrences (all)	16	13	
Product issues			
Product issue			
subjects affected / exposed	0 / 140 (0.00%)	1 / 129 (0.78%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			

subjects affected / exposed	37 / 140 (26.43%)	21 / 129 (16.28%)	
occurrences (all)	55	32	
Congenital, familial and genetic disorders			
Congenital familial and genetic disorder			
subjects affected / exposed	0 / 140 (0.00%)	3 / 129 (2.33%)	
occurrences (all)	0	3	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	37 / 140 (26.43%)	33 / 129 (25.58%)	
occurrences (all)	46	49	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	24 / 140 (17.14%)	16 / 129 (12.40%)	
occurrences (all)	30	26	
Blood and lymphatic system disorders			
Blood and lymphatic system disorder			
subjects affected / exposed	9 / 140 (6.43%)	5 / 129 (3.88%)	
occurrences (all)	9	6	
Ear and labyrinth disorders			
Ear and labyrinth disorder			
subjects affected / exposed	4 / 140 (2.86%)	1 / 129 (0.78%)	
occurrences (all)	4	1	
Eye disorders			
Eye disorder			
subjects affected / exposed	9 / 140 (6.43%)	8 / 129 (6.20%)	
occurrences (all)	11	9	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	41 / 140 (29.29%)	34 / 129 (26.36%)	
occurrences (all)	82	67	
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	4 / 140 (2.86%)	3 / 129 (2.33%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			

subjects affected / exposed	12 / 140 (8.57%)	6 / 129 (4.65%)	
occurrences (all)	16	7	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	6 / 140 (4.29%)	5 / 129 (3.88%)	
occurrences (all)	8	12	
Endocrine disorders			
Endocrin disorder			
subjects affected / exposed	14 / 140 (10.00%)	15 / 129 (11.63%)	
occurrences (all)	17	18	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	26 / 140 (18.57%)	23 / 129 (17.83%)	
occurrences (all)	43	47	
Infections and infestations			
Infections and infestatations			
subjects affected / exposed	48 / 140 (34.29%)	34 / 129 (26.36%)	
occurrences (all)	90	64	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	46 / 140 (32.86%)	33 / 129 (25.58%)	
occurrences (all)	61	50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2010	Amendemnt 3: make some of the selection criteria provided by the protocol less restrictive, in order to facilitate the inclusion of patients without changing the design, objectives, or general philosophy of the initial project.
13 April 2012	Amendment 8: despite the change in the selection criteria, the expansion of the number of participating Centers and the progressive selection of the more "compliant" Centers to the commitments foreseen by the study, the enrollment trend is still not entirely satisfactory. We then revised the criteria for the sample estimate to see if it was possible to reduce the study size without changing the power of analysis. Assuming that the effect of treatment does not change, the number of patients to be randomized decreases from 312 per group to 133 per group, for a total of 266 patients (instead of the 624 originally expected).
05 October 2012	Amendment 9: updating of the participating centers list
18 February 2015	Amendment 11: Change of the Principal Investigator of the Coordinating Centre

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported