

**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 |
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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 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 <sup>[1]</sup> |
| Number of subjects completed | 269                |

### Pre-assignment subject non-completion reasons

|                            |   |
|----------------------------|---|
| Reason: Number of subjects | Adverse event, non-fatal: 2             |
| Reason: Number of subjects | Adverse event, serious fatal: 4         |
| Reason: Number of subjects | Consent withdrawn by subject: 9         |
| Reason: Number of subjects | Protocol deviation: 1                   |
| Reason: Number of subjects | did not fulfil eligibility criteria: 24 |
| Reason: Number of subjects | Unsatisfactory compliance: 3            |
| 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      |
| <b>Arm title</b>             | 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.

|   |                           |
|---|---------------------------|
| <b>Arm title</b>                              | Non-RAS Inhibitor         |
| Arm description:<br>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.

| <b>Number of subjects in period 1</b> | 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:<br>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:<br>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<br>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<br>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<br>therapies<br>Units: Subjects        |     |     |     |
| Diuretics   | 74  | 54  | 128 |
| No diuretic therapies   | 66  | 75  | 141 |
| Lipid lowering agents<br>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<br>agents<br>Units: Subjects              |     |     |     |
| Anti-platelet therapy   | 89  | 74  | 163 |
| No Therapy  | 51  | 55  | 106 |
| Anti-thrombotic agents<br>Units: Subjects                                       |     |     |     |
| Anti-thrombotic agents  | 23  | 30  | 53  |
| No therapy  | 117 | 99  | 216 |
| Baseline stratification data Left<br>ventricular hypertrophy<br>Units: Subjects |     |     |     |
| Left ventricular hypertrophy  | 95  | 83  | 178 |
| No Left ventricular hypertrophy   | 45  | 46  | 91  |
| Baseline stratification data Diabetes<br>mellitus<br>Units: Subjects            |     |     |     |
| Diabetes mellitus   | 37  | 28  | 65  |
| No Diabetes mellitus  | 103 | 101 | 204 |
| Other antihypertensive agents -<br>Calcium-channel blockers<br>Units: Subjects  |     |     |     |
| Calcium-channel blockers  | 77  | 62  | 139 |
| No Calcium-channel blockers<br>therapies  | 63  | 67  | 130 |
| Other antihypertensive agents - Beta<br>Blockers<br>Units: Subjects             |     |     |     |

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

|   |                   |                   |   |
|---|-------------------|-------------------|---|
| Pre-dialysis BMI<br>Units: Kg/m2<br>arithmetic mean<br>standard deviation         | 25.6<br>± 4.4     | 25<br>± 4.2       | - |
| SBP before dialysis<br>Units: mmHg<br>arithmetic mean<br>standard deviation       | 145<br>± 19       | 143<br>± 20       | - |
| DBP before dialysis<br>Units: mmHg<br>arithmetic mean<br>standard deviation       | 75<br>± 13        | 76<br>± 13        | - |
| SBP after dialysis<br>Units: mmHg<br>arithmetic mean<br>standard deviation        | 145<br>± 22       | 138<br>± 22       | - |
| DBP after dialysis<br>Units: mmHg<br>arithmetic mean<br>standard deviation        | 78<br>± 16        | 75<br>± 14        | - |
| Duration of dialysis<br>Units: Months<br>median<br>inter-quartile range (Q1-Q3)   | 30<br>15 to 63    | 37<br>13 to 76    | - |
| eKT/V<br>Units: eKT/V<br>arithmetic mean<br>standard deviation                    | 1.1<br>± 0.2      | 1.1<br>± 0.3      | - |
| Interdialytic weight change<br>Units: Kg<br>arithmetic mean<br>standard deviation | 2.6<br>± 1.1      | 2.5<br>± 1        | - |
| Total cholesterol<br>Units: mg/dL<br>median<br>inter-quartile range (Q1-Q3)       | 148<br>129 to 181 | 159<br>132 to 188 | - |
| Triglycerides<br>Units: mg/dL<br>median<br>inter-quartile range (Q1-Q3)           | 133<br>104 to 185 | 153<br>112 to 196 | - |
| Hemoglobin<br>Units: g/dL<br>arithmetic mean<br>standard deviation                | 11.3<br>± 1.2     | 11.1<br>± 1.3     | - |
| Hematocrit<br>Units: percent<br>arithmetic mean<br>standard deviation             | 34.9<br>± 3.9     | 34.9<br>± 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:<br>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:<br>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:<br>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.<br>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:<br>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:<br>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:<br>To compare the incidence of the single components of the combined end-point: Fatal cardiovascular event |  |
| End point type  | Secondary  |
| End point timeframe:<br>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:<br>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)<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>To compare the incidence of the single components of the combined end-point: non-fatal stroke event |  |
| End point type  | Secondary  |
| End point timeframe:<br>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:<br>To compare 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:<br>During the observational period   |                                |

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

### Statistical analyses

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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 occurring 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 %

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 16 September 2010 | Amendement 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.<br>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.<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported