



## Clinical trial results:

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

### Summary

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

### Results information

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

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | AIFA VALID |
|-----------------------|------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Istituto di Ricerche Farmacologiche Mario Negri IRCCS                                                                                      |
| Sponsor organisation address | V. G. B. Camozzi, 3, Ranica / Bergamo, Italy, 24020                                                                                        |
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Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 15 January 2019 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 15 April 2016   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 15 April 2016   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This study was conducted in conformance with Declaration of Helsinki, Good Clinical Practice standards and applicable country regulations regarding ethical committee review, informed consent, protection of human subjects participating in biomedical research and privacy.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 05 June 2007 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Slovenia: 30 |
| Country: Number of subjects enrolled | Italy: 73    |
| Worldwide total number of subjects   | 103          |
| EEA total number of subjects         | 103          |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 51 |
| From 65 to 84 years       | 52 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 158 <sup>[1]</sup> |
| Number of subjects completed | 103                |

### Pre-assignment subject non-completion reasons

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

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 158 patient assessed for eligibility. 53 patient were not enrolled due to several causes

### Period 1

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

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Benazepril |

Arm description:

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

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

Dosage and administration details:

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

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Valsartan |
|------------------|-----------|

**Arm description:**

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

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

**Dosage and administration details:**

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

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Combination Benazepril/Valsartan |
|------------------|----------------------------------|

**Arm description:**

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

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

**Dosage and administration details:**

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

| <b>Number of subjects in period 1</b> | Benazepril | Valsartan | Combination Benazepril/Valsartan |
|---------------------------------------|------------|-----------|----------------------------------|
| Started                               | 34         | 36        | 33                               |
| Completed                             | 34         | 36        | 33                               |

## Baseline characteristics

### Reporting groups

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

| Reporting group values                             | Benazepril | Valsartan | Combination Benazepril/Valsartan |
|----------------------------------------------------|------------|-----------|----------------------------------|
| Number of subjects                                 | 34         | 36        | 33                               |
| Age categorical                                    |            |           |                                  |
| Units: Subjects                                    |            |           |                                  |
| In utero                                           | 0          | 0         | 0                                |
| Preterm newborn infants (gestational age < 37 wks) | 0          | 0         | 0                                |
| Newborns (0-27 days)                               | 0          | 0         | 0                                |
| Infants and toddlers (28 days-23 months)           | 0          | 0         | 0                                |
| Children (2-11 years)                              | 0          | 0         | 0                                |
| Adolescents (12-17 years)                          | 0          | 0         | 0                                |
| Adults (18-64 years)                               | 19         | 19        | 19                               |
| From 65-84 years                                   | 15         | 17        | 14                               |
| 85 years and over                                  | 0          | 0         | 0                                |
| Age continuous                                     |            |           |                                  |
| Units: years                                       |            |           |                                  |
| arithmetic mean                                    | 66.3       | 63.9      | 63.1                             |
| standard deviation                                 | ± 7.1      | ± 9.2     | ± 9                              |
| Gender categorical                                 |            |           |                                  |
| Units: Subjects                                    |            |           |                                  |
| Female                                             | 4          | 5         | 6                                |
| Male                                               | 30         | 31        | 27                               |
| Smoker                                             |            |           |                                  |
| Units: Subjects                                    |            |           |                                  |
| Never                                              | 12         | 18        | 12                               |
| Former                                             | 13         | 13        | 8                                |
| Current                                            | 9          | 5         | 13                               |

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

|                                                                                            |                      |                     |                     |
|--------------------------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| Measured GFR<br>Units: mL/min/1.73m <sup>2</sup><br>median<br>inter-quartile range (Q1-Q3) | 39.9<br>29.7 to 47.5 | 42<br>34.4 to 69.1  | 39.7<br>31.9 to 49  |
| 24-hour proteinuria<br>Units: gram<br>median<br>inter-quartile range (Q1-Q3)               | 3.01<br>2.13 to 5.25 | 2.98<br>1.9 to 4.45 | 4.17<br>2.29 to 6.2 |
| Known duration of diabetes<br>Units: years<br>arithmetic mean<br>standard deviation        | 19.5<br>± 0          | 17.7<br>± 0         | 18.1<br>± 0         |

| Reporting group values                                                  | Total |  |  |
|-------------------------------------------------------------------------|-------|--|--|
| Number of subjects                                                      | 103   |  |  |
| Age categorical<br>Units: Subjects                                      |       |  |  |
| In utero                                                                | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                   | 0     |  |  |
| Newborns (0-27 days)                                                    | 0     |  |  |
| Infants and toddlers (28 days-23 months)                                | 0     |  |  |
| Children (2-11 years)                                                   | 0     |  |  |
| Adolescents (12-17 years)                                               | 0     |  |  |
| Adults (18-64 years)                                                    | 57    |  |  |
| From 65-84 years                                                        | 46    |  |  |
| 85 years and over                                                       | 0     |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -     |  |  |
| Gender categorical<br>Units: Subjects                                   |       |  |  |
| Female                                                                  | 15    |  |  |
| Male                                                                    | 88    |  |  |
| Smoker<br>Units: Subjects                                               |       |  |  |
| Never                                                                   | 42    |  |  |
| Former                                                                  | 34    |  |  |
| Current                                                                 | 27    |  |  |
| BMI<br>Units: Kg/m <sup>2</sup><br>median<br>standard deviation         | -     |  |  |
| Systolic BP<br>Units: mm Hg<br>arithmetic mean<br>standard deviation    | -     |  |  |
| Diastolic BP<br>Units: mm Hg<br>arithmetic mean                         |       |  |  |

|                                  |   |  |  |
|----------------------------------|---|--|--|
| standard deviation               | - |  |  |
| MAP                              |   |  |  |
| Units: mm Hg                     |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| HbA1c                            |   |  |  |
| Units: mmol/mol                  |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| Serum glucose                    |   |  |  |
| Units: mg/dl                     |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| Serum potassium                  |   |  |  |
| Units: mg/dl                     |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| haemoglobin                      |   |  |  |
| Units: g/dl                      |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| Total cholesterol                |   |  |  |
| Units: mmol/L                    |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| HDL                              |   |  |  |
| Units: mmol/L                    |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| LDL                              |   |  |  |
| Units: mmol/L                    |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| Triglycerides                    |   |  |  |
| Units: mmol/mol                  |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| Serum creatinine                 |   |  |  |
| Units: µmol/L                    |   |  |  |
| arithmetic mean                  |   |  |  |
| standard deviation               | - |  |  |
| Measured GFR                     |   |  |  |
| Units: mL/min/1.73m <sup>2</sup> |   |  |  |
| median                           |   |  |  |
| inter-quartile range (Q1-Q3)     | - |  |  |
| 24-hour proteinuria              |   |  |  |
| Units: gram                      |   |  |  |
| median                           |   |  |  |
| inter-quartile range (Q1-Q3)     | - |  |  |
| Known duration of diabetes       |   |  |  |
| Units: years                     |   |  |  |
| arithmetic mean                  |   |  |  |

|                    |   |  |  |
|--------------------|---|--|--|
| standard deviation | - |  |  |
|--------------------|---|--|--|

|  |
|--|
|  |
|--|

## End points

### End points reporting groups

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

### Primary: Progression to End Stage Renal Disease

|                                                                                                                                                                                                   |                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| End point title                                                                                                                                                                                   | Progression to End Stage Renal Disease |
| End point description:                                                                                                                                                                            |                                        |
| End point type                                                                                                                                                                                    | Primary                                |
| End point timeframe:<br>The Progression to End Stage Renal Disease defined as the need for chronic RRT by dialysis or kidney transplantation,during a median (IQR) follow-up of 41 (18-54 )months |                                        |

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

### Statistical analyses

|                                                                                                                                                                                                                |                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                     | Primary End Point                                         |
| Statistical analysis description:<br>The Progression to End Stage Renal Disease defined as the need for chronic RRT by dialysis or kidney transplantation,during a median (IQR) follow-up of 41 (18-54 )months |                                                           |
| Comparison groups                                                                                                                                                                                              | Benazepril v Valsartan v Combination Benazepril/Valsartan |

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

Notes:

[1] - Three comparisons were performed:

Valsartan vs Benazepril: p=0.018

Valsartan vs Combination: p=0.038

Benazepril vs Combination: NS

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse events will be reported during whole study up to 30 days after last dose of study drug.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

### Reporting groups

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

Reporting group description:

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

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

Reporting group description:

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

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Combination Benazepril/Valsartan |
|-----------------------|----------------------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30793466>