



## Clinical trial results:

**The Insulin Resistance Intervention after Stroke Trial A randomized, placebo-controlled trial of pioglitazone, compared with placebo, for prevention of stroke and myocardial infarction after ischemic stroke and transient ischemic attack**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2008-005546-23    |
| Trial protocol           | DE GB IT          |
| Global end of trial date | 01 September 2015 |

### Results information

|                                   |                                                                                  |
|-----------------------------------|----------------------------------------------------------------------------------|
| Result version number             | v1 (current)                                                                     |
| This version publication date     | 16 July 2016                                                                     |
| First version publication date    | 16 July 2016                                                                     |
| Summary attachment (see zip file) | Article with Main Results (Kernan.pdf)<br>Article supplement (Kernan_supapp.pdf) |

### Trial information

#### Trial identification

|                       |                        |
|-----------------------|------------------------|
| Sponsor protocol code | Protocol version 1.4.2 |
|-----------------------|------------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00091949 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                              |
|------------------------------|------------------------------------------------------------------------------|
| Sponsor organisation name    | Yale University School of Medicine                                           |
| Sponsor organisation address | 2 Church Street South, New Haven, United States, 06515                       |
| Public contact               | Walter N. Kernan, Department of Internal Medicine,<br>walter.kernan@yale.edu |
| Scientific contact           | Walter N. Kernan, Department of Internal Medicine,<br>walter.kernan@yale.edu |

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                       | 17 February 2016  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 01 September 2015 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 01 September 2015 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To determine if pioglitazone (a drug to treat insulin resistance), compared to placebo (a dummy medication), will reduce the overall risk for fatal or non-fatal stroke or fatal or non-fatal myocardial infarction (MI, commonly known as 'heart attack') among non-diabetic men and women aged 40 years or older with insulin resistance, who have experienced a recent stroke or transient ischaemic attack (a TIA, sometimes termed a 'mini-stroke'). We hypothesize that, among non-diabetics with insulin resistance, pioglitazone will reduce the rate of occurrence of any main outcome (fatal or non-fatal stroke or MI) within four years from 27% to 22%.

Protection of trial subjects:

Participants were contacted every 2 weeks during the initial 3 months of participation and then quarterly from month 4 to completion of follow-up. Frequent contacts during the first few months when dose of study drug was being titrated from 15mg to 45mg per day (pioglitazone or matching placebo) were designed to ensure that dose increases could be held or dose could be reduced if needed to manage potential adverse effects, such as excess weight gain, or new or worsened shortness of breath or edema.

Background therapy:

Under the IRIS protocol, administration of conventional therapies for secondary stroke prevention and for clinical abnormalities including hypertension, dyslipidemia, coronary artery disease, and obesity were the responsibility of the participants' primary care physicians, although the IRIS investigators monitored these therapies and encourage their use by feedback and educational outreach to participants and their physicians.

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 07 February 2005 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 256 |
| Country: Number of subjects enrolled | Germany: 151        |
| Country: Number of subjects enrolled | Italy: 48           |
| Country: Number of subjects enrolled | Israel: 178         |
| Country: Number of subjects enrolled | Australia: 108      |
| Country: Number of subjects enrolled | Canada: 543         |
| Country: Number of subjects enrolled | United States: 2592 |
| Worldwide total number of subjects   | 3876                |
| EEA total number of subjects         | 455                 |

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|-------------------------------------------|------|
| 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)                      | 2228 |
| From 65 to 84 years                       | 1571 |
| 85 years and over                         | 77   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited over the following periods:

United States: 07FEB05 through 03JAN13

Australia: 05OCT09 through 06JAN13

Canada: 26MAY05 through 15JAN13

Germany: 04FEB10 through 02JAN13

Israel: 27AUG07 through 11JAN13

Italy: 03JUN10 through 29NOV12

United Kingdom: 08MAR10 through 15JAN13

### Pre-assignment

Screening details:

Patients meeting inclusion criteria and who consented to participate had a fasting blood test at least 14 days after the qualifying stroke or TIA to determine final eligibility prior to randomization: Insulin resistance defined by HOMA-IR>3.0; glucose <7.0 mmol/l, hemoglobin A1c <7.0%, ALT < 2.5 ULN, hemoglobin>8.5 mg/dl.

### Pre-assignment period milestones

|                                            |                                            |
|--------------------------------------------|--------------------------------------------|
| Number of subjects started                 | 7548 <sup>[1]</sup>                        |
| Intermediate milestone: Number of subjects | Screening blood test completed: 7548       |
| Intermediate milestone: Number of subjects | HOMA > 3.0: 4776                           |
| Intermediate milestone: Number of subjects | Non diabetic: 4595                         |
| Intermediate milestone: Number of subjects | No other exclusions on blood test: 4579    |
| Intermediate milestone: Number of subjects | No other exclusions after blood test: 4427 |
| Number of subjects completed               | 3876                                       |

### Pre-assignment subject non-completion reasons

|                            |                                         |
|----------------------------|-----------------------------------------|
| Reason: Number of subjects | Did not meet eligibility criteria: 3672 |
|----------------------------|-----------------------------------------|

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: Participants underwent a screening blood test to determine final eligibility prior to being randomized into the trial.

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Baseline                                                      |
| Is this the baseline period? | Yes                                                           |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                                                                                                                                                                                                                      |              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| <b>Arm title</b>                                                                                                                                                                                                     | Placebo      |
| Arm description:                                                                                                                                                                                                     |              |
| Participants assigned to receive inactive tablet.                                                                                                                                                                    |              |
| Arm type                                                                                                                                                                                                             | Placebo      |
| Investigational medicinal product name                                                                                                                                                                               | placebo      |
| Investigational medicinal product code                                                                                                                                                                               |              |
| Other name                                                                                                                                                                                                           |              |
| Pharmaceutical forms                                                                                                                                                                                                 | Tablet       |
| Routes of administration                                                                                                                                                                                             | Oral use     |
| Dosage and administration details:                                                                                                                                                                                   |              |
| Protocol                                                                                                                                                                                                             |              |
| <b>Arm title</b>                                                                                                                                                                                                     | Pioglitazone |
| Arm description:                                                                                                                                                                                                     |              |
| Patients assigned to received pioglitazone.                                                                                                                                                                          |              |
| Arm type                                                                                                                                                                                                             | Experimental |
| Investigational medicinal product name                                                                                                                                                                               | pioglitazone |
| Investigational medicinal product code                                                                                                                                                                               |              |
| Other name                                                                                                                                                                                                           |              |
| Pharmaceutical forms                                                                                                                                                                                                 | Tablet       |
| Routes of administration                                                                                                                                                                                             | Oral use     |
| Dosage and administration details:                                                                                                                                                                                   |              |
| Protocol was for study drug dose of 1 15mg tablet per day for 1 month, then 2 15 mg tablets per day for 1 month, then 3 15mg tablets per day for 1 month, then 1 45 mg tablet per day for remainder of participation |              |

| Number of subjects in period 1 | Placebo | Pioglitazone |
|--------------------------------|---------|--------------|
| Started                        | 1937    | 1939         |
| Completed                      | 1937    | 1939         |

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| <b>Period 2</b>              |                                                               |
| Period 2 title               | Follow-up                                                     |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |
| <b>Arms</b>                  |                                                               |
| Are arms mutually exclusive? | Yes                                                           |

|                                                                       |          |
|-----------------------------------------------------------------------|----------|
| <b>Arm title</b>                                                      | Placebo  |
| Arm description:<br>Participants assigned to receive inactive tablet. |          |
| Arm type                                                              | Placebo  |
| Investigational medicinal product name                                | placebo  |
| Investigational medicinal product code                                |          |
| Other name                                                            |          |
| Pharmaceutical forms                                                  | Tablet   |
| Routes of administration                                              | Oral use |

Dosage and administration details:

Protocol called for 1 pill/day for 1 month, then 2 pills/day for 1 month, then 3 pills/day for 1 month, then 1 (larger) pill for day for remainder of participation

|                                                                 |              |
|-----------------------------------------------------------------|--------------|
| <b>Arm title</b>                                                | Pioglitazone |
| Arm description:<br>Patients assigned to received pioglitazone. |              |
| Arm type                                                        | Experimental |
| Investigational medicinal product name                          | pioglitazone |
| Investigational medicinal product code                          |              |
| Other name                                                      |              |
| Pharmaceutical forms                                            | Tablet       |
| Routes of administration                                        | Oral use     |

Dosage and administration details:

Protocol dose was 15 mgs/day for 1 month, then 30 mgs/day for 1 month, then 45 mg/day for remainder of participation

| <b>Number of subjects in period 2</b> | Placebo | Pioglitazone |
|---------------------------------------|---------|--------------|
| Started                               | 1937    | 1939         |
| Completed                             | 1786    | 1764         |
| Not completed                         | 151     | 175          |
| Consent withdrawn by subject          | 110     | 117          |
| Lost to follow-up                     | 41      | 58           |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants assigned to receive inactive tablet.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Pioglitazone |
|-----------------------|--------------|

Reporting group description:

Patients assigned to received pioglitazone.

| Reporting group values                                | Placebo | Pioglitazone | Total |
|-------------------------------------------------------|---------|--------------|-------|
| Number of subjects                                    | 1937    | 1939         | 3876  |
| Age categorical<br>Units: Subjects                    |         |              |       |
| In utero                                              | 0       | 0            | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0            | 0     |
| Newborns (0-27 days)                                  | 0       | 0            | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0       | 0            | 0     |
| Children (2-11 years)                                 | 0       | 0            | 0     |
| Adolescents (12-17 years)                             | 0       | 0            | 0     |
| Adults (18-64 years)                                  | 1115    | 1113         | 2228  |
| From 65-84 years                                      | 783     | 788          | 1571  |
| 85 years and over                                     | 39      | 38           | 77    |
| Age continuous<br>Units: years                        |         |              |       |
| arithmetic mean                                       | 63.5    | 63.5         |       |
| standard deviation                                    | ± 10.6  | ± 10.7       | -     |
| Gender categorical<br>Units: Subjects                 |         |              |       |
| Female                                                | 692     | 646          | 1338  |
| Male                                                  | 1245    | 1293         | 2538  |

## End points

### End points reporting groups

|                                                                                   |              |
|-----------------------------------------------------------------------------------|--------------|
| Reporting group title                                                             | Placebo      |
| Reporting group description:<br>Participants assigned to receive inactive tablet. |              |
| Reporting group title                                                             | Pioglitazone |
| Reporting group description:<br>Patients assigned to received pioglitazone.       |              |
| Reporting group title                                                             | Placebo      |
| Reporting group description:<br>Participants assigned to receive inactive tablet. |              |
| Reporting group title                                                             | Pioglitazone |
| Reporting group description:<br>Patients assigned to received pioglitazone.       |              |

### Primary: Stroke or MI

|                                         |              |
|-----------------------------------------|--------------|
| End point title                         | Stroke or MI |
| End point description:                  |              |
| End point type                          | Primary      |
| End point timeframe:<br>During followup |              |

| End point values                  | Placebo         | Pioglitazone    |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 1937            | 1939            |  |  |
| Units: Patients with stroke or MI | 228             | 175             |  |  |

### Statistical analyses

|                                                                                                           |                         |
|-----------------------------------------------------------------------------------------------------------|-------------------------|
| Statistical analysis title                                                                                | Time to primary outcome |
| Statistical analysis description:<br>Cox regression model for time to first stroke or MI during followup. |                         |
| Comparison groups                                                                                         | Placebo v Pioglitazone  |
| Number of subjects included in analysis                                                                   | 3876                    |
| Analysis specification                                                                                    | Pre-specified           |
| Analysis type                                                                                             | superiority             |
| P-value                                                                                                   | = 0.0067 <sup>[1]</sup> |
| Method                                                                                                    | Regression, Cox         |
| Parameter estimate                                                                                        | Hazard ratio (HR)       |
| Point estimate                                                                                            | 0.76                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.62    |
| upper limit         | 0.93    |

Notes:

[1] - p-value was adjusted for interim looks.

## Secondary: Stroke alone

|                                       |              |
|---------------------------------------|--------------|
| End point title                       | Stroke alone |
| End point description:                |              |
| Ischemic or hemorrhagic stroke events |              |
| End point type                        | Secondary    |
| End point timeframe:                  |              |
| During followup                       |              |

| End point values            | Placebo         | Pioglitazone    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 1937            | 1939            |  |  |
| Units: participants         | 154             | 127             |  |  |

## Statistical analyses

|                                         |                        |
|-----------------------------------------|------------------------|
| Statistical analysis title              | Time to stroke         |
| Statistical analysis description:       |                        |
| Time to first stroke during followup    |                        |
| Comparison groups                       | Placebo v Pioglitazone |
| Number of subjects included in analysis | 3876                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.19 [2]             |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.82                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.61                   |
| upper limit                             | 1.1                    |

Notes:

[2] - P-value has been correct for multiplicity (5 secondary outcomes).

## Secondary: Acute coronary syndrome

|                 |                         |
|-----------------|-------------------------|
| End point title | Acute coronary syndrome |
|-----------------|-------------------------|

|                                                     |           |
|-----------------------------------------------------|-----------|
| End point description:                              |           |
| Myocardial infarction or episode of unstable angina |           |
| End point type                                      | Secondary |
| End point timeframe:                                |           |
| During followup                                     |           |

| End point values            | Placebo         | Pioglitazone    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 1937            | 1939            |  |  |
| Units: participants         | 249             | 206             |  |  |

## Statistical analyses

| Statistical analysis title                                        | Time to ACS            |
|-------------------------------------------------------------------|------------------------|
| Statistical analysis description:                                 |                        |
| Time to first myocardial infarction or episode of unstable angina |                        |
| Comparison groups                                                 | Placebo v Pioglitazone |
| Number of subjects included in analysis                           | 3876                   |
| Analysis specification                                            | Pre-specified          |
| Analysis type                                                     | superiority            |
| P-value                                                           | = 0.11 <sup>[3]</sup>  |
| Method                                                            | Regression, Cox        |
| Parameter estimate                                                | Hazard ratio (HR)      |
| Point estimate                                                    | 0.75                   |
| Confidence interval                                               |                        |
| level                                                             | 95 %                   |
| sides                                                             | 2-sided                |
| lower limit                                                       | 0.52                   |
| upper limit                                                       | 1.07                   |

Notes:

[3] - P-value was adjusted for multiplicity (5 secondary outcomes).

## Secondary: Stroke, myocardial infarction or serious heart failure

|                                                                                                                                             |                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                                                             | Stroke, myocardial infarction or serious heart failure |
| End point description:                                                                                                                      |                                                        |
| Time to first stroke, myocardial infarction or serious episode of heart failure (i.e., heart failure resulting in hospitalization or death) |                                                        |
| End point type                                                                                                                              | Secondary                                              |
| End point timeframe:                                                                                                                        |                                                        |
| During followup                                                                                                                             |                                                        |

| End point values            | Placebo         | Pioglitazone    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 1937            | 1939            |  |  |
| Units: participants         | 249             | 206             |  |  |

## Statistical analyses

| Statistical analysis title                        | Time to stroke, MI or serious heart failure |
|---------------------------------------------------|---------------------------------------------|
| Statistical analysis description:                 |                                             |
| Time to first stroke, MI or serious heart failure |                                             |
| Comparison groups                                 | Placebo v Pioglitazone                      |
| Number of subjects included in analysis           | 3876                                        |
| Analysis specification                            | Pre-specified                               |
| Analysis type                                     | superiority                                 |
| P-value                                           | = 0.11 <sup>[4]</sup>                       |
| Method                                            | Regression, Cox                             |
| Parameter estimate                                | Hazard ratio (HR)                           |
| Point estimate                                    | 0.82                                        |
| Confidence interval                               |                                             |
| level                                             | 95 %                                        |
| sides                                             | 2-sided                                     |
| lower limit                                       | 0.65                                        |
| upper limit                                       | 1.05                                        |

Notes:

[4] - P-value corrected for multiplicity (5 secondary outcomes)

## Secondary: Diabetes mellitus

| End point title            | Diabetes mellitus |
|----------------------------|-------------------|
| End point description:     |                   |
| Time to new onset diabetes |                   |
| End point type             | Secondary         |
| End point timeframe:       |                   |
| During followup            |                   |

| End point values            | Placebo         | Pioglitazone    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 1937            | 1939            |  |  |
| Units: participants         | 149             | 73              |  |  |

## Statistical analyses

| Statistical analysis title | Time to new onset diabetes |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

|                                         |                        |
|-----------------------------------------|------------------------|
| Statistical analysis description:       |                        |
| Time to onset of diabetes               |                        |
| Comparison groups                       | Placebo v Pioglitazone |
| Number of subjects included in analysis | 3876                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | < 0.001 <sup>[5]</sup> |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.48                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.33                   |
| upper limit                             | 0.69                   |

Notes:

[5] - P value has been adjusted for multiplicity (5 secondary outcomes)

## Secondary: Death

|                              |           |
|------------------------------|-----------|
| End point title              | Death     |
| End point description:       |           |
| Time to death from any cause |           |
| End point type               | Secondary |
| End point timeframe:         |           |
| During followp               |           |

| End point values            | Placebo         | Pioglitazone    |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 1937            | 1939            |  |  |
| Units: participants         | 146             | 136             |  |  |

## Statistical analyses

|                                         |                        |
|-----------------------------------------|------------------------|
| Statistical analysis title              | Time to death          |
| Statistical analysis description:       |                        |
| Time to death from any cause            |                        |
| Comparison groups                       | Placebo v Pioglitazone |
| Number of subjects included in analysis | 3876                   |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.52 <sup>[6]</sup>  |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.93                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.73    |
| upper limit         | 1.17    |

Notes:

[6] - P value adjusted for multiplicity (5 secondary outcomes)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During followup.

Adverse event reporting additional description:

Participants were interviewed every 2 weeks during first 3 months and then quarterly from month 4 to month 60 (or last scheduled contact before July 2015).

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

|                       |              |
|-----------------------|--------------|
| Reporting group title | Pioglitazone |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events                               | Placebo                                                                                     | Pioglitazone           |  |
|------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------|--|
| Total subjects affected by serious adverse events    |                                                                                             |                        |  |
| subjects affected / exposed                          | 987 / 1937<br>(50.96%)                                                                      | 950 / 1939<br>(48.99%) |  |
| number of deaths (all causes)                        | 146                                                                                         | 136                    |  |
| number of deaths resulting from adverse events       | 0                                                                                           | 0                      |  |
| Cardiac disorders                                    |                                                                                             |                        |  |
| Heart failure                                        | Additional description: Heart failure resulting in hospitalization or death during followup |                        |  |
| subjects affected / exposed                          | 42 / 1937 (2.17%)                                                                           | 51 / 1939 (2.63%)      |  |
| occurrences causally related to treatment / all      | 0 / 55                                                                                      | 0 / 61                 |  |
| deaths causally related to treatment / all           | 0 / 2                                                                                       | 0 / 3                  |  |
| General disorders and administration site conditions |                                                                                             |                        |  |
| Hospitalisation                                      | Additional description: Hospital stays over 24 hours during followup.                       |                        |  |
| subjects affected / exposed                          | 946 / 1937<br>(48.84%)                                                                      | 908 / 1939<br>(46.83%) |  |
| occurrences causally related to treatment / all      | 97 / 2023                                                                                   | 134 / 1844             |  |
| deaths causally related to treatment / all           | 0 / 0                                                                                       | 0 / 0                  |  |
| Cancer                                               | Additional description: Incident cancer during follow-up                                    |                        |  |
| subjects affected / exposed                          | 150 / 1937 (7.74%)                                                                          | 133 / 1939 (6.86%)     |  |
| occurrences causally related to treatment / all      | 0 / 163                                                                                     | 0 / 144                |  |
| deaths causally related to treatment / all           | 0 / 33                                                                                      | 0 / 27                 |  |
| Bone fracture                                        | Additional description: Bone fracture requiring surgery or hospitalization during           |                        |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
|                                                 | followup          |                   |  |
| subjects affected / exposed                     | 62 / 1937 (3.20%) | 99 / 1939 (5.11%) |  |
| occurrences causally related to treatment / all | 0 / 99            | 0 / 178           |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |

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

| Non-serious adverse events                            | Placebo                                                                                         | Pioglitazone         |  |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                                                                                                 |                      |  |
| subjects affected / exposed                           | 1549 / 1937 (79.97%)                                                                            | 1666 / 1939 (85.92%) |  |
| Cardiac disorders                                     |                                                                                                 |                      |  |
| Heart failure                                         | Additional description: Heart failure not resulting in death or hospitalization during followup |                      |  |
| subjects affected / exposed                           | 32 / 1937 (1.65%)                                                                               | 29 / 1939 (1.50%)    |  |
| occurrences (all)                                     | 33                                                                                              | 29                   |  |
| General disorders and administration site conditions  |                                                                                                 |                      |  |
| Bone fracture                                         | Additional description: Bone fracture not requiring surgery or hospitalization during followup  |                      |  |
| subjects affected / exposed                           | 94 / 1937 (4.85%)                                                                               | 133 / 1939 (6.86%)   |  |
| occurrences (all)                                     | 126                                                                                             | 198                  |  |
| Excessive weight gain                                 | Additional description: Weight gain > 13.6 kgs from baseline at any time during followup        |                      |  |
| subjects affected / exposed                           | 88 / 1937 (4.54%)                                                                               | 221 / 1939 (11.40%)  |  |
| occurrences (all)                                     | 305                                                                                             | 892                  |  |
| Edema                                                 | Additional description: New or worse swelling of feet or lower legs                             |                      |  |
| subjects affected / exposed                           | 483 / 1937 (24.94%)                                                                             | 691 / 1939 (35.64%)  |  |
| occurrences (all)                                     | 731                                                                                             | 1093                 |  |
| Shortness of breath                                   | Additional description: Shortness of breath that was new or worse during followup               |                      |  |
| subjects affected / exposed                           | 292 / 1937 (15.07%)                                                                             | 342 / 1939 (17.64%)  |  |
| occurrences (all)                                     | 379                                                                                             | 444                  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 August 2011 | Protocol amendment dealing with risk of bladder cancer. Protocol revised to v.1.5.<br>Bladder Cancer section (D.11.3.3) revised to bring the science up-to-date and describe recent regulatory changes. In 2011, two observational studies were published or completed that reported an association between use of pioglitazone for treatment of diabetes and increased risk for bladder cancer. These studies were consistent with trends reported in clinical trials. As a result of these studies, the US FDA modified the package insert for pioglitazone on August 4, 2011 to include a warning about the risk and a description of the observational studies, and recommended against use in persons with bladder cancer. The European Medicine Agency (EMA) recommended changes very similar to the FDA but included unexplained gross (macroscopic) hematuria as a contraindication for use of pioglitazone. In response to these development, we added new exclusion for patients who may be at high risk for bladder cancer (see section D.5.12.2 and added additional query regarding interval development of gross hematuria to the Annual Interview. |

Notes:

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### 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/26886418>