



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) Article supplement (Kernan_supapp.pdf)

Trial information

Trial identification

Sponsor protocol code	Protocol version 1.4.2
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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, walter.kernan@yale.edu
Scientific contact	Walter N. Kernan, Department of Internal Medicine, 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:

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)	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 ^[1]
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
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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
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Arm title	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	
Arm title	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

Period 2	
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
Arms	
Are arms mutually exclusive?	Yes

Arm title	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 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

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

Number of subjects in period 2	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
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Reporting group description:

Participants assigned to receive inactive tablet.

Reporting group title	Pioglitazone
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Reporting group description:

Patients assigned to received pioglitazone.

Reporting group values	Placebo	Pioglitazone	Total
Number of subjects	1937	1939	3876
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)	1115	1113	2228
From 65-84 years	783	788	1571
85 years and over	39	38	77
Age continuous Units: years			
arithmetic mean	63.5	63.5	
standard deviation	± 10.6	± 10.7	-
Gender categorical Units: Subjects			
Female	692	646	1338
Male	1245	1293	2538

End points

End points 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 title	Placebo
Reporting group description: Participants assigned to receive inactive tablet.	
Reporting group title	Pioglitazone
Reporting group description: 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: 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: 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 ^[1]
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
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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 ^[3]
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 ^[4]
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
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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 ^[5]
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 ^[6]
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Pioglitazone
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Reporting group description: -

Serious adverse events	Placebo	Pioglitazone	
Total subjects affected by serious adverse events			
subjects affected / exposed	987 / 1937 (50.96%)	950 / 1939 (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 (48.84%)	908 / 1939 (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. 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26886418>