



Clinical trial results:

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Ranolazine When Added to Glimepiride in Subjects with Type 2 Diabetes Mellitus

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-000997-77 |
| Trial protocol | HU CZ PL SK |
| Global end of trial date | 28 August 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 22 March 2016 |
| First version publication date | 05 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-259-0110 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01494987 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Clinical Trial Mailbox, Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |

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 | 28 August 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 August 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study to determine the effect of ranolazine when added to glimepiride on glycemic control in adults with type 2 diabetes mellitus (T2DM) who are inadequately controlled despite current treatment with stable sulfonylurea or metformin therapy in addition to diet and exercise.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Treatment period: participants received glimepiride 4 mg once daily for 24 weeks.

Participants were required to maintain their diet and exercise regimen.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 12 January 2012 |
| 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 | Poland: 9 |
| Country: Number of subjects enrolled | Slovakia: 3 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Russian Federation: 203 |
| Country: Number of subjects enrolled | Ukraine: 53 |
| Country: Number of subjects enrolled | United States: 121 |
| Country: Number of subjects enrolled | Romania: 20 |
| Country: Number of subjects enrolled | South Africa: 7 |
| Country: Number of subjects enrolled | Serbia: 4 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 431 |
| EEA total number of subjects | 43 |

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) | 314 |
| From 65 to 84 years | 117 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled (during the Qualifying Period) at a total of 103 study sites in Asia, Europe, South Africa, and the United States. The first participant was screened on 12 January 2012. The last participant observation occurred on 28 August 2013.

Pre-assignment

Screening details:

595 participants entered the qualifying period (355 required and completed the glimepiride stabilization period); 431 were randomized and treated (Safety Analysis Set). Of these, 14 were excluded due to major eligibility criteria protocol violation or had no baseline or ontreatment data; thus, 417 were included in the Full Analysis Set.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall study (overall period) |
| 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 |
| Arm title | Placebo+Glimepiride |

Arm description:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period.

Treatment period: participants were randomized to receive placebo to match ranolazine plus glimepiride 4 mg once daily for 24 weeks.

Participants were required to maintain their diet and exercise regimen.

| | |
|--|-----------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to match ranolazine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to match ranolazine tablet(s) for the duration of the study

| | |
|--|-------------|
| Investigational medicinal product name | Glimepiride |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Glimepiride tablets (2 mg or 4 mg) administered orally once daily with the morning dose of study drug or placebo. The target dosing regimen for glimepiride is 4 mg once daily.

| | |
|------------------|------------------------|
| Arm title | Ranolazine+Glimepiride |
|------------------|------------------------|

Arm description:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period.

Treatment period: participants were randomized to receive ranolazine (1 x 500 mg tablet) twice daily plus glimepiride 4 mg once daily on Days 1 through 7, followed by ranolazine 1000 mg (2 x 500 mg tablets) twice daily plus glimepiride 4 mg once daily from Day 8 (or by Day 16 if not well tolerated) through Week 24.

Participants were required to maintain their diet and exercise regimen.

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

Dosage and administration details:

Ranolazine tablet(s) (1 or 2 x 500 mg) administered orally twice daily

| | |
|--|-------------|
| Investigational medicinal product name | Glimepiride |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Glimepiride tablets (2 mg or 4 mg) administered orally once daily with the morning dose of study drug or placebo. The target dosing regimen for glimepiride was 4 mg once daily.

| Number of subjects in period 1 | Placebo+Glimepiride | Ranolazine+Glimepiride |
|---------------------------------------|---------------------|------------------------|
| Started | 216 | 215 |
| Completed | 188 | 187 |
| Not completed | 28 | 28 |
| Subject Non-Compliance | 9 | 10 |
| Subject Withdrew Consent | 2 | 3 |
| Adverse event, non-fatal | 6 | 5 |
| Investigator's Discretion | 1 | 2 |
| Protocol Violation | 3 | 3 |
| Lost to follow-up | 1 | 1 |
| Hyperglycemia | 6 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo+Glimepiride |
|-----------------------|---------------------|

Reporting group description:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period.

Treatment period: participants were randomized to receive placebo to match ranolazine plus glimepiride 4 mg once daily for 24 weeks.

Participants were required to maintain their diet and exercise regimen.

| | |
|-----------------------|------------------------|
| Reporting group title | Ranolazine+Glimepiride |
|-----------------------|------------------------|

Reporting group description:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period.

Treatment period: participants were randomized to receive ranolazine (1 x 500 mg tablet) twice daily plus glimepiride 4 mg once daily on Days 1 through 7, followed by ranolazine 1000 mg (2 x 500 mg tablets) twice daily plus glimepiride 4 mg once daily from Day 8 (or by Day 16 if not well tolerated) through Week 24.

Participants were required to maintain their diet and exercise regimen.

| Reporting group values | Placebo+Glimepiride | Ranolazine+Glimepiride | Total |
|------------------------|---------------------|------------------------|-------|
| Number of subjects | 216 | 215 | 431 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|-----------|-----------|-----|
| Age continuous | | | |
| Baseline characteristics are reported for the Safety Analysis Set following randomization. The Safety Analysis Set includes randomized participants who received at least one dose of study treatment. | | | |
| Units: years | | | |
| arithmetic mean | 59 | 59 | |
| standard deviation | ± 8.6 | ± 8.8 | - |
| Gender categorical | | | |
| Safety Analysis Set | | | |
| Units: Subjects | | | |
| Female | 123 | 120 | 243 |
| Male | 93 | 95 | 188 |
| Race/Ethnicity | | | |
| Safety Analysis Set | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 4 | 3 | 7 |
| Black or African American | 10 | 3 | 13 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| White | 198 | 204 | 402 |
| Other | 2 | 5 | 7 |

| | | | |
|---|---------|---------|---|
| Body Mass Index | | | |
| Safety Analysis Set | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 32.8 | 32.2 | |
| standard deviation | ± 4.35 | ± 3.88 | - |
| Glycosylated hemoglobin (HbA1c) | | | |
| Safety Analysis Set | | | |
| Units: percent glycosylated hemoglobin | | | |
| arithmetic mean | 8.1 | 8.07 | |
| standard deviation | ± 0.746 | ± 0.776 | - |
| Fasting Serum Glucose | | | |
| Safety Analysis Set | | | |
| Units: mg/dL | | | |
| arithmetic mean | 177.2 | 177.4 | |
| standard deviation | ± 34.27 | ± 37.03 | - |
| Duration of Diabetes | | | |
| Participants in the Safety Analysis Set with available data were analyzed (n = 215 in both groups). | | | |
| Units: years | | | |
| arithmetic mean | 7 | 7.1 | |
| standard deviation | ± 5.07 | ± 4.92 | - |
| Estimated glomerular filtration rate (eGFR) | | | |
| Safety Analysis Set | | | |
| Units: mL/min/1.73m ² | | | |
| arithmetic mean | 83.2 | 81.2 | |
| standard deviation | ± 18.77 | ± 20.85 | - |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | Placebo+Glimepiride |
| Reporting group description: | |
| Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily. | |
| Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period. | |
| Treatment period: participants were randomized to receive placebo to match ranolazine plus glimepiride 4 mg once daily for 24 weeks. | |
| Participants were required to maintain their diet and exercise regimen. | |
| Reporting group title | Ranolazine+Glimepiride |
| Reporting group description: | |
| Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily. | |
| Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period. | |
| Treatment period: participants were randomized to receive ranolazine (1 x 500 mg tablet) twice daily plus glimepiride 4 mg once daily on Days 1 through 7, followed by ranolazine 1000 mg (2 x 500 mg tablets) twice daily plus glimepiride 4 mg once daily from Day 8 (or by Day 16 if not well tolerated) through Week 24. | |
| Participants were required to maintain their diet and exercise regimen. | |
| Subject analysis set title | Placebo+Glimepiride FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo+Glimepiride Full Analysis Set (FAS): randomized participants who received ≥ 1 dose of study treatment with a baseline and at least one postbaseline measurement of HbA1c, excluding participants with major eligibility violations and analyzed based on randomized treatment, regardless of actual treatment received. | |
| Subject analysis set title | Ranolazine+Glimepiride FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Ranolazine+Glimepiride Full Analysis Set: randomized participants who received ≥ 1 dose of study treatment with a baseline and at least one postbaseline measurement of HbA1c, excluding participants with major eligibility violations and analyzed based on randomized treatment, regardless of actual treatment received. | |
| Subject analysis set title | Placebo+Glimepiride MMTT FAS |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Placebo+Glimepiride Mixed Meal Tolerance Test (MMTT) Full Analysis Set: randomized participants who received at least one dose of study treatment with a baseline and at least one postbaseline measurement of serum glucose at T=120 minutes during the MMTT, administered under fasting conditions, excluding participants with major eligibility protocol violations, analyzed based on the randomized treatment regardless of actual treatment received. | |
| Subject analysis set title | Ranolazine+Glimepiride MMTT FAS |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Ranolazine+Glimepiride MMTT Full Analysis Set: randomized participants who received at least one dose of study treatment with a baseline and at least one postbaseline measurement of serum glucose at T=120 minutes during the MMTT, administered under fasting conditions, excluding participants with major eligibility protocol violations, analyzed based on the randomized treatment regardless of actual treatment received. | |

Primary: Change From Baseline in Percent Glycosylated Hemoglobin (HbA1c) at Week 24

| | |
|--|--|
| End point title | Change From Baseline in Percent Glycosylated Hemoglobin (HbA1c) at Week 24 |
| End point description: The average (mean) change from baseline in HbA1c at Week 24 was analyzed. Participants in the Full Analysis Set with available data were analyzed. | |
| End point type | Primary |
| End point timeframe: Baseline; Week 24 | |

| End point values | Placebo+Glimepiride FAS | Ranolazine+Glimepiride FAS | | |
|--|-------------------------|----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 184 | 188 | | |
| Units: percent glycosylated hemoglobin | | | | |
| arithmetic mean (standard deviation) | | | | |
| HbA1c at Week 24 | 8.08 (± 1.07) | 7.58 (± 1.089) | | |
| Change from baseline in HbA1c at Week 24 | 0.03 (± 0.949) | -0.47 (± 0.971) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Placebo vs Ranolazine: Change in Percent HbA1c |
| Statistical analysis description: Assuming a common standard deviation of 1.2%, an effective sample size of 400 would provide at least 90% power to detect a statistically significant treatment difference of -0.5% (ranolazine vs. placebo) for the reduction of HbA1c from baseline at Week 24 based on a 2-sided alpha of 0.05 and 1:1 randomization. | |
| Comparison groups | Placebo+Glimepiride FAS v Ranolazine+Glimepiride FAS |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | < 0.001 ^[2] |
| Method | Mixed Effects Model Analysis |
| Parameter estimate | difference in least squares mean (LSM) |
| Point estimate | -0.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.71 |
| upper limit | -0.32 |

Notes:

[1] - The primary analysis of the change from Baseline in HbA1c at Week 24 was performed using a mixed models repeated measures (MMRM) approach which accounts for correlations among observations within a subject, allows for baseline adjustment, and uses all available data. Effects include baseline HbA1c value, prior anti-hyperglycemic therapy, treatment group, visit week, and treatment group by visit week interaction term.

[2] - P-value is from a mixed-effect model including terms for baseline HbA1c value, prior

Secondary: Change From Baseline in Incremental Change of 2-hour Postprandial Serum Glucose at Week 24

| | |
|---|--|
| End point title | Change From Baseline in Incremental Change of 2-hour Postprandial Serum Glucose at Week 24 |
| End point description: The average (mean) change from baseline in incremental change of 2-hour postprandial serum glucose at Week 24 was analyzed. Participants in the Mixed Meal Tolerance Test (MMTT) Full Analysis Set with available data were analyzed. | |
| End point type | Secondary |
| End point timeframe: Baseline; Week 24 | |

| End point values | Placebo+Glimepiride MMTT FAS | Ranolazine+Glimepiride MMTT FAS | | |
|--------------------------------------|------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 169 | 168 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -2 (± 42.6) | 1 (± 44.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Serum Glucose at Week 24

| | |
|--|--|
| End point title | Change From Baseline in Fasting Serum Glucose at Week 24 |
| End point description: The average (mean) change from baseline in fasting serum glucose at Week 24 was analyzed. Participants in the Full Analysis Set with available data were analyzed. | |
| End point type | Secondary |
| End point timeframe: Baseline; Week 24 | |

| End point values | Placebo+Glimepiride FAS | Ranolazine+Glimepiride FAS | | |
|--------------------------------------|-------------------------|----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 181 | 183 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | 8 (± 40.7) | 2 (± 45.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 2-hour Postprandial Serum Glucose at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in 2-hour Postprandial Serum Glucose at Week 24 |
|-----------------|--|

End point description:

The average (mean) change from baseline in 2-hour postprandial serum glucose at Week 24 was analyzed. Participants in the MMTT Full Analysis Set with available data were analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline; Week 24

| End point values | Placebo+Glimepiride MMTT FAS | Ranolazine+Glimepiride MMTT FAS | | |
|--------------------------------------|------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 175 | 172 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | 4 (± 58) | 1 (± 59.6) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 weeks plus 30 days

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo+Glimepiride |
|-----------------------|---------------------|

Reporting group description:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period.

Treatment period: participants were randomized to receive placebo to match ranolazine plus glimepiride 4 mg once daily for 24 weeks.

Participants were required to maintain their diet and exercise regimen.

| | |
|-----------------------|------------------------|
| Reporting group title | Ranolazine+Glimepiride |
|-----------------------|------------------------|

Reporting group description:

Glimepiride stabilization period (up to 8 weeks): participants not on stable glimepiride at a dose of 4 mg once daily received glimepiride 2 mg once daily, and if tolerated the dose was increased on Day 8 (+ 2 days) to 4 mg once daily.

Qualifying period: participants received placebo to match ranolazine twice daily in addition to glimepiride for 14 days (+ 2 days) and if $\geq 80\%$ compliant and meeting eligibility criteria continued to the treatment period.

Treatment period: participants were randomized to receive ranolazine (1 x 500 mg tablet) twice daily plus glimepiride 4 mg once daily on Days 1 through 7, followed by ranolazine 1000 mg (2 x 500 mg tablets) twice daily plus glimepiride 4 mg once daily from Day 8 (or by Day 16 if not well tolerated) through Week 24.

Participants were required to maintain their diet and exercise regimen.

| Serious adverse events | Placebo+Glimepiride | Ranolazine+Glimepiride | |
|---|---------------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 216 (1.85%) | 4 / 215 (1.86%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 216 (0.00%) | 1 / 215 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 216 (0.46%) | 0 / 215 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 216 (0.00%) | 1 / 215 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 216 (0.46%) | 0 / 215 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 216 (0.46%) | 0 / 215 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 0 / 216 (0.00%) | 1 / 215 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal vein thrombosis | | | |
| subjects affected / exposed | 0 / 216 (0.00%) | 1 / 215 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 216 (0.46%) | 0 / 215 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 216 (0.00%) | 1 / 215 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo+Glimepiride | Ranolazine+Glimepiride | |
|---|---------------------|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 216 (21.30%) | 42 / 215 (19.53%) | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 7 / 216 (3.24%) | 11 / 215 (5.12%) | |
| occurrences (all) | 8 | 11 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycemia | | | |
| subjects affected / exposed | 32 / 216 (14.81%) | 21 / 215 (9.77%) | |
| occurrences (all) | 37 | 25 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 10 / 216 (4.63%) | 13 / 215 (6.05%) | |
| occurrences (all) | 11 | 15 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 09 May 2012 | Secondary efficacy endpoints were revised as follows: specified that the change from baseline in PPG through Week 24 was the incremental change of 2-hour PPG; and added the change from baseline in 2-hour PPG at Week 24 to the endpoint of change from baseline in FSG at Week 24. |
| 07 September 2012 | The exclusion criterion regarding participants undergoing dialysis treatments was modified to additionally exclude participants with severe renal impairment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported