



## Clinical trial results:

### A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ranolazine Monotherapy in Subjects With Type 2 Diabetes Mellitus

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-002931-25  |
| Trial protocol           | HU CZ PL SK     |
| Global end of trial date | 21 October 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-259-0131 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01472185 |
| 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,<br>ClinicalTrialDisclosures@gilead.com |
| Scientific contact           | Clinical Trial Mailbox, Gilead Sciences International Ltd,<br>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                       | 21 October 2013 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 21 October 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 given as monotherapy on glycemic control in subjects with type 2 diabetes mellitus (T2DM) who were inadequately controlled with diet and exercise alone and who were treatment naive to antihyperglycemic therapy or had not received antihyperglycemic therapy in the 90 days (or thiazolidinediones [TZDs] for at least 24 weeks) prior to screening, and to characterize the relationship between HbA1c reduction and other glycemic parameters in subjects with T2DM.

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 under a US Investigational New Drug Application (IND) 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. These standards are consistent with the requirements of [the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312)], and the European Community Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 November 2011 |
| 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: 18              |
| Country: Number of subjects enrolled | Slovakia: 21            |
| Country: Number of subjects enrolled | Hungary: 21             |
| Country: Number of subjects enrolled | Russian Federation: 165 |
| Country: Number of subjects enrolled | United States: 118      |
| Country: Number of subjects enrolled | Ukraine: 75             |
| Country: Number of subjects enrolled | South Africa: 24        |
| Country: Number of subjects enrolled | Romania: 21             |
| Country: Number of subjects enrolled | Serbia: 2               |
| Worldwide total number of subjects   | 465                     |
| EEA total number of subjects         | 81                      |

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)                      | 397 |
| From 65 to 84 years                       | 68  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at a total of 113 study sites in the United States, South Africa, Europe, and Russia. The first participant was screened on 15 November 2011. The last participant observation occurred on 21 October 2013.

### Pre-assignment

Screening details:

605 participants entered the qualifying period; 465 were randomized, and 464 were randomized and treated (Safety Analysis Set). Of these, 8 were excluded due to major eligibility criteria protocol violation or had baseline but no on-treatment data; thus, 456 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     |
| <b>Arm title</b>             | Placebo |

Arm description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Placebo to match ranolazine for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

|  |          |
|--|----------|
| 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:

Placebo to match ranolazine administered orally (Qualifying Period = 1 tablet twice daily; Treatment Period = Days 1–7: 1 tablet twice daily; 2 tablets twice daily thereafter)

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

Arm description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Ranolazine tablets for up to 24 weeks.

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 tablets administered orally (Days 1–7: 1 × 500 mg twice daily; 2 × 500 mg twice daily thereafter)

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

Dosage and administration details:

Placebo to match ranolazine administered orally (1 tablet twice daily)

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo | Ranolazine |
|---|---------|------------|
| Started   | 232     | 232        |
| Completed   | 198     | 199        |
| Not completed                                       | 34      | 33         |
| Subject Withdrew Consent                            | 6       | 3          |
| Adverse Event Other than Hyperglycemia              | 3       | 10         |
| Investigator's Discretion                           | 3       | 1          |
| Subject Noncompliance                               | 8       | 15         |
| Lost to follow-up                                   | 4       | 1          |
| Hyperglycemia                                       | 5       | 2          |
| Protocol deviation                                  | 5       | 1          |

Notes:

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

Justification: One participant who was enrolled but not treated is not included in the subject disposition table.

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Placebo to match ranolazine for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

|                       |            |
|-----------------------|------------|
| Reporting group title | Ranolazine |
|-----------------------|------------|

Reporting group description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Ranolazine tablets for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

| Reporting group values | Placebo | Ranolazine | Total |
|------------------------|---------|------------|-------|
| Number of subjects     | 232     | 232        | 464   |
| Age categorical        |         |            |       |
| Units: Subjects        |         |            |       |

|  |         |         |     |
|--|---------|---------|-----|
| Age Continuous                         |         |         |     |
| Units: years                           |         |         |     |
| arithmetic mean                        | 56      | 55      |     |
| standard deviation                     | ± 9.3   | ± 9.5   | -   |
| Gender, Male/Female                    |         |         |     |
| Units: participants                    |         |         |     |
| Female                                 | 113     | 123     | 236 |
| Male                                   | 119     | 109     | 228 |
| Ethnicity                              |         |         |     |
| Units: Subjects                        |         |         |     |
| Hispanic or Latino                     | 31      | 29      | 60  |
| Not Hispanic or Latino                 | 201     | 202     | 403 |
| Unknown or Not Reported                | 0       | 1       | 1   |
| Race                                   |         |         |     |
| Units: Subjects                        |         |         |     |
| Asian                                  | 10      | 9       | 19  |
| Black or African-American              | 10      | 9       | 19  |
| White                                  | 209     | 213     | 422 |
| Other                                  | 2       | 1       | 3   |
| Not Permitted                          | 1       | 0       | 1   |
| Body Mass Index                        |         |         |     |
| Units: kg/m <sup>2</sup>               |         |         |     |
| arithmetic mean                        | 32.8    | 32.8    |     |
| standard deviation                     | ± 4.85  | ± 4.75  | -   |
| Glycosylated hemoglobin (HbA1c)        |         |         |     |
| Units: percent glycosylated hemoglobin |         |         |     |
| arithmetic mean                        | 8.01    | 8.06    |     |
| standard deviation                     | ± 0.727 | ± 0.732 | -   |

|  |                  |                  |   |
|--|------------------|------------------|---|
| Fasting Serum Glucose<br>Units: mg/dL<br>arithmetic mean<br>standard deviation   | 171.5<br>± 34.45 | 172.1<br>± 34.32 | - |
| Duration of Diabetes<br>Units: years<br>arithmetic mean<br>standard deviation  | 3<br>± 4         | 3<br>± 4.29      | - |
| Estimated glomerular filtration rate (eGFR)<br>Units: mL/min/1.73m <sup>2</sup><br>arithmetic mean<br>standard deviation | 83.3<br>± 18.4   | 84.5<br>± 18.8   | - |

## End points

### End points reporting groups

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

Reporting group description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Placebo to match ranolazine for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

|                       |            |
|-----------------------|------------|
| Reporting group title | Ranolazine |
|-----------------------|------------|

Reporting group description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Ranolazine tablets for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

### 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 (randomized participants who received  $\geq 1$  dose of study treatment with a baseline and at least one postbaseline measurement of HbA1c, excluding subjects with major eligibility violations and analyzed based on the randomized treatment regardless of actual treatment received) with available data were analyzed.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline; Week 24

| End point values                         | Placebo              | Ranolazine          |  |  |
|--|----------------------|---------------------|--|--|
| Subject group type                       | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed              | 195                  | 199                 |  |  |
| Units: percent of HbA1c in blood         |                      |                     |  |  |
| arithmetic mean (standard deviation)     |                      |                     |  |  |
| HbA1c at Week 24                         | 7.7 ( $\pm$ 1.183)   | 7.26 ( $\pm$ 1.101) |  |  |
| Change from baseline in HbA1c at Week 24 | -0.27 ( $\pm$ 1.027) | -0.8 ( $\pm$ 1.02)  |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Placebo vs Ranolazine: Change in 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                       | Ranolazine v Placebo                   |
| Number of subjects included in analysis | 394                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.0001 <sup>[1]</sup>                |
| Method                                  | Mixed Effects Model Analysis           |
| Parameter estimate                      | Difference in least squares mean (LSM) |
| Point estimate                          | -0.56                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -0.76                                  |
| upper limit                             | -0.36                                  |

Notes:

[1] - P-value is from a mixed effects model including terms for baseline HbA1c value, treatment group, visit week, and treatment by visit week interaction. Unstructured covariance matrix was used.

### 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         | Ranolazine      |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 191             | 197             |  |  |
| Units: mg/dL                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 1 (± 42.2)      | -7 (± 37.5)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with HbA1c < 7% at Week 24

|  |   |
|--|---|
| End point title  | Percentage of participants with HbA1c < 7% at Week 24 |
| End point description:   |   |
| Participants in the Full Analysis Set with Baseline HbA1c ≥ 7% and available data were analyzed. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Week 24  |   |

| End point values                  | Placebo         | Ranolazine      |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 195             | 199             |  |  |
| Units: percentage of participants |                 |                 |  |  |
| number (not applicable)           | 25.6            | 41.2            |  |  |

## 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.

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 time [T] = 120 minutes during the MMTT, administered under fasting conditions, excluding participants with major eligibility protocol violations and analyzed based on the randomized treatment regardless of actual treatment received.

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         | Ranolazine      |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 178             | 185             |  |  |
| Units: mg/dL                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 2 (± 65.1)      | -19 (± 53.8)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### 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 |
|-----------------|--|

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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.

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

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End point timeframe:

Baseline; Week 24

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| End point values                     | Placebo         | Ranolazine      |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 173             | 180             |  |  |
| Units: mg/dL                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | -1 (± 47.7)     | -12 (± 37.9)    |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 24 Weeks plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: randomized participants who received at least one dose of study treatment, analyzed based on actual treatment received.

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

### Dictionary used

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

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

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Ranolazine |
|-----------------------|------------|

Reporting group description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Ranolazine tablets for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

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

Reporting group description:

Qualifying Period: Placebo to match ranolazine for 14 days.

Treatment Period: Placebo to match ranolazine for up to 24 weeks.

Participants were required to maintain their diet and exercise regimen.

| Serious adverse events  | Ranolazine      | Placebo         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                 |                 |  |
| subjects affected / exposed   | 6 / 232 (2.59%) | 7 / 232 (3.02%) |  |
| 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) |                 |                 |  |
| Non-small cell lung cancer stage IV                                 |                 |                 |  |
| subjects affected / exposed   | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Uterine cancer  |                 |                 |  |
| subjects affected / exposed   | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Superior vena cava syndrome                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 232 (0.43%) | 0 / 232 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block second degree            |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 232 (0.43%) | 0 / 232 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Sinoatrial block                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 232 (0.43%) | 0 / 232 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis chronic                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 232 (0.00%) | 1 / 232 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 232 (0.43%) | 0 / 232 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Infected dermal cyst                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 232 (0.43%) | 0 / 232 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hyperglycaemia                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 232 (0.43%) | 0 / 232 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Ranolazine        | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 28 / 232 (12.07%) | 31 / 232 (13.36%) |  |
| Nervous system disorders                              |                   |                   |  |
| Headache  |                   |                   |  |
| subjects affected / exposed                           | 12 / 232 (5.17%)  | 10 / 232 (4.31%)  |  |
| occurrences (all)                                     | 13                | 14                |  |
| Metabolism and nutrition disorders                    |                   |                   |  |
| Hyperglycaemia  |                   |                   |  |
| subjects affected / exposed                           | 18 / 232 (7.76%)  | 23 / 232 (9.91%)  |  |
| occurrences (all)                                     | 32                | 27                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 09 May 2012       | <p>The secondary efficacy endpoints were revised to clarify that the change from baseline in postprandial serum glucose (PPG) through Week 24 referred to the incremental change of 2-hour PPG and the change from baseline in 2-hour PPG at Week 24 was added as a secondary endpoint. The unblinding procedures were revised to allow the investigator to unblind a subject's treatment in an emergency situation without prior contact with the sponsor's medical monitor. Rescue visit study procedures and waist circumference measurement procedures were added. The number of investigative centers worldwide was also increased.</p> <p>Inclusion criteria were revised as follows:</p> <ul style="list-style-type: none"><li>- The lower body mass index (BMI) threshold for inclusion was changed from 27 kg/m<sup>2</sup> to 25 kg/m<sup>2</sup></li><li>- The serum C-peptide threshold was changed from &gt; 1 ng/mL to ≥ 0.8 ng/mL</li></ul> <p>Exclusion criteria were revised as follows:</p> <ul style="list-style-type: none"><li>- An exclusion criterion was added for the thresholds of elevated transaminases and serum total bilirubin</li><li>- An exclusion criterion was added for subjects with a history of cancer</li><li>- The time frame in the exclusion criterion related to alcohol or other drug abuse was changed to &lt; 12 months prior to screening</li><li>- The exclusion criterion defining usage of antihyperglycemic agents was revised to specify that the use of TZDs for 24 weeks prior to screening was prohibited</li><li>- The exclusion criterion defining treatment with strong or moderate cytochrome P450 (CYP)3A inhibitors was revised to add the use of P glycoprotein (Pgp) inhibitors</li><li>- The exclusion criterion defining treatment with simvastatin was revised to exclude subjects taking lovastatin at a daily dose &gt; 40 mg</li></ul> |
| 07 September 2012 | <p>The exclusion criterion regarding participants undergoing dialysis treatments was modified to additionally exclude participants with severe renal impairment.</p>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes: