



## 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
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##### 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:

<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)	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
<b>Arm title</b>	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.

<b>Arm title</b>	Ranolazine+Glimepiride
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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.

<b>Number of subjects in period 1</b>	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
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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
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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	$\pm 8.6$	$\pm 8.8$	-
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 <sup>2</sup>			
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 <sup>2</sup>			
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 $\geq 1$ 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 $\geq 1$ 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 <sup>[1]</sup>
P-value	< 0.001 <sup>[2]</sup>
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
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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
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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	Placebo+Glimepiride
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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
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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 %

<b>Non-serious adverse events</b>	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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported