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, 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	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:

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)	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	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	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)

Arm title	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)

Number of subjects in period 1[1]	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^2			
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			
Units: mg/dL			
arithmetic mean	171.5	172.1	
standard deviation	± 34.45	± 34.32	-
Duration of Diabetes			
Units: years			
arithmetic mean	3	3	
standard deviation	± 4	± 4.29	-
Estimated glomerular filtration rate (eGFR)			
Units: mL/min/1.73m^2			
arithmetic mean	83.3	84.5	
standard deviation	± 18.4	± 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 ≥ 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 (± 1.183)	7.26 (± 1.101)		
Change from baseline in HbA1c at Week 24	-0.27 (± 1.027)	-0.8 (± 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 [1]
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

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	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

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 %

Non-serious adverse events	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	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. Inclusion criteria were revised as follows: - The lower body mass index (BMI) threshold for inclusion was changed from 27 kg/m^2 to 25 kg/m^2 - The serum C-peptide threshold was changed from > 1 ng/mL to ≥ 0.8 ng/mL Exclusion criteria were revised as follows: - An exclusion criterion was added for the thresholds of elevated transaminases and serum total bilirubin - An exclusion criterion was added for subjects with a history of cancer - The time frame in the exclusion criterion related to alcohol or other drug abuse was changed to < 12 months prior to screening - 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 - 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 - The exclusion criterion defining treatment with simvastatin was revised to exclude subjects taking lovastatin at a daily dose > 40 mg
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

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: