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 Metformin in Subjects with Type 2 Diabetes Mellitus

Summary

EudraCT number	2012-001259-37
Trial protocol	CZ HU PL
Global end of trial date	01 October 2013

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	GS-US-259-0147

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01555164
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	01 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 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, multicenter study to determine the effect of ranolazine when added to metformin on glycemic control in adults with type 2 diabetes mellitus (T2DM) who were inadequately controlled despite current treatment with stable 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: -

Evidence for comparator: -

Actual start date of recruitment	28 June 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: 5
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	United States: 149
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Russian Federation: 86
Country: Number of subjects enrolled	Ukraine: 64
Country: Number of subjects enrolled	India: 93
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Israel: 3
Worldwide total number of subjects	442
EEA total number of subjects	22

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)	372
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled (during the Qualifying Period) at a total of 112 study sites in Canada, Europe, Asia, Mexico, South Africa, and the United States. The first participant was screened on 28 June 2012. The last participant observation occurred on 01 October 2013.

Pre-assignment

Screening details:

580 participants enrolled in the Qualifying Period prior to randomization.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo+Metformin

Arm description:

Qualifying phase: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at Screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment phase.

Treatment phase: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily through Week 24.

Participants were required to maintain their diet and exercise regimen.

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin 1000 mg (2 x 500 mg tablets) administered twice daily

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 administered twice daily

Arm title	Ranolazine+metformin

Arm description:

Qualifying phase: Metformin 1000 mg + placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment phase.

Treatment phase: Ranolazine 500 mg + metformin 500 mg + placebo to match metformin twice daily on Days 1 through 7, followed by ranolazine 1000 mg + metformin 500 mg + placebo to match metformin twice daily from Day 8 through Week 24.

Participants were required to maintain their diet and exercise regimen.

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin 1000 mg (2 x 500 mg tablets) administered twice daily

Investigational medicinal product name	Ranolazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ranolazine 500 mg administered twice daily on Days 1 through 7, followed by ranolazine 1000 mg administered twice daily from Day 8 through Week 24.

Number of subjects in period 1	Placebo+Metformin	Ranolazine+metformin
Started	222	220
Completed	182	185
Not completed	40	35
'Subject Withdrew Consent '	6	11
Adverse event, non-fatal	5	7
Protocol violation	9	5
Hyperglycaemia	-	1
Investigator's Discretion	2	2
Subject Non-compliance	14	6
Lost to follow-up	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo+Metformin

Reporting group description:

Qualifying phase: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at Screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment phase.

Treatment phase: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily through Week 24.

Participants were required to maintain their diet and exercise regimen.

Reporting group title	Ranolazine+metformin

Reporting group description:

Qualifying phase: Metformin 1000 mg + placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment phase.

Treatment phase: Ranolazine 500 mg + metformin 500 mg + placebo to match metformin twice daily on Days 1 through 7, followed by ranolazine 1000 mg + metformin 500 mg + placebo to match metformin twice daily from Day 8 through Week 24.

Participants were required to maintain their diet and exercise regimen.

Reporting group values	Placebo+Metformin	Ranolazine+metformin	Total
Number of subjects	222	220	442
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	56	56	
standard deviation	± 8.9	± 9.3	-
Gender categorical Units: Subjects			
Female	98	121	219
Male	124	99	223
Ethnicity Units: Subjects			
Hispanic or Latino	53	37	90
Not Hispanic or Latino	166	181	347
Unknown or Not Reported	3	2	5
Race Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	52	54	106
Black or African American	8	11	19
White	160	153	313
Other	0	2	2

Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	31.2	31.6	
standard deviation	± 4.46	± 4.95	-
Estimated glomerular filtration rate (eGFR) Units: mL/min/1.73m^2			
arithmetic mean	90.8	89.9	
standard deviation	± 20.01	± 21.82	-
Glycosylated hemoglobin (HbA1c) Units: % hemoglobin which is glycosylated			
arithmetic mean	8.09	8.1	
standard deviation	± 0.729	± 0.692	-
Fasting Serum Glucose (FSG) Units: mg/dL			
arithmetic mean	170	168.8	
standard deviation	± 35.97	± 32.86	-
Duration of Diabetes Units: years			
arithmetic mean	6.7	6.4	
standard deviation	± 5.31	± 5.37	-

End points

End points reporting groups

Reporting group title	Placebo+Metformin

Reporting group description:

Qualifying phase: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at Screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment phase.

Treatment phase: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily through Week 24.

Participants were required to maintain their diet and exercise regimen.

Reporting group title	Ranolazine+metformin

Reporting group description:

Qualifying phase: Metformin 1000 mg + placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment phase.

Treatment phase: Ranolazine 500 mg + metformin 500 mg + placebo to match metformin twice daily on Days 1 through 7, followed by ranolazine 1000 mg + metformin 500 mg + placebo to match metformin twice daily from Day 8 through Week 24.

Participants were required to maintain their diet and exercise regimen.

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

End point title	Change From Baseline in 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 participants with major eligibility violations, and analyzed based on 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+Metformin	Ranolazine+metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	179		
Units: % hemoglobin which is glycosylated				
arithmetic mean (standard deviation)				
HbA1c at Week 24	7.86 (± 1.003)	7.72 (± 1.069)		
Change from baseline in HbA1c at Week 24	-0.2 (± 0.949)	-0.37 (± 0.916)		

Statistical analyses

Statistical analysis title	Difference in change from baseline
Comparison groups	Placebo+Metformin v Ranolazine+metformin
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.306 [2]
Method	Mixed Effects Model Analysis
Parameter estimate	difference in least squares mean
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.1

Notes:

[1] - 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 -0.4% (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.

[2] - P-value 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+Metformin	Ranolazine+metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	176		
Units: mg/dL				
arithmetic mean (standard deviation)	-3 (± 44.7)	3 (± 42.5)		

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.

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.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Placebo+Metformin	Ranolazine+metformin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	173		
Units: mg/dL				
arithmetic mean (standard deviation)	-4 (± 54)	7 (± 58.2)		

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo+Metformin

Reporting group description:

Qualifying period: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at Screening) and participants who were ≥ 80% compliant and meeting eligibility criteria continued to the treatment period.
Treatment period: Metformin 1000 mg (2 x 500 mg tablets) twice daily plus placebo to match ranolazine twice daily through Week 24.
Participants were required to maintain their diet and exercise regimen.

Reporting group title	Ranolazine+metformin

Reporting group description:

Qualifying Period: Participants will receive metformin 1000 mg + placebo to match ranolazine twice daily for either 2 or 8 weeks (dependent on metformin dose and HbA1c level at Screening).

Treatment Period: Participants will receive ranolazine 500 mg + metformin 500 mg + placebo to match metformin twice daily on Days 1 through 7, followed by ranolazine 1000 mg + metformin 500 mg + placebo to match metformin twice daily from Day 8 through Week 24.

Participants are required to maintain their diet and exercise regimen.

Serious adverse events	Placebo+Metformin	Ranolazine+metformin	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 222 (0.90%)	3 / 220 (1.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			

subjects affected / exposed	1 / 222 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 222 (0.45%)	0 / 220 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 222 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 222 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 220 (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			
Metabolic acidosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 220 (0.45%)	
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+Metformin	Ranolazine+metformin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 222 (6.31%)	18 / 220 (8.18%)	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	14 / 222 (6.31%)	18 / 220 (8.18%)	
occurrences (all)	19	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2012	Amendment 1: addition of a paragraph which describes the safety of ranolazine in subjects with mild, moderate and severe renal impairment; addition of bicarbonate to the standard safety panel at every study visit.

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.

Significantly lower metformin (MET) trough concentrations were observed in the ranolazine (RAN) 1000mg/MET 500mg group vs the placebo/MET 1000mg group-this may have contributed to the observed results with respect to the HbA1c and glucose endpoints.

Notes: