



Clinical trial results:

A phase 2, proof of concept, randomised, placebo-controlled, parallel group study to evaluate the effect of ranolazine and dronedarone when given alone and in combination on atrial fibrillation burden in subjects with paroxysmal atrial fibrillation

Summary

EudraCT number	2011-001134-42
Trial protocol	DE GB NL
Global end of trial date	10 March 2014

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-291-0102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01522651
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	10 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the effect of ranolazine and of low dose dronedarone when given alone and in combination at different dose levels on atrial fibrillation burden (AFB) over 12 weeks of treatment. AFB was defined as the total time a subject is in atrial tachycardia/atrial fibrillation (AT/AF) expressed as a percentage of total recording time.

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	24 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	134
EEA total number of subjects	86

Notes:

Subjects enrolled per age group

In utero	0
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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)	22
From 65 to 84 years	104
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Poland, Germany, Israel, Italy, and the Netherlands. The first participant was screened on 24 January 2012. The last study visit occurred on 10 March 2014.

Pre-assignment

Screening details:

327 participants were screened.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo to match ranolazine (ran) + placebo to match dronedarone (dron) for 12 weeks

Arm type	Placebo
Investigational medicinal product name	Ranolazine placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match ranolazine tablet administered orally twice daily

Investigational medicinal product name	Dronedarone placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match dronedarone capsule administered orally twice daily

Arm title	Ranolazine
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Arm description:

Ranolazine + placebo to match dronedarone for 12 weeks

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

Dosage and administration details:

Ranolazine 750 mg tablet administered orally twice daily

Investigational medicinal product name	Dronedarone placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match dronedarone capsule administered orally twice daily

Arm title	Dronedarone
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Arm description:

Placebo to match ranolazine + dronedarone 225 mg for 12 weeks

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

Dosage and administration details:

Placebo to match ranolazine tablet administered orally twice daily

Investigational medicinal product name	Dronedarone 225 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dronedarone 225 mg capsule administered orally twice daily

Arm title	Ranolazine+Dronedarone 225 mg
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Arm description:

Ranolazine + dronedarone 225 mg for 12 weeks

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

Dosage and administration details:

Ranolazine 750 mg tablet administered orally twice daily

Investigational medicinal product name	Dronedarone 225 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dronedarone 225 mg capsule administered orally twice daily

Arm title	Ranolazine+Dronedarone 150 mg
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Arm description:

Ranolazine + dronedarone 150 mg for 12 weeks

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

Dosage and administration details:

Ranolazine 750 mg tablet administered orally twice daily

Investigational medicinal product name	Dronedarone 150 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dronedarone 150 mg capsule administered orally twice daily

Number of subjects in period 1^[1]	Placebo	Ranolazine	Dronedarone
Started	26	26	26
Completed	17	19	22
Not completed	9	7	4
Device malfunction	-	1	-
Adverse event, non-fatal	3	4	4
Protocol violation	3	-	-
Subject non-compliance	1	-	-
Discontinued from study by sponsor	-	-	-
Cardioversion	1	-	-
Withdrew consent	1	1	-
Investigator's discretion	-	1	-

Number of subjects in period 1^[1]	Ranolazine+Dronedarone 225 mg	Ranolazine+Dronedarone 150 mg
Started	27	26
Completed	20	21
Not completed	7	5
Device malfunction	-	-
Adverse event, non-fatal	5	4
Protocol violation	-	-
Subject non-compliance	-	-

Discontinued from study by sponsor	1	-
Cardioversion	-	-
Withdrew consent	1	1
Investigator's discretion	-	-

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: Three participants who were randomized but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo to match ranolazine (ran) + placebo to match dronedarone (dron) for 12 weeks

Reporting group title	Ranolazine
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Reporting group description:

Ranolazine + placebo to match dronedarone for 12 weeks

Reporting group title	Dronedarone
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Reporting group description:

Placebo to match ranolazine + dronedarone 225 mg for 12 weeks

Reporting group title	Ranolazine+Dronedarone 225 mg
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Reporting group description:

Ranolazine + dronedarone 225 mg for 12 weeks

Reporting group title	Ranolazine+Dronedarone 150 mg
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Reporting group description:

Ranolazine + dronedarone 150 mg for 12 weeks

Reporting group values	Placebo	Ranolazine	Dronedarone
Number of subjects	26	26	26
Age categorical			
Units: Subjects			
< 65 years	6	5	2
≥ 65 to < 75 years	10	11	10
≥ 75 years	10	10	14
Age continuous			
Units: years			
arithmetic mean	72	70	75
standard deviation	± 8.4	± 10.8	± 7.8
Gender categorical			
Units: Subjects			
Female	13	16	16
Male	13	10	10
Race			
Units: Subjects			
Asian	0	0	0
White	26	26	26
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	22	25	26
Not Reported	2	1	0

Reporting group values	Ranolazine+Dronedarone 225 mg	Ranolazine+Dronedarone 150 mg	Total
Number of subjects	27	26	131

Age categorical			
Units: Subjects			
< 65 years	5	4	22
≥ 65 to < 75 years	13	9	53
≥ 75 years	9	13	56
Age continuous			
Units: years			
arithmetic mean	71	73	
standard deviation	± 7.1	± 9.4	-
Gender categorical			
Units: Subjects			
Female	12	11	68
Male	15	15	63
Race			
Units: Subjects			
Asian	0	1	1
White	27	25	130
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	1	6
Not Hispanic or Latino	24	25	122
Not Reported	0	0	3

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo to match ranolazine (ran) + placebo to match dronedarone (dron) for 12 weeks	
Reporting group title	Ranolazine
Reporting group description: Ranolazine + placebo to match dronedarone for 12 weeks	
Reporting group title	Dronedarone
Reporting group description: Placebo to match ranolazine + dronedarone 225 mg for 12 weeks	
Reporting group title	Ranolazine+Dronedarone 225 mg
Reporting group description: Ranolazine + dronedarone 225 mg for 12 weeks	
Reporting group title	Ranolazine+Dronedarone 150 mg
Reporting group description: Ranolazine + dronedarone 150 mg for 12 weeks	

Primary: Percent change from baseline in atrial fibrillation burden (AFB) by Week 12

End point title	Percent change from baseline in atrial fibrillation burden (AFB) by Week 12
End point description: AFB is defined as the total time a subject is in atrial tachycardia (AT)/atrial fibrillation (AF) expressed as a percentage of total recording time. Data are presented for baseline-adjusted AFB over 12 weeks of treatment.	
End point type	Primary
End point timeframe: Week 12	

End point values	Placebo	Ranolazine	Dronedarone	Ranolazine+Dronedarone 225 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	23	20
Units: percentage				
median (standard error)	-5.9 (± 18)	-23 (± 21.17)	3.5 (± 15.68)	-59.1 (± 10.47)

End point values	Ranolazine+Dronedarone 150			
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	mg			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: percentage				
median (standard error)	-45.5 (± 10.73)			

Statistical analyses

Statistical analysis title

Ranolazine vs Placebo

Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Placebo v Ranolazine
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.493
Method	F-test
Parameter estimate	Estimate
Point estimate	-19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.5
upper limit	51.5

Notes:

[1] - Comparative analysis

Statistical analysis title

Dronedarone vs Placebo

Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Placebo v Dronedarone
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.78
Method	F-test
Parameter estimate	Estimate
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.2
upper limit	98.2

Notes:

[2] - Comparative analysis

Statistical analysis title	Ranolazine+Dronedarone 225 mg vs Placebo
Statistical analysis description: An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.	
Comparison groups	Placebo v Ranolazine+Dronedarone 225 mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.008
Method	F-test
Parameter estimate	Estimate
Point estimate	-57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-76.8
upper limit	-20.1

Notes:

[3] - Comparative analysis

Statistical analysis title	Ranolazine+Dronedarone 150 mg vs Placebo
Statistical analysis description: An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.	
Comparison groups	Placebo v Ranolazine+Dronedarone 150 mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.072
Method	F-test
Parameter estimate	Estimate
Point estimate	-42.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.7
upper limit	5.2

Notes:

[4] - Comparative analysis

Statistical analysis title	Ranolazine vs Dronedarone
Statistical analysis description: An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise	

comparisons.

Comparison groups	Ranolazine v Dronedarone
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.315
Method	F-test

Notes:

[5] - Comparative analysis

Statistical analysis title	Ranolazine vs Ranolazine+Dronedarone 225 mg
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Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Ranolazine v Ranolazine+Dronedarone 225 mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.049
Method	F-test

Notes:

[6] - Comparative analysis

Statistical analysis title	Dronedarone vs Ranolazine+Dronedarone 225 mg
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Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Dronedarone v Ranolazine+Dronedarone 225 mg
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	= 0.002
Method	F-test

Notes:

[7] - Comparative analysis

Statistical analysis title	Dronedarone vs Ranolazine+Dronedarone 150 mg
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Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Dronedarone v Ranolazine+Dronedarone 150 mg
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	= 0.028
Method	F-test

Notes:

[8] - Comparative analysis

Statistical analysis title	Ran+Dron 225 mg vs Ran+Dron 150 mg
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Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Ranolazine+Dronedarone 150 mg v Ranolazine+Dronedarone 225 mg
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.334
Method	F-test

Notes:

[9] - Comparative analysis

Statistical analysis title	All Treatment Groups Comparison
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Statistical analysis description:

An equal-slopes ANCOVA (analysis of covariance) model was fitted to log-transformed AFB over 12 weeks, with baseline AFB as the covariate. AFB values < 1% (> 99%) were set to 1% (99%) before transformation. The global F-test of equality of all 5 treatment group means was followed by all pairwise comparisons.

Comparison groups	Ranolazine+Dronedarone 150 mg v Ranolazine+Dronedarone 225 mg v Placebo v Dronedarone v Ranolazine
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	= 0.012
Method	F-test

Notes:

[10] - Comparative analysis

Primary: Absolute change from baseline in AFB by Week 12

End point title	Absolute change from baseline in AFB by Week 12 ^[11]
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End point description:

AFB is defined as the total time a subject is in atrial tachycardia (AT)/atrial fibrillation (AF) expressed as a percentage of total recording time. Data are presented for baseline-adjusted AFB over 12 weeks of treatment.

End point type	Primary
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End point timeframe:

Week 12

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was performed for the percent change from baseline in AFB by Week

12. No statistical analysis was performed or presented on the absolute change from baseline.

End point values	Placebo	Ranolazine	Dronedarone	Ranolazine+Dronedarone 225 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	23	20
Units: percentage of total recording time				
arithmetic mean (standard error)	4.6 (± 3.19)	-3.1 (± 2.17)	5.6 (± 2.65)	-4.7 (± 3.24)

End point values	Ranolazine+Dronedarone 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: percentage of total recording time				
arithmetic mean (standard error)	-3.9 (± 3.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who have ≥ 30%, ≥ 50%, or ≥ 70% reduction from baseline in AFB

End point title	Percentage of participants who have ≥ 30%, ≥ 50%, or ≥ 70% reduction from baseline in AFB
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End point description:

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Ranolazine	Dronedarone	Ranolazine+Dronedarone 225 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	23	20
Units: percentage of participants				
number (not applicable)				
≥ 30%	22.2	50	21.7	45
≥ 50%	16.7	22.2	13	45
≥ 70%	11.1	16.7	8.7	45

End point values	Ranolazine+Dr onedarone 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: percentage of participants				
number (not applicable)				
≥ 30%	54.5			
≥ 50%	54.5			
≥ 70%	27.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 weeks plus 14 days; Serious adverse events (SAEs) that occurred later than 14 days after the last dose of study drugs and were considered related to study drug were also reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo to match ranolazine + placebo to match dronedarone for 12 weeks

Reporting group title	Ranolazine
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Reporting group description:

Ranolazine + placebo to match dronedarone for 12 weeks

Reporting group title	Dronedarone
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Reporting group description:

Placebo to match ranolazine + dronedarone 225 mg for 12 weeks

Reporting group title	Ranolazine+Dronedarone 225 mg
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Reporting group description:

Ranolazine + dronedarone 225 mg for 12 weeks

Reporting group title	Ranolazine+Dronedarone 150 mg
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Reporting group description:

Ranolazine + dronedarone 150 mg for 12 weeks

Serious adverse events	Placebo	Ranolazine	Dronedarone
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	7 / 26 (26.92%)	2 / 26 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal bacteraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ranolazine+Dronedarsone 225 mg	Ranolazine+Dronedarsone 150 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	1 / 26 (3.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (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	Placebo	Ranolazine	Dronedarone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 26 (34.62%)	15 / 26 (57.69%)	14 / 26 (53.85%)
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Prothrombin time prolonged			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Hypertension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	4 / 26 (15.38%)
occurrences (all)	2	0	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)	2 / 26 (7.69%)
occurrences (all)	1	3	2
Presyncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 26 (11.54%) 3	0 / 26 (0.00%) 0
Asthenia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	3 / 26 (11.54%) 3
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 26 (11.54%) 3	0 / 26 (0.00%) 0
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	1 / 26 (3.85%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 26 (11.54%) 3	1 / 26 (3.85%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 26 (7.69%) 2	2 / 26 (7.69%) 3
Abdominal pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	3 / 26 (11.54%) 3
Abdominal distension subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	2 / 26 (7.69%) 2
Gastritis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 26 (3.85%) 1	2 / 26 (7.69%) 2
Cough subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	2 / 26 (7.69%) 2
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 26 (7.69%) 2	0 / 26 (0.00%) 0
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4	1 / 26 (3.85%) 1	2 / 26 (7.69%) 2
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 26 (7.69%) 2	1 / 26 (3.85%) 1

Non-serious adverse events	Ranolazine+Dronedara rone 225 mg	Ranolazine+Dronedara rone 150 mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 27 (44.44%)	14 / 26 (53.85%)	
Investigations International normalised ratio increased subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	2 / 26 (7.69%) 2	
Prothrombin time prolonged subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 26 (0.00%) 0	
Injury, poisoning and procedural complications Overdose subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 26 (0.00%) 0	

Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 27 (11.11%)	1 / 26 (3.85%)	
occurrences (all)	4	3	
Haematoma			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Presyncope			
subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)	1 / 26 (3.85%)	
occurrences (all)	2	3	
Asthenia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	4	
Oedema peripheral			
subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 27 (3.70%)	4 / 26 (15.38%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	2 / 27 (7.41%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Gastritis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	

Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 26 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 26 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2011	Increased the number of subjects per treatment group from 20 to 30, changed the study from single-blind to double-blind, and reduced the total number of treatment groups in the study by combining treatment groups.
03 April 2012	Changed AFB at randomization from: $\geq 3\%$ and $\leq 50\%$ to $\geq 2\%$ and $\leq 70\%$.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported