ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS)

This study has been terminated.
(The study was stopped because of safety concerns)

Sponsor:	Sanofi
Collaborators:	
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT01151137

Purpose

Primary Objective:

- Demonstrate the efficacy of Dronedarone in preventing major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death) or unplanned cardiovascular hospitalization or death from any cause in patients with permanent Atrial Fibrillation [AF] and additional risk factors

Secondary Objective:

- Demonstrate the efficacy of Dronedarone in preventing cardiovascular death

This was an event-driven study where a common study end date [CSED] was to be determined by Steering Committee based on the number of events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death).

Condition	Intervention	Phase
Atrial Fibrillation	Drug: Dronedarone Drug: Placebo (for Dronedarone)	Phase 3

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator, Outcomes Assessor), Randomized, Efficacy Study
Official Title: A Randomized, Double Blind, Placebo Controlled, Parallel Group Trial for Assessing the Clinical Benefit of Dronedarone 400mg BID on Top of Standard Therapy in Patients With Permanent Atrial Fibrillation and Additional Risk Factors

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overview of the Two Co-primary Outcomes [Time Frame: From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)] [Designated as safety issue: No]
  First co-primary outcome was defined as the first event among stroke, systemic arterial embolism, Myocardial Infarctions [MI], or cardiovascular death. Second co-primary outcome was defined as the first event among unscheduled cardiovascular hospitalization or death from any cause. Both co-primary outcomes were determined based on the central review and adjudication by a blinded Adjudication Committee of all reported deaths (from any cause), MI, systemic arterial embolisms, strokes, Transient Ischemic Attacks [TIA], Heart Failure hospitalization and unplanned hospitalisations for cardiovascular cause.
- Time to First Co-primary Outcome (Cumulative Incidence Function) [Time Frame: From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)] [Designated as safety issue: No]
  Time to first co-primary outcome was defined as the time from randomization to the first event among stroke, systemic arterial embolism, MI or cardiovascular death. Cumulative incidence function in each treatment group was calculated using non-parametric Kaplan-Meier estimate. 95% confidence interval was computed at each time-point using Greenwood's variance estimation.
- Time to Second Co-primary Outcome (Cumulative Incidence Function) [Time Frame: From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)] [Designated as safety issue: No]
  Time to second co-primary outcome was defined as the time from randomization to the first event among unscheduled cardiovascular hospitalization or death from any cause. Cumulative incidence function in each treatment group was calculated using non-parametric Kaplan-Meier estimate. 95% confidence interval was computed at each time-point using Greenwood's variance estimation.

Secondary Outcome Measures:

- Deaths [Time Frame: From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)] [Designated as safety issue: No]
  Deaths were classified according to the primary cause of death.
- Time to Cardiovascular Death (Cumulative Incidence Function) [Time Frame: From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)] [Designated as safety issue: No]
  Time to cardiovascular death was defined as the time from randomization to the death. Cumulative incidence function in each treatment group was calculated using non-parametric Kaplan-Meier estimate. 95% confidence interval was computed at each time-point using Greenwood's variance estimation.

Other Pre-specified Outcome Measures:

- Overview of Cardiovascular Events [Time Frame: From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)] [Designated as safety issue: No]
- Overview of Adverse Events [AE] [Time Frame: from first study drug intake up to 10 days after the last study drug intake] [Designated as safety issue: Yes]
  AE are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.

Enrollment: 3236
Study Start Date: July 2010
Primary Completion Date: September 2011
Study Completion Date: September 2011

Arms	Assigned Interventions
Experimental: Dronedarone Dronedarone 400 mg twice a day until the CSED	Drug: Dronedarone Film-coated tablet Oral administration under fed conditions (during breakfast and dinner) Other Names: MULTAQ SR33589
Placebo Comparator: placebo Placebo (for Dronedarone) twice a day until the CSED	Drug: Placebo (for Dronedarone) film-coated tablet strictly identical in appearance Oral administration under fed conditions (during breakfast and dinner)

Detailed Description:

The study period per participant was variable depending on the enrollment in the study.

A final follow-up visit had to occur within 1 month after the CSED.

Eligibility

Ages Eligible for Study: 65 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion criteria:

- Permanent AF defined by the presence of all of the following criteria:
  - Availability of one 12-lead ECG not more than 14 days prior to randomization showing that the patient is in AF or atrial flutter;
  - Availability of documentation (including either rhythm strips or medical report of the rhythm) showing that the patient was in AF or atrial flutter at least 6 months prior to randomization;
  - No evidence of sinus rhythm in the period between these two documentations of AF;
  - Decision of the patient and physician to allow AF to continue without further efforts to restore sinus rhythm.
- At least one of the following risk criteria:
  - Coronary artery disease;
  - Prior stroke or Transient Ischemic Attack [TIA];
  - Symptomatic heart failure;
  - Left ventricular ejection fraction [LVEF] less or equal to 0.40;
  - Peripheral arterial occlusive disease;

- Aged 75 years or older with both hypertension and diabetes mellitus.

Exclusion criteria:

- Paroxysmal AF;
- Persistent AF without a decision to allow AF to continue without further efforts to restore sinus rhythm;
- Heart failure of New-York Heart Association [NYHA] class IV or recent unstable NYHA class III.

The above information is not intended to contain all considerations relevant to a patient's potential participation in a clinical trial.

Contacts and Locations

Locations

United States, New Jersey
sanofi-aventis administrative office
Bridgewater, New Jersey, United States, 08807

Argentina
sanofi-aventis administrative office
Buenos Aires, Argentina

Australia
sanofi-aventis administrative office
Macquarie Park, Australia

Austria
sanofi-aventis administrative office
Vienna, Austria

Belgium
sanofi-aventis administrative office
Diegem, Belgium

Brazil
sanofi-aventis administrative office
Sao Paulo, Brazil

Bulgaria
sanofi-aventis administrative office
Sofia, Bulgaria

Canada
sanofi-aventis administrative office
Laval, Canada

Chile
sanofi-aventis administrative office
Providencia Santiago, Chile

Czech Republic
sanofi-aventis administrative office
Praha, Czech Republic

Denmark
sanofi-aventis administrative office

Horsholm, Denmark
Finland
sanofi-aventis administrative office
Helsinki, Finland
France
sanofi-aventis administrative office
Paris, France
Germany
sanofi-aventis administrative office
Frankfurt, Germany
Greece
sanofi-aventis administrative office
Kallithea, Greece
Hong Kong
sanofi-aventis administrative office
Hong Kong, Hong Kong
Hungary
sanofi-aventis administrative office
Budapest, Hungary
Israel
sanofi-aventis administrative office
Natanya, Israel
Italy
sanofi-aventis administrative office
Milan, Italy
Korea, Republic of
sanofi-aventis administrative office
Seoul, Korea, Republic of
Malaysia
sanofi-aventis administrative office
Kuala Lumpur, Malaysia
Mexico
sanofi-aventis administrative office
Col. Coyoacan, Mexico
Netherlands
sanofi-aventis administrative office
Gouda, Netherlands
New Zealand
sanofi-aventis administrative office
Auckland, New Zealand
Norway
sanofi-aventis administrative office
Lysaker, Norway
Poland
sanofi-aventis administrative office

Warsaw, Poland
Romania
sanofi-aventis administrative office
Bucuresti, Romania
Russian Federation
sanofi-aventis administrative office
Moscow, Russian Federation
Singapore
sanofi-aventis administrative office
Singapore, Singapore
Slovakia
sanofi-aventis administrative office
Bratislava, Slovakia
South Africa
sanofi-aventis administrative office
Gauteng, South Africa
Spain
sanofi-aventis administrative office
Barcelona, Spain
Sweden
sanofi-aventis administrative office
Bromma, Sweden
Switzerland
sanofi-aventis administrative office
Geneva, Switzerland
Taiwan
sanofi-aventis administrative office
Taipei, Taiwan
Ukraine
sanofi-aventis administrative office
Kiev, Ukraine
United Kingdom
sanofi-aventis administrative office
Guildford Surrey, United Kingdom

Investigators

Study Director:	Clinical Sciences & Operations	sanofi-aventis

More Information

Results Publications:

Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum Á, Blomström P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacrétaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbüchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS,

Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsányi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH; PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 2011 Dec 15;365(24):2268-76. doi: 10.1056/NEJMoa1109867. Epub 2011 Nov 14. Erratum in: N Engl J Med. 2012 Feb 16;366(7):672.

Responsible Party: Sanofi
Study ID Numbers: EFC11405
2010-019791-73 [EudraCT Number]
U1111-1116-5566 [UTN]
Health Authority: United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	Recruitment initiated in July 2010 was discontinued on July 6, 2011 upon recommendations of the Data Monitoring Committee due to an increased number of observed cardiovascular events in the Dronedarone group. The common study end date [CSED] was defined as July 15, 2011. At that time 494 sites in 37 countries had enrolled at least one patient.
Pre-Assignment Details	Assignment to groups was done centrally using an Interactive Voice Response System [IVRS] or an Interactive Web Response System [IWRS] in a 1:1 ratio. A total of 3236 participants were randomized at 489 sites (instead of 10800 as initially planned). The median duration of their participation in the study was 3.5 months.

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Overall Study

	Placebo	Dronedarone
Started	1617	1619
Treated	1610 [1]	1613
Discontinued Treatment	171	342
Completed	1601	1591

	Placebo	Dronedarone
Not Completed	16	28
Death	15	27
Lost to Follow-up	1	1

[1] One participant randomized to the placebo group received Dronedarone for 7 days by mistake

Baseline Characteristics

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Baseline Measures

	Placebo	Dronedarone	Total
Number of Participants	1617	1619	3236
Age, Continuous [units: years] Mean (Standard Deviation)	75.0 (5.9)	75.0 (5.9)	75.0 (5.9)
Gender, Male/Female [units: participants]			
Female	577	568	1145
Male	1040	1051	2091
Region of Enrollment [1] [units: participants]			
North America	281	266	547
South America	227	236	463
Western Europe	459	475	934
Eastern Europe	495	488	983
Asia	53	47	100
Rest of the word	102	107	209

	Placebo	Dronedarone	Total
Permanent atrial fibrillation [AF] history [units: participants]			
6 months to 2 years	490	498	988
> 2 years	1124	1119	2243
Unknown	3	2	5
CHADS2 Score [2] [units: participants]			
< 2	172	191	363
≥ 2	1444	1427	2871
Unavailable	1	1	2
New York Heart Association [NYHA] class [3] [units: participants]			
No congestive heart failure [CHF]	535	512	1047
NYHA Class I	209	234	443
NYHA Class II	749	732	1481
NYHA Class III	124	141	265

[1] Regions were defined as follows:

- North America: Canada, United States
- South America: Argentina, Brazil, Chile, Mexico
- Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom
- Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, Ukraine Asia: Hong Kong, Republic of Korea, Malaysia, Singapore, Taiwan Rest of the World: Australia, Israel, New zealand, South Africa

[2] CHADS2 is a risk-prediction score ranging from 0 to 6 used estimate Stroke Risk in Atrial Fibrillation patients.

CHADS2 score is obtained by adding together the points that correspond to the conditions that are present:

- C: Congestive Heart Failure history: 1 point
- H: Hypertension history: 1 point
- A: Age ≥75 years: 1 point
- D: Diabetes Mellitus history: 1 point

- S: Stroke symptoms previously or Transient Ischemic Attack [TIA]: 2 points

[3] NYHA classification is a functional classification that places the patient in one of 4 categories, based on how much he/she is limited during physical activity:

- Class I: no limitation of activities; the patient suffers no symptoms from ordinary activities.
- Class II: slight, mild limitation of activity; the patient is comfortable with rest or with mild exertion.
- Class III: marked limitation of activity; the patient is comfortable only at rest.
- Class IV: complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overview of the Two Co-primary Outcomes
Measure Description	First co-primary outcome was defined as the first event among stroke, systemic arterial embolism, Myocardial Infarctions [MI], or cardiovascular death. Second co-primary outcome was defined as the first event among unscheduled cardiovascular hospitalization or death from any cause. Both co-primary outcomes were determined based on the central review and adjudication by a blinded Adjudication Committee of all reported deaths (from any cause), MI, systemic arterial embolisms, strokes, Transient Ischemic Attacks [TIA], Heart Failure hospitalization and unplanned hospitalisations for cardiovascular cause.
Time Frame	From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized participants considered in the treatment group to which they were randomized regardless of the treatment they actually received

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1617	1619
Overview of the Two Co-primary Outcomes [units: participants]		

	Placebo	Dronedarone
First co-primary endpoint	19	43
Second co-primary endpoint	67	127

2. Primary Outcome Measure:

Measure Title	Time to First Co-primary Outcome (Cumulative Incidence Function)
Measure Description	Time to first co-primary outcome was defined as the time from randomization to the first event among stroke, systemic arterial embolism, MI or cardiovascular death. Cumulative incidence function in each treatment group was calculated using non-parametric Kaplan-Meier estimate. 95% confidence interval was computed at each time-point using Greenwood's variance estimation.
Time Frame	From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population as previously defined

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1617	1619
Time to First Co-primary Outcome (Cumulative Incidence Function) [units: proportion of participants] Number (95% Confidence Interval)		
Cumulative incidence at 14 days	0.002 (0.000 to 0.004)	0.009 (0.005 to 0.014)
Cumulative incidence at 30 days	0.003 (0.000 to 0.006)	0.013 (0.008 to 0.019)
Cumulative incidence at 90 days	0.007 (0.003 to 0.012)	0.021 (0.014 to 0.029)
Cumulative incidence at 180 days	0.013 (0.006 to 0.021)	0.042 (0.028 to 0.056)

	Placebo	Dronedarone
Cumulative incidence at 270 days	0.038 (0.012 to 0.064)	0.045 (0.030 to 0.061)
Cumulative incidence at 360 days	0.038 (0.012 to 0.064)	0.045 (0.030 to 0.061)

Statistical Analysis 1 for Time to First Co-primary Outcome (Cumulative Incidence Function)

Statistical Analysis Overview	Comparison Groups	Placebo, Dronedarone
	Comments	As a consequence of the early termination of the study, the analysis was performed for information only without any adjustment.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0019
	Comments	A priori threshold for statistical significance: 0.05
	Method	Log Rank
	Comments	2-sided Log-rank's asymptotic test

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	2.294
	Confidence Interval	(2-Sided) 95% 1.337 to 3.936
	Estimation Comments	Hazard ratio (HR) of Dronedarone versus placebo for stroke, systemic arterial embolism, myocardial infarction or cardiovascular death HR and confidence interval were estimated using Cox regression model with treatment group as the only factor.

3. Primary Outcome Measure:

Measure Title	Time to Second Co-primary Outcome (Cumulative Incidence Function)
Measure Description	Time to second co-primary outcome was defined as the time from randomization to the first event among unscheduled cardiovascular hospitalization or death from any cause. Cumulative incidence function in each treatment group was calculated using non-parametric Kaplan-Meier estimate. 95% confidence interval was computed at each time-point using Greenwood's variance estimation.

Time Frame	From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population as previously defined

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1617	1619
Time to Second Co-primary Outcome (Cumulative Incidence Function) [units: proportion of participants] Number (95% Confidence Interval)		
Cumulative incidence at 14 days	0.005 (0.002 to 0.008)	0.020 (0.013 to 0.027)
Cumulative incidence at 30 days	0.014 (0.008 to 0.020)	0.034 (0.025 to 0.043)
Cumulative incidence at 90 days	0.033 (0.023 to 0.042)	0.069 (0.055 to 0.083)
Cumulative incidence at 180 days	0.059 (0.043 to 0.075)	0.110 (0.089 to 0.130)
Cumulative incidence at 270 days	0.099 (0.062 to 0.137)	0.137 (0.107 to 0.167)
Cumulative incidence at 360 days	0.099 (0.062 to 0.137)	0.137 (0.107 to 0.167)

Statistical Analysis 1 for Time to Second Co-primary Outcome (Cumulative Incidence Function)

Statistical Analysis Overview	Comparison Groups	Placebo, Dronedarone
	Comments	As a consequence of the early termination of the study, the analysis was performed for information only without any adjustment.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A priori threshold for statistical significance: 0.05
	Method	Log Rank
	Comments	2-sided Log-rank's asymptotic test

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.947
	Confidence Interval	(2-Sided) 95% 1.448 to 2.617
	Estimation Comments	Hazard ratio (HR) of Dronedarone versus placebo for unscheduled cardiovascular hospitalization or death from any cause HR and confidence interval were estimated using Cox regression model with treatment group as the only factor.

4. Secondary Outcome Measure:

Measure Title	Deaths
Measure Description	Deaths were classified according to the primary cause of death.
Time Frame	From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population as previously defined

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1617	1619
Deaths [units: participants]		

	Placebo	Dronedarone
Any death	13	25
- Cardiovascular death	10	21
--- Cardiac arrhythmic death	4	13

5. Secondary Outcome Measure:

Measure Title	Time to Cardiovascular Death (Cumulative Incidence Function)
Measure Description	Time to cardiovascular death was defined as the time from randomization to the death. Cumulative incidence function in each treatment group was calculated using non-parametric Kaplan-Meier estimate. 95% confidence interval was computed at each time-point using Greenwood's variance estimation.
Time Frame	From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population as previously defined

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1617	1619
Time to Cardiovascular Death (Cumulative Incidence Function) [units: proportion of participants] Number (95% Confidence Interval)		
Cumulative incidence at 14 days	0.001 (0.000 to 0.003)	0.003 (0.000 to 0.006)
Cumulative incidence at 30 days	0.003 (0.000 to 0.006)	0.005 (0.002 to 0.009)
Cumulative incidence at 90 days	0.004 (0.001 to 0.007)	0.008 (0.003 to 0.012)

	Placebo	Dronedarone
Cumulative incidence at 180 days	0.004 (0.001 to 0.007)	0.022 (0.012 to 0.033)
Cumulative incidence at 270 days	0.027 (0.001 to 0.052)	0.026 (0.013 to 0.038)
Cumulative incidence at 360 days	0.027 (0.001 to 0.052)	0.026 (0.013 to 0.038)

Statistical Analysis 1 for Time to Cardiovascular Death (Cumulative Incidence Function)

Statistical Analysis Overview	Comparison Groups	Placebo, Dronedarone
	Comments	As a consequence of the early termination of the study, the analysis was performed for information only without any adjustment.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0460
	Comments	A priori threshold for statistical significance: 0.05
	Method	Log Rank
	Comments	2-sided Log-rank's asymptotic test

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	2.115
	Confidence Interval	(2-Sided) 95% 0.996 to 4.490
	Estimation Comments	Hazard ratio (HR) of Dronedarone versus placebo for cardiovascular death HR and confidence interval were estimated using Cox regression model with treatment group as the only factor.

6. Other Pre-specified Outcome Measure:

Measure Title	Overview of Cardiovascular Events
Measure Description	
Time Frame	From randomization up to the CSED which occurred at study termination (maximum follow-up of 1 year)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population as previously defined

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1617	1619
Overview of Cardiovascular Events [units: participants]		
MI or unstable angina pectoris	8	15
- MI	2	3
Stroke	10	23
- Ischemic stroke	9	18
Systemic arterial embolism	0	1
Episode of heart failure	55	115
- Hospitalization due to heart failure	24	43
Unplanned hospitalization for cardiovascular cause	59	113

7. Other Pre-specified Outcome Measure:

Measure Title	Overview of Adverse Events [AE]
Measure Description	AE are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.
Time Frame	from first study drug intake up to 10 days after the last study drug intake
Safety Issue?	Yes

Analysis Population Description

Safety population: all randomized and treated participants. Participants were considered according to the treatment actually received. Consequently the participant randomized to the placebo group who received Dronedarone was included in the Dronedarone group.

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Measured Values

	Placebo	Dronedarone
Number of Participants Analyzed	1609	1614
Overview of Adverse Events [AE] [units: participants]		
Any AE	600	797
- Any serious AE	77	113
- Any AE leading to death	0	4
- Any AE leading to treatment discontinuation	80	212
- Any AE leading to hospitalization	71	95

Reported Adverse Events

Time Frame	All Adverse Events (AE) were collected regardless of seriousness or relationship to the drug, spanning from signature of the Informed Consent Form up to the last visit.
Additional Description	The analysis included all randomized participants who received at least one dose of study drug and all AE that developed or worsened from randomization up to 10 days after last study drug intake. Participants were considered according to the treatment actually received regardless the amount of treatment administered.

Reporting Groups

	Description
Placebo	Placebo twice daily until the CSED (median treatment duration of 87.5 days)

	Description
Dronedarone	Dronedarone 400 mg twice daily until the CSED (median treatment duration of 74 days)

Serious Adverse Events

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	77/1609 (4.79%)	113/1614 (7%)
Blood and lymphatic system disorders		
Anaemia [A] *	1/1609 (0.06%)	2/1614 (0.12%)
Coagulopathy [A] *	1/1609 (0.06%)	0/1614 (0%)
Iron deficiency anaemia [A] *	1/1609 (0.06%)	2/1614 (0.12%)
Cardiac disorders		
Bradycardia [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Tachycardia [A] *	0/1609 (0%)	1/1614 (0.06%)
Ear and labyrinth disorders		
Vertigo [A] *	0/1609 (0%)	1/1614 (0.06%)
Eye disorders		
Cataract [A] *	0/1609 (0%)	1/1614 (0.06%)
Optic ischaemic neuropathy [A] *	0/1609 (0%)	1/1614 (0.06%)
Gastrointestinal disorders		
Abdominal pain [A] *	1/1609 (0.06%)	0/1614 (0%)
Abdominal wall haematoma [A] *	1/1609 (0.06%)	0/1614 (0%)
Colitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Constipation [A] *	1/1609 (0.06%)	0/1614 (0%)
Diarrhoea [A] *	0/1609 (0%)	1/1614 (0.06%)
Dyspepsia [A] *	0/1609 (0%)	1/1614 (0.06%)

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Enteritis [A] *	1/1609 (0.06%)	0/1614 (0%)
Gastric haemorrhage [A] *	0/1609 (0%)	1/1614 (0.06%)
Gastric perforation [A] *	0/1609 (0%)	1/1614 (0.06%)
Gastric ulcer haemorrhage [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Gastrointestinal haemorrhage [A] *	0/1609 (0%)	3/1614 (0.19%)
Gastrointestinal necrosis [A] *	0/1609 (0%)	1/1614 (0.06%)
Gastrointestinal ulcer haemorrhage [A] *	0/1609 (0%)	2/1614 (0.12%)
Ileitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Inguinal hernia [A] *	0/1609 (0%)	1/1614 (0.06%)
Large intestine perforation [A] *	0/1609 (0%)	1/1614 (0.06%)
Nausea [A] *	0/1609 (0%)	1/1614 (0.06%)
Pancreatitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Rectal haemorrhage [A] *	0/1609 (0%)	1/1614 (0.06%)
Subileus [A] *	0/1609 (0%)	1/1614 (0.06%)
Vomiting [A] *	0/1609 (0%)	1/1614 (0.06%)
General disorders		
Chest pain [A] *	0/1609 (0%)	2/1614 (0.12%)
Generalised oedema [A] *	1/1609 (0.06%)	0/1614 (0%)
Non-cardiac chest pain [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Oedema peripheral [A] *	1/1609 (0.06%)	0/1614 (0%)
Hepatobiliary disorders		
Acute hepatic failure [A] *	0/1609 (0%)	1/1614 (0.06%)

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Bile duct obstruction [A] *	0/1609 (0%)	1/1614 (0.06%)
Bile duct stone [A] *	1/1609 (0.06%)	0/1614 (0%)
Cholangitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Cholecystitis [A] *	0/1609 (0%)	2/1614 (0.12%)
Cholecystitis acute [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Cholelithiasis [A] *	2/1609 (0.12%)	2/1614 (0.12%)
Hepatic congestion [A] *	0/1609 (0%)	1/1614 (0.06%)
Hepatitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Infections and infestations		
Appendicitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Arthritis bacterial [A] *	0/1609 (0%)	1/1614 (0.06%)
Bronchitis [A] *	1/1609 (0.06%)	2/1614 (0.12%)
Bronchopneumonia [A] *	0/1609 (0%)	1/1614 (0.06%)
Cellulitis [A] *	1/1609 (0.06%)	0/1614 (0%)
Clostridial infection [A] *	0/1609 (0%)	1/1614 (0.06%)
Clostridium difficile colitis [A] *	1/1609 (0.06%)	0/1614 (0%)
Cystitis [A] *	1/1609 (0.06%)	0/1614 (0%)
Diverticulitis [A] *	2/1609 (0.12%)	0/1614 (0%)
Erysipelas [A] *	2/1609 (0.12%)	0/1614 (0%)
Escherichia sepsis [A] *	0/1609 (0%)	1/1614 (0.06%)
Fungal peritonitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Gangrene [A] *	1/1609 (0.06%)	0/1614 (0%)

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Gastroenteritis [A] *	0/1609 (0%)	3/1614 (0.19%)
Intervertebral discitis [A] *	0/1609 (0%)	1/1614 (0.06%)
Lobar pneumonia [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Otitis media chronic [A] *	0/1609 (0%)	1/1614 (0.06%)
Pneumonia [A] *	9/1609 (0.56%)	10/1614 (0.62%)
Pneumonia bacterial [A] *	0/1609 (0%)	2/1614 (0.12%)
Postoperative wound infection [A] *	0/1609 (0%)	1/1614 (0.06%)
Pyelonephritis [A] *	1/1609 (0.06%)	0/1614 (0%)
Respiratory tract infection [A] *	0/1609 (0%)	1/1614 (0.06%)
Sepsis [A] *	0/1609 (0%)	1/1614 (0.06%)
Urinary tract infection [A] *	2/1609 (0.12%)	2/1614 (0.12%)
Urosepsis [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Injury, poisoning and procedural complications		
Cervical vertebral fracture [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Contusion [A] *	0/1609 (0%)	1/1614 (0.06%)
Fall [A] *	1/1609 (0.06%)	0/1614 (0%)
Fractured sacrum [A] *	1/1609 (0.06%)	0/1614 (0%)
Hand fracture [A] *	1/1609 (0.06%)	0/1614 (0%)
Head injury [A] *	0/1609 (0%)	1/1614 (0.06%)
Hip fracture [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Joint dislocation [A] *	1/1609 (0.06%)	0/1614 (0%)
Lumbar vertebral fracture [A] *	1/1609 (0.06%)	0/1614 (0%)

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Multiple fractures [A] *	0/1609 (0%)	1/1614 (0.06%)
Post procedural complication [A] *	0/1609 (0%)	1/1614 (0.06%)
Rib fracture [A] *	0/1609 (0%)	1/1614 (0.06%)
Road traffic accident [A] *	1/1609 (0.06%)	0/1614 (0%)
Toxicity to various agents [A] *	0/1609 (0%)	1/1614 (0.06%)
Upper limb fracture [A] *	0/1609 (0%)	1/1614 (0.06%)
Investigations		
Alanine aminotransferase increased [A] *	0/1609 (0%)	1/1614 (0.06%)
Blood creatinine increased [A] *	0/1609 (0%)	2/1614 (0.12%)
Hepatic enzyme increased [A] *	1/1609 (0.06%)	5/1614 (0.31%)
International normalised ratio increased [A] *	1/1609 (0.06%)	0/1614 (0%)
Metabolism and nutrition disorders		
Dehydration [A] *	2/1609 (0.12%)	2/1614 (0.12%)
Diabetic foot [A] *	1/1609 (0.06%)	0/1614 (0%)
Electrolyte depletion [A] *	0/1609 (0%)	1/1614 (0.06%)
Electrolyte imbalance [A] *	0/1609 (0%)	1/1614 (0.06%)
Gout [A] *	2/1609 (0.12%)	1/1614 (0.06%)
Hyperglycaemia [A] *	1/1609 (0.06%)	0/1614 (0%)
Hypoglycaemia [A] *	1/1609 (0.06%)	2/1614 (0.12%)
Hyponatraemia [A] *	3/1609 (0.19%)	0/1614 (0%)
Metabolic acidosis [A] *	0/1609 (0%)	1/1614 (0.06%)
Musculoskeletal and connective tissue disorders		

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Back pain [A] *	2/1609 (0.12%)	0/1614 (0%)
Musculoskeletal chest pain [A] *	0/1609 (0%)	1/1614 (0.06%)
Osteoarthritis [A] *	2/1609 (0.12%)	3/1614 (0.19%)
Rhabdomyolysis [A] *	0/1609 (0%)	1/1614 (0.06%)
Spinal column stenosis [A] *	0/1609 (0%)	1/1614 (0.06%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
B-cell lymphoma [A] *	1/1609 (0.06%)	0/1614 (0%)
Bladder cancer [A] *	1/1609 (0.06%)	0/1614 (0%)
Hepatic neoplasm malignant [A] *	1/1609 (0.06%)	0/1614 (0%)
Myeloproliferative disorder [A] *	1/1609 (0.06%)	0/1614 (0%)
Prostate cancer [A] *	0/1609 (0%)	1/1614 (0.06%)
Prostate cancer recurrent [A] *	0/1609 (0%)	1/1614 (0.06%)
Renal cancer [A] *	0/1609 (0%)	1/1614 (0.06%)
Skin cancer [A] *	1/1609 (0.06%)	0/1614 (0%)
Squamous cell carcinoma [A] *	1/1609 (0.06%)	0/1614 (0%)
Uterine leiomyoma [A] *	0/1609 (0%)	1/1614 (0.06%)
Nervous system disorders		
Cognitive disorder [A] *	1/1609 (0.06%)	0/1614 (0%)
Dementia [A] *	1/1609 (0.06%)	0/1614 (0%)
Diabetic neuropathy [A] *	0/1609 (0%)	1/1614 (0.06%)
Dizziness [A] *	1/1609 (0.06%)	0/1614 (0%)
Encephalitis [A] *	0/1609 (0%)	1/1614 (0.06%)

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Epilepsy [A] *	0/1609 (0%)	1/1614 (0.06%)
Peripheral sensory neuropathy [A] *	0/1609 (0%)	1/1614 (0.06%)
Presyncope [A] *	0/1609 (0%)	2/1614 (0.12%)
Syncope [A] *	2/1609 (0.12%)	1/1614 (0.06%)
Psychiatric disorders		
Delirium [A] *	1/1609 (0.06%)	0/1614 (0%)
Mental status changes [A] *	0/1609 (0%)	1/1614 (0.06%)
Renal and urinary disorders		
Haematuria [A] *	1/1609 (0.06%)	2/1614 (0.12%)
Nephrolithiasis [A] *	1/1609 (0.06%)	0/1614 (0%)
Proteinuria [A] *	0/1609 (0%)	1/1614 (0.06%)
Renal failure [A] *	2/1609 (0.12%)	3/1614 (0.19%)
Renal failure acute [A] *	1/1609 (0.06%)	8/1614 (0.5%)
Renal failure chronic [A] *	0/1609 (0%)	1/1614 (0.06%)
Reproductive system and breast disorders		
Acquired hydrocele [A] *	0/1609 (0%)	1/1614 (0.06%)
Acquired phimosis [A] *	1/1609 (0.06%)	0/1614 (0%)
Balanoposthitis [A] *	1/1609 (0.06%)	0/1614 (0%)
Benign prostatic hyperplasia [A] *	1/1609 (0.06%)	1/1614 (0.06%)
Respiratory, thoracic and mediastinal disorders		
Acute pulmonary oedema [A] *	1/1609 (0.06%)	0/1614 (0%)
Acute respiratory failure [A] *	0/1609 (0%)	1/1614 (0.06%)
Atelectasis [A] *	0/1609 (0%)	1/1614 (0.06%)

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Chronic obstructive pulmonary disease [A] *	5/1609 (0.31%)	6/1614 (0.37%)
Dyspnoea [A] *	0/1609 (0%)	2/1614 (0.12%)
Epistaxis [A] *	1/1609 (0.06%)	0/1614 (0%)
Idiopathic pulmonary fibrosis [A] *	0/1609 (0%)	1/1614 (0.06%)
Lung infiltration [A] *	1/1609 (0.06%)	0/1614 (0%)
Organising pneumonia [A] *	1/1609 (0.06%)	0/1614 (0%)
Pleural effusion [A] *	0/1609 (0%)	1/1614 (0.06%)
Pleurisy [A] *	0/1609 (0%)	1/1614 (0.06%)
Pneumonia aspiration [A] *	0/1609 (0%)	1/1614 (0.06%)
Pulmonary hypertension [A] *	0/1609 (0%)	1/1614 (0.06%)
Respiratory failure [A] *	0/1609 (0%)	2/1614 (0.12%)
Skin and subcutaneous tissue disorders		
Dermatitis [A] *	0/1609 (0%)	2/1614 (0.12%)
Eczema [A] *	1/1609 (0.06%)	0/1614 (0%)
Skin ulcer haemorrhage [A] *	1/1609 (0.06%)	0/1614 (0%)
Toxic skin eruption [A] *	0/1609 (0%)	1/1614 (0.06%)
Surgical and medical procedures		
Eventration procedure [A] *	1/1609 (0.06%)	0/1614 (0%)
Vascular disorders		
Haemorrhage [A] *	1/1609 (0.06%)	0/1614 (0%)
Hypovolaemic shock [A] *	0/1609 (0%)	1/1614 (0.06%)
Orthostatic hypotension [A] *	1/1609 (0.06%)	0/1614 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDra 14.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo	Dronedarone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	38/1609 (2.36%)	100/1614 (6.2%)
Gastrointestinal disorders		
Diarrhoea [A] *	38/1609 (2.36%)	100/1614 (6.2%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDra 14.0

Limitations and Caveats

Given that the study was prematurely discontinued after 3236 patients were randomized (30% of the initial planned number), p-values were provided for information without any adjustment for multiplicity.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

If no publication has occurred within 12 months after trial completion, the investigator can present or publish trial results. A copy is submitted to the sponsor for review and comment at least 30 days in advance of any presentation or submission for publication.

The sponsor can require to delay the communication for a period not exceeding 90 days to allow for filing a patent application or such other measures as sponsor deems appropriate to establish and preserve its proprietary rights.

Results Point of Contact:

Name/Official Title: Trial Transparency Team
Organization: sanofi-aventis
Phone:
Email: Contact_US@sanofi.com