



Clinical trial results:

A double-blinded, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics, and acute cardiovascular responses of a 7-day oral treatment with the partial adenosine A1 receptor agonist BAY 1067197 in patients with chronic systolic heart failure: the PARSiFAL-pilot study

Summary

EudraCT number	2013-002522-23
Trial protocol	DE IT NL
Global end of trial date	02 April 2015

Results information

Result version number	v2 (current)
This version publication date	08 September 2016
First version publication date	09 April 2016
Version creation reason	<ul style="list-style-type: none">• New data added to full data set• Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY1067197/16782
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02040233
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	02 April 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate the safety and tolerability of a multiple dose 7-day once-daily (OD) BAY1067197 add-on treatment versus a 7-day add-on placebo treatment in subjects with chronic systolic heart failure (HF), determined by the incidence and severity of adverse events, newly-occurring laboratory and electrocardiogram (ECG) abnormalities and to investigate the pharmacokinetics (PK) of a 7-day BAY1067197 add-on treatment in subjects with chronic systolic HF.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2014
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	Germany: 11
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 1
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	24
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centres in 4 countries, between 28 January 2014 (first subject, first visit) and 29 January 2015 (last subject, last visit).

Pre-assignment

Screening details:

Overall 61 subjects were screened, of them 25 were screen failure. The remaining 36 subjects were randomized to treatment, of them 5 were drop outs before study drug administration and 31 were assigned to treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY1067197, 10 milligram (mg)

Arm description:

Subjects received multiple oral doses of 10 mg of BAY1067197 tablet once daily (1 x 10 mg immediate-release [IR] tablet) for 7 days.

Arm type	Experimental
Investigational medicinal product name	BAY1067197
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received multiple oral doses of BAY1067197 10mg (1x10 mg) tablet once daily for 7 days.

Arm title	BAY1067197, 20 mg
------------------	-------------------

Arm description:

Subjects received multiple oral doses of 20 mg BAY1067197 tablet once daily (2 x 10 mg IR tablet) for 7 days.

Arm type	Experimental
Investigational medicinal product name	BAY1067197
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received multiple oral doses of 20 mg BAY1067197 tablet once daily (2 x 10 mg IR tablet) for 7 days.

Arm title	Placebo
------------------	---------

Arm description:

Subjects received multiple oral doses of placebo matched to BAY1067197 tablet once daily for 7 days.

Arm type	Placebo
----------	---------

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

Dosage and administration details:

Subjects received multiple oral doses of placebo matched to BAY1067197 tablet once daily for 7 days.

Number of subjects in period 1^[1]	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo
Started	10	11	10
Subjects received treatment	10	11	10
Fulfilled Requirements of FAS Population	10	11	10
Completed	10	11	10

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: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	BAY1067197, 10 milligram (mg)
Reporting group description: Subjects received multiple oral doses of 10 mg of BAY1067197 tablet once daily (1 x 10 mg immediate-release [IR] tablet) for 7 days.	
Reporting group title	BAY1067197, 20 mg
Reporting group description: Subjects received multiple oral doses of 20 mg BAY1067197 tablet once daily (2 x 10 mg IR tablet) for 7 days.	
Reporting group title	Placebo
Reporting group description: Subjects received multiple oral doses of placebo matched to BAY1067197 tablet once daily for 7 days.	

Reporting group values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo
Number of subjects	10	11	10
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	55.8 ± 10.2	56.9 ± 9.3	57.8 ± 9.8
Gender categorical Units: subjects			
Female	3	4	0
Male	7	7	10

Reporting group values	Total		
Number of subjects	31		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: subjects			
Female	7		
Male	24		

End points

End points reporting groups

Reporting group title	BAY1067197, 10 milligram (mg)
Reporting group description: Subjects received multiple oral doses of 10 mg of BAY1067197 tablet once daily (1 x 10 mg immediate-release [IR] tablet) for 7 days.	
Reporting group title	BAY1067197, 20 mg
Reporting group description: Subjects received multiple oral doses of 20 mg BAY1067197 tablet once daily (2 x 10 mg IR tablet) for 7 days.	
Reporting group title	Placebo
Reporting group description: Subjects received multiple oral doses of placebo matched to BAY1067197 tablet once daily for 7 days.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: SAF (N=31) included subjects who received at least 1 dose of study drug.	
Subject analysis set title	Pharmacokinetic (PK) analysis set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: PKS (N=21) included subjects with at least 1 valid PK profile.	
Subject analysis set title	Efficacy Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: Efficacy analysis set (N=31) included subjects who had post-baseline efficacy data. Subjects with a major protocol deviation defined as no Cardiac Magnetic Resonance imaging (CMR) (Day 07d) and no echocardiography (Day 05d) were excluded from the efficacy evaluation.	
Subject analysis set title	Pharmacodynamic (PD) analysis set (PDS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: PDS (N=31) included subjects with at least 1 valid PD profile.	

Primary: Change From Baseline in Left Ventricular Ejection Fraction (LVEF) Measured by Cardiac Magnetic Resonance Imaging (CMR) at Day 7

End point title	Change From Baseline in Left Ventricular Ejection Fraction (LVEF) Measured by Cardiac Magnetic Resonance Imaging (CMR) at Day 7 ^[1]
End point description: The change in LVEF between the post and the pre-treatment measurements were analyzed using Bayesian statistics to quantify the difference between BAY1067197 treatment and placebo measured by CMR. LVEF is the fraction of blood (in percent) pumped out of the heart's left ventricular chamber with each heart beat, and is a measure of cardiac output for the heart.	
End point type	Primary
End point timeframe: Baseline and Day 7	

Notes:

[1] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[2]	11 ^[3]	10 ^[4]	
Units: percentage of ejection fraction				
arithmetic mean (standard deviation)				
Baseline	30.67 (± 10.52)	32.11 (± 7.64)	33.76 (± 9.88)	
Change at Day 7	0.12 (± 3.07)	2.15 (± 2.81)	1.77 (± 4.12)	

Notes:

[2] - Efficacy analysis set

[3] - Efficacy analysis set

[4] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration of BAY84-3174 in Plasma (Cmax) After First Dose of BAY1067197

End point title	Maximum Observed Concentration of BAY84-3174 in Plasma (Cmax) After First Dose of BAY1067197 ^[5] ^[6]
-----------------	--

End point description:

Maximum observed BAY84-3174 concentration in plasma, directly taken from analytical data. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[5] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[7]	11 ^[8]		
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	31.2 (± 49.4)	55.1 (± 54.2)		

Notes:

[7] - PKS

[8] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration of BAY84-3174 in Plasma Divided by Dose (Cmax/D) After First Dose of BAY1067197

End point title	Maximum Observed Concentration of BAY84-3174 in Plasma
-----------------	--

End point description:

Maximum observed drug concentration, directly taken from analytical data, divided by dose. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[9] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[11]	11 ^[12]		
Units: 1 per liter*10 ⁻³				
geometric mean (geometric coefficient of variation)	3.9 (± 49.4)	3.44 (± 54.2)		

Notes:

[11] - PKS

[12] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval (AUCtau) After First Dose of BAY1067197

End point title	Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval (AUCtau) After First Dose of BAY1067197 ^[13] ^[14]
-----------------	--

End point description:

AUCtau is defined as area under the plasma concentration time profile from time zero to the end of the dosing interval after the first dose and dosing interval was 24 h for both arms. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[13] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[15]	11 ^[16]		
Units: microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)	454 (± 42.5)	800 (± 47.4)		

Notes:

[15] - PKS

[16] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval Divided by Dose (AUCtau/D) After First Dose of BAY1067197

End point title	Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval Divided by Dose (AUCtau/D) After First Dose of BAY1067197 ^{[17][18]}
-----------------	--

End point description:

AUCtau/D is defined as area under the plasma concentration time profile from time zero to the end of the dosing interval divided by dose after the first dose and dosing interval was 24 h for both arms. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[17] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[19]	11 ^[20]		
Units: hour per liter*10 ⁻³				
geometric mean (geometric coefficient of variation)	56.7 (± 42.5)	49.9 (± 47.4)		

Notes:

[19] - PKS

[20] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration of BAY84-3174 in Plasma (Cmax,md) After Multiple Dose Administration During a Dosing Interval

End point title	Maximum Observed Concentration of BAY84-3174 in Plasma
-----------------	--

End point description:

C_{max,md} is defined as maximum observed drug concentration in plasma after multiple-dose administrations during a dosing interval directly taken from analytical data. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 7: pre dose and 0.5, 1, 2, 3, 4, 6 and 12 hours post dose; Day 8, Day 14, Day 22 and Day 29

Notes:

[21] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[23]	11 ^[24]		
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	66.3 (± 15.2)	120 (± 41.5)		

Notes:

[23] - PKS

[24] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration of BAY84-3174 in Plasma Divided by Dose (C_{max,md}/D) After Multiple Dose Administration During a Dosing Interval

End point title	Maximum Observed Concentration of BAY84-3174 in Plasma Divided by Dose (C _{max,md} /D) After Multiple Dose Administration During a Dosing Interval ^{[25][26]}
-----------------	---

End point description:

Maximum observed drug concentration, directly taken from analytical data divided by dose after multiple doses. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 7: pre dose and 0.5, 1, 2, 3, 4, 6 and 12 hours post dose; Day 8, Day 14, Day 22 and Day 29

Notes:

[25] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[27]	11 ^[28]		
Units: one Per liter*10 ⁻³				
geometric mean (geometric coefficient of variation)	8.28 (± 15.2)	7.5 (± 41.5)		

Notes:

[27] - PKS

[28] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve of BAY84-3174 During any Dosing Interval (AUC_{tau,md}) After Multiple Dose Administration

End point title	Area Under the Concentration Versus Time Curve of BAY84-3174 During any Dosing Interval (AUC _{tau,md}) After Multiple Dose Administration ^{[29][30]}
-----------------	---

End point description:

AUC_{tau,md} is defined as area under the plasma concentration time profile from time zero during the dosing interval after multiple-dose administrations and dosing interval was 24 h for both arms. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 7: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[29] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[31]	11 ^[32]		
Units: microgram*hours per liter				
geometric mean (geometric coefficient of variation)	1190 (± 14)	2030 (± 37.4)		

Notes:

[31] - PKS

[32] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve of BAY84-3174 During any Dosing Interval Divided by Dose (AUC_{tau,md}/D) After Multiple Dose Administration

End point title	Area Under the Concentration Versus Time Curve of BAY84-
-----------------	--

End point description:

AUC_{tau,md/D} is defined as area under the plasma concentration time profile from time zero to the end of the dosing interval after multiple dose of administrations divided by dose and dosing interval was 24 h for both arms. Geometric mean and %CV were reported.

End point type	Primary
----------------	---------

End point timeframe:

Day 7: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[33] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[35]	11 ^[36]		
Units: Hours per liter*10 ⁻³				
geometric mean (geometric coefficient of variation)	149 (± 14)	127 (± 37.4)		

Notes:

[35] - PKS

[36] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Relevant Changes in Heart Rate

End point title	Number of Subjects With Relevant Changes in Heart Rate ^[37]
-----------------	--

End point description:

Heart rate was measured by monitor measurements after 30 minutes resting in a supine position. The relevant changes in heart rate were recorded and analysed.

End point type	Primary
----------------	---------

End point timeframe:

From the start of study treatment up to Day 29

Notes:

[37] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[38]	11 ^[39]	10 ^[40]	
Units: subjects	0	0	0	

Notes:

[38] - SAF

[39] - SAF

[40] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Relevant Changes in Blood Pressure

End point title	Number of Subjects With Relevant Changes in Blood
-----------------	---

End point description:

Blood pressure was measured by monitor measurements after 30 minutes resting in a supine position. The relevant changes in blood pressure were recorded and analysed.

End point type	Primary
----------------	---------

End point timeframe:

From the start of study treatment up to Day 29

Notes:

[41] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[42]	11 ^[43]	10 ^[44]	
Units: subjects	0	0	0	

Notes:

[42] - SAF

[43] - SAF

[44] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With More than First Degree Atrio-Ventricular (AV) Block

End point title	Number of Subjects With More than First Degree Atrio-Ventricular (AV) Block ^[45]
-----------------	---

End point description:

A complete standard 12-lead ECG was recorded and evaluated parameters such as heart rate, PR/PQ interval, QRSD interval, QT interval (uncorrected). Clinically relevant findings in ECG such as a second degree AV-block Mobitz type I (Wenkebach), Mobitz type II - or any third-degree AV block were recorded and reported. A 24-hour Holter ECG was recorded with a standard Holter ECG recorder for the purpose of detecting AV blocks, no higher degree AV blocks > 1 or clinically relevant effect on HR were observed during Holter monitoring periods.

End point type	Primary
----------------	---------

End point timeframe:

From the start of study treatment up to Day 29

Notes:

[45] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[46]	11 ^[47]	10 ^[48]	
Units: subjects				
12-lead ECG	0	0	0	
24-hour Holter ECG	0	0	0	

Notes:

[46] - SAF

[47] - SAF

[48] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline for Wall Motion Score Index at Day (WMSI) as Measured by Cardiac Magnetic Resonance at Day 7

End point title	Changes From Baseline for Wall Motion Score Index at Day (WMSI) as Measured by Cardiac Magnetic Resonance at Day 7
-----------------	--

End point description:

WMSI is evaluated using the American Heart Association (AHA) 17-segment model. The total WMS was obtained by adding the score for each segment. The WMSI was calculated by dividing the total WMS by 17. The wall motion score index was derived as the sum of all segmental scores divided by the number of segments visualized. In general, higher numbers are reflecting worsening cardiac function, normal function would be a wall motion score index of 1. Thus, range for the wall motion score index could be theoretically between 1 (normal) and 4. Thus, a decrease in wall motion score means improved function. Wall motion score index will cover the changes in wall motion score from baseline also.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Day 7

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[49]	11 ^[50]	10 ^[51]	
Units: scores on scale				
geometric mean (standard deviation)				
Baseline	1.9 (± 0.584)	1.754 (± 0.548)	1.488 (± 0.678)	
Change at Day 7	-0.035 (± 0.084)	-0.118 (± 0.204)	-0.065 (± 0.217)	

Notes:

[49] - Efficacy analysis set

[50] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Relevant Changes Observed in Echocardiography Parameters

End point title	Number of Subjects With Clinically Relevant Changes Observed in Echocardiography Parameters
-----------------	---

End point description:

The echo parameters like Septal mitral annulus (e' septal), Lateral mitral annulus (e' lateral), E/e' average (average of e' lateral and e' septal), E/e' Lateral ratio, E/e' Septal ratio, Peak early doppler transmitral flow velocity (E), Peak atrial doppler transmitral flow velocity (A), E/A Ratio, Deceleration time (DT), Global longitudinal strain, Cardiac output, Stroke volume, Stroke volume index, Peak systolic tissue Doppler Velocity (Smax), Left ventricular end-systolic volume (LVESV), Left ventricular end-diastolic volume (LVEDV), Left atrial volume index (LAVI), Peak pulmonary systolic pressure (PAPsys) of which systolic and diastolic functions are measured by echocardiography.

End point type	Secondary
End point timeframe:	
Baseline, Day 6 and 15	

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[52]	11 ^[53]	10 ^[54]	
Units: Subjects	0	0	0	

Notes:

[52] - Efficacy analysis set

[53] - Efficacy analysis set

[54] - Efficacy analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Relevant Changes Observed in Biomarkers

End point title	Number of Subjects With Clinically Relevant Changes Observed in Biomarkers
-----------------	--

End point description:

N-terminal prohormone of brain natriuretic peptide (NT-proBNP), renin, mid-region pro-atrial natriuretic peptide (MR-proANP) are biomarkers which show effect on neurohormones.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to Day 15

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[55]	11 ^[56]	10 ^[57]	
Units: subjects	0	0	0	

Notes:

[55] - PDS

[56] - PDS

[57] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Concentration of BAY84-3174 in Plasma (tmax) After First Dose of BAY1067197

End point title	Time to Reach Maximum Observed Concentration of BAY84-3174 in Plasma (tmax) After First Dose of BAY1067197 ^[58]
-----------------	--

End point description:

Time to reach maximum drug concentration in the measured matrix, directly taken from analytical data

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[59]	11 ^[60]		
Units: hours				
median (full range (min-max))	3.42 (2.92 to 4.08)	4.05 (2.92 to 6.03)		

Notes:

[59] - PKS

[60] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval Divided by Dose per Body Weight (AUCtau,md,norm) After Multiple Dose Administration

End point title	Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval Divided by Dose per Body Weight (AUCtau,md,norm) After Multiple Dose Administration ^[61]
End point description: AUCtau,md,norm is defined as area under the plasma concentration time profile from time zero to the end of the dosing interval after multiple dosing divided by dose per body weight. The dosing interval was 24 h for both arms. Geometric mean and %CV were reported.	
End point type	Secondary
End point timeframe: Day 7: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose	

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[62]	11 ^[63]		
Units: kilogram* hour per liter				
geometric mean (geometric coefficient of variation)	12.6 (± 15.9)	9.84 (± 37.9)		

Notes:

[62] - PKS

[63] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration of BAY84-3174 in Plasma Divided by Dose per Body Weight (Cmax,md,norm) After Multiple Dose Administration

End point title	Maximum Observed Concentration of BAY84-3174 in Plasma Divided by Dose per Body Weight (Cmax,md,norm) After Multiple Dose Administration ^[64]
End point description: Cmax,md,norm defined as maximum observed drug concentration in plasma after the first dose followed by multiple-dose administrations during a dosing interval divided by dose per body weight. Geometric mean and %CV were reported.	
End point type	Secondary
End point timeframe: Day 7: pre dose and 0.5, 1, 2, 3, 4, 6 and 12 hours post dose; Day 8, Day 14, Day 22 and Day 29	

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[65]	11 ^[66]		
Units: kilogram per liter				
geometric mean (geometric coefficient of variation)	0.703 (± 16.2)	0.582 (± 38)		

of variation)

Notes:

[65] - PKS

[66] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Concentration of BAY84-3174 in Plasma (t_{max,md}) After Multiple Dose Administration

End point title	Time to Reach Maximum Observed Concentration of BAY84-3174 in Plasma (t _{max,md}) After Multiple Dose Administration ^[67]
-----------------	--

End point description:

t_{max,md} defines as time to reach maximum drug concentration in the measured matrix after multiple dose administrations directly taken from analytical data.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 7: pre dose and 0.5, 1, 2, 3, 4, 6 and 12 hours post dose; Day 8, Day 14, Day 22 and Day 29

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[68]	11 ^[69]		
Units: hours				
median (full range (min-max))	3.41 (2.08 to 6.08)	4 (2.03 to 5.97)		

Notes:

[68] - PKS

[69] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life Associated With the Terminal Slope (t_{1/2,md}) After Multiple-Dose Administration

End point title	Half-Life Associated With the Terminal Slope (t _{1/2,md}) After Multiple-Dose Administration ^[70]
-----------------	--

End point description:

t_{1/2,md} is defined as time to reach maximum observed drug concentration in plasma after the first dose followed by multiple-dose administrations. Geometric mean and %CV were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 7: pre dose and 0.5, 1, 2, 3, 4, 6 and 12 hours post dose; Day 8, Day 14, Day 22 and Day 29

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[71]	11 ^[72]		
Units: hours				
geometric mean (geometric coefficient of variation)	307 (± 28.5)	312 (± 40.2)		

Notes:

[71] - PKS

[72] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration of BAY84-3174 in Plasma After First Dose Divided by Dose per Body Weight (C_{max,norm})

End point title	Maximum Observed Concentration of BAY84-3174 in Plasma After First Dose Divided by Dose per Body Weight (C _{max,norm}) ^[73]
-----------------	--

End point description:

C_{max,norm} is defined as maximum observed drug concentration in plasma after the first dose divided by dose per body weight. Geometric mean and %CV were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[74]	11 ^[75]		
Units: kilogram per liter				
geometric mean (geometric coefficient of variation)	0.331 (± 36.5)	0.267 (± 55.6)		

Notes:

[74] - PKS

[75] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval Divided by Dose per Body Weight (AUC_{tau,norm}) After First Dose of

BAY1067197

End point title	Area Under the Concentration Versus Time Curve of BAY84-3174 for the Dosing Interval Divided by Dose per Body Weight (AUCtau,norm) After First Dose of BAY1067197 ^[76]
-----------------	---

End point description:

AUCtau,norm is defined as area under the plasma concentration time profile from time zero to the end of the dosing interval divided by dose per body weight after the first dose. Dosing interval was 24 h for both arms. Geometric mean and %CV were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1: pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo-treated subjects (N=10) were excluded from the Pharmacokinetic analysis.

End point values	BAY1067197, 10 milligram (mg)	BAY1067197, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[77]	11 ^[78]		
Units: kilogram*hour per liter				
geometric mean (geometric coefficient of variation)	4.82 (± 31.7)	3.87 (± 54.9)		

Notes:

[77] - PKS

[78] - PKS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment up to 49 days after the last dose of study drug

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.1
--------------------	------

Reporting groups

Reporting group title	BAY1067197, 10 mg
-----------------------	-------------------

Reporting group description:

Subjects received multiple oral doses of 10 mg of BAY1067197 tablet once daily (1 x 10 mg IR tablet) for 7 days.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects received multiple oral doses of placebo tablet matched BAY1067197 once daily for 7 days.

Reporting group title	BAY1067197, 20 mg
-----------------------	-------------------

Reporting group description:

Subjects received multiple oral doses of 20 mg BAY1067197 tablet once daily (2 x 10 mg IR tablet) for 7 days.

Serious adverse events	BAY1067197, 10 mg	Placebo	BAY1067197, 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BAY1067197, 10 mg	Placebo	BAY1067197, 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	4 / 10 (40.00%)	8 / 11 (72.73%)
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0
Blood potassium increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1
Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0
Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	1 / 10 (10.00%) 2	2 / 11 (18.18%) 3
Angina pectoris subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0
Sinus arrest subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 2	0 / 11 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0
Ventricular tachycardia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	3 / 10 (30.00%) 4	2 / 11 (18.18%) 2
Nervous system disorders Presyncope subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0

Headache subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0
Immune system disorders Allergic oedema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Epigastric discomfort subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0
Renal and urinary disorders Nephropathy subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all) Hyperkalaemia	1 / 10 (10.00%) 2	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2013	Increase the lower limit for the HR at rest from 40 Beats Per Minute (BPM) to 50 (BPM) because of possible additive bradycardia-inducing effects of BAY1067197 in combination with metoprolol. Add an additional study visit on Day 21d. Exclude subjects with untreated hyperthyroidism or hypothyroidism and nonstable thyroid function (intake of stable thyroid hormone substitution was allowed).
10 March 2014	About 35 days after the last dose of BAY1067197, BAY84-3174 is largely eliminated from plasma, that is AUC at that time equals 96.875% of the total AUC consistent with the degree of elimination after 5 half-lives. Assuming a longer half-live in HF subjects compared to healthy subjects, an additional follow-up telephone contact was added on Day 49d (43 days after the last intake of study drug) for AE questioning. Hydroxybutyrate dehydrogenase (HBDH) and glutamate dehydrogenase (GLDH) were considered not relevant and excluded from the safety laboratory parameters.

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.

Occurrence of "±" in relation with geometric CV is auto-generated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero.

Notes: