Clinical trial results:
A single blind, placebo controlled pilot study to explore the safety and tolerability of a single oral dose of 30 mg BAY1067197 in patients with chronic heart failure on the background of preexisting beta-blocker therapy

Summary

EudraCT number	2013-001287-34
Trial protocol	NL
Global end of trial date	17 March 2015

Results information

Result version number	v1
This version publication date	27 March 2016
First version publication date	27 March 2016

Trial information

Trial identification

Sponsor protocol code	BAY1067197/16718

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01945606
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	17 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this pilot study was to investigate the safety, tolerability and pharmacodynamic interaction of a single dose administration of 30 milligram (mg) BAY1067197 with selected beta-blockers in subjects with stable chronic systolic heart failure under evidence based standard therapy including selected beta-blockers.

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 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:

Subjects on stable standard therapy including pre-existing (for a minimum of 4 weeks) beta-blocker therapy.

Evidence for comparator: -

Actual start date of recruitment	29 November 2013
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	Netherlands: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	7
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at one study center in Netherlands, between 29 November 2013 (first subject first visit) and 09 September 2014 (last subject last visit).

Pre-assignment

Screening details:

Overall 14 subjects were screened, of them, 3 were screen failure and 11 were assigned to treatment.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Placebo then BAY1067197

Arm description:

Subjects received single oral dose of placebo matched to BAY1067197 with selected standard betablocker therapy in fasted condition (treatment 1), and then followed by a single oral dose of 30 mg BAY1067197 tablet with selected standard betablocker therapy (either greater than or equal to [>=] 95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol immediate release [IR] tablet or >=5 mg nebivolol IR tablet) in fasted condition (treatment 2).

Arm type	Experimental
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 single oral dose of placebo matched to BAY1067197 tablet on Day -1 in fasted condition.

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

Dosage and administration details:

Subjects received single oral dose of 30mg BAY1067197 tablet on Day 0 in fasted condition.

Investigational medicinal product name	Beta-blockers
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received beta-blocker therapy with either >= 95mg metoprolol succinate (controlled release tablet) or >= 5mg bisoprolol (IR tablet) or >= 5mg nebivolol (IR tablet) with 30 mg BAY1067197 in treatment 2 and with placebo in treatment 1.

Number of subjects in period 1	Placebo then BAY1067197
Started	11
Completed	11

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

Subjects received single oral dose of placebo matched to BAY1067197 with selected standard beta blocker therapy in fasted condition (treatment 1), and then followed by a single oral dose of 30 milligram (mg) BAY1067197 tablet with selected standard beta blocker therapy (either greater than or equal to [>=] 95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol immediate release [IR] tablet or >=5 mg nebivolol IR tablet) in fasted condition (treatment 2).

Reporting group values	Overall Trial	Total	
Number of subjects	11	11	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 60.6 ± 7.3	 -	
Gender Categorical Units: Subjects			
Male	8	8	
Female	3	3	

End points

End points reporting groups

Reporting group title	Placebo then BAY1067197

Reporting group description:

Subjects received single oral dose of placebo matched to BAY1067197 with selected standard betablocker therapy in fasted condition (treatment 1), and then followed by a single oral dose of 30 mg BAY1067197 tablet with selected standard betablocker therapy (either greater than or equal to [>=] 95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol immediate release [IR] tablet or >=5 mg nebivolol IR tablet) in fasted condition (treatment 2).

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF (N=11) included all subjects who received at least one dose of the study medication.

Subject analysis set title	Pharmacodynamics (PD) analysis set (PDS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PDS (N=11) included all subjects who completed the study without major changes versus protocol.

Subject analysis set title	Pharmacokinetics (PK) analysis set (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PKS (N=11) included all subjects who completed the study without major changes versus protocol.

Subject analysis set title	Placebo + Beta-blocker
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subject received a single oral dose of placebo matched to BAY1067197 under fasted condition (treatment 1) along with selected standard beta-blocker therapy (either >=95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol IR tablet or >=5 mg nebivolol IR tablet).

Subject analysis set title	BAY1067197 30 mg + Beta-blocker
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single oral dose of 30 mg (3 X 10 mg) BAY1067197 tablet under fasted condition (treatment 2) along with selected standard beta-blocker therapy (either >=95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol IR tablet or >=5 mg nebivolol IR tablet)

Primary: Number of Subjects With Atrio-Ventricular (AV)-Block Greater than (>) one Degree (1^0) Under Therapy With BAY1067197 and Pre-existing Beta-blocker Therapy

End point title	Number of Subjects With Atrio-Ventricular (AV)-Block Greater than (>) one Degree (1^0) Under Therapy With BAY1067197 and Pre-existing Beta-blocker Therapy[1]

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). ECG finding AV block >1^0 were recorded and reported.

End point type	Primary

End point timeframe:

From start of study drug administration until last follow-up (Day 22)

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	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[2]	11[3]		
Units: Subjects	0	0		

Notes:

[2] - SAF

[3] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAE) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAE) and Treatment-emergent Serious Adverse Events (TESAEs)[4]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; and another medically important serious event as judged by the investigator. Treatment-emergent were events between administration of study drug and up to Day 22 that were absent before treatment or that worsened relative to pre-treatment state.

End point type	Primary

End point timeframe:

From start of study drug administration until last follow-up (Day 22)

Notes:

[4] - 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	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[5]	11[6]		
Units: Subjects				
Treatment Emergent Adverse Event (TEAE)	3	7		
Treatment Emergent Serious Adverse Event (TESAE)	0	0		

Notes:

[5] - SAF

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Laboratory Findings Reported as Treatment-emergent Adverse Events

End point title	Number of Subjects With Abnormal Laboratory Findings Reported as Treatment-emergent Adverse Events[7]

End point description:

Clinical laboratory examinations included hematology, clotting status, serum chemistry, virology, vasoactive hormones, bioanalytics and urinalysis. Abnormal laboratory parameters were reported as treatment-emergent adverse events. Treatment-emergent were events between administration of study drug and up to Day 22 that were absent before treatment or that worsened relative to pre-treatment state.

End point type	Primary

End point timeframe:

From start of study drug administration until last follow-up (Day 22)

Notes:

[7] - 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	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[8]	11[9]		
Units: Subjects	0	0		

Notes:

[8] - SAF

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Heart Rate at Specified Time Point

End point title	Change From Baseline in Heart Rate at Specified Time Point[10]

End point description:

Heart rate after resting in supine position for at least 30 minute was recorded and analysed. In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively. '99999' in the below table indicates that the data were not analysed for a respective reporting at specified time-points.

End point type	Primary

End point timeframe:

From start of study drug administration until last follow-up (Day 22)

Notes:

[10] - 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: EudraCT database does auto-addition of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[11]	11[12]		
Units: Beats/minutes				
arithmetic mean (standard deviation)				
Baseline, -1D 00H 00M	62.5 (± 8.4)	99999 (± 99999)		
Change at, -0D 23H 30M (n=11, 11)	-2.5 (± 10.2)	99999 (± 99999)		

Change at, -0D 23H 00M (n=11, 11)	-3.1 (± 9.4)	99999 (± 99999)		
Change at, -0D 22H 30M (n=11, 11)	-4.8 (± 10.4)	99999 (± 99999)		
Change at, -0D 22H 00M (n=11, 11)	-3.3 (± 11.3)	99999 (± 99999)		
Change at, -0D 21H 00M (n=11, 11)	-4.5 (± 10.4)	99999 (± 99999)		
Change at, -0D 20H 00M (n=11, 11)	-4.3 (± 9.3)	99999 (± 99999)		
Change at, -0D 18H 00M (n=11, 11)	0.7 (± 10.4)	99999 (± 99999)		
Change at, -0D 16H 00M (n=11, 11)	-1.5 (± 10.3)	99999 (± 99999)		
Change at, -0D 12H 00M (n=11, 11)	-4.1 (± 9.5)	99999 (± 99999)		
Baseline: 0D 00H 00M	99999 (± 99999)	58.7 (± 5.6)		
Change at, 0D 00H 30M (n=11, 11)	99999 (± 99999)	-0.9 (± 2.3)		
Change at, 0D 01H 00M (n=11, 11)	99999 (± 99999)	-1.1 (± 4.2)		
Change at, 0D 01H 30M (n=11, 11)	99999 (± 99999)	-0.3 (± 5.4)		
Change at, 0D 02H 00M (n=11, 11)	99999 (± 99999)	-1.2 (± 4.5)		
Change at, 0D 03H 00M (n=11, 11)	99999 (± 99999)	-1.5 (± 4.9)		
Change at, 0D 04H 00M (n=11, 11)	99999 (± 99999)	-4.2 (± 3.6)		
Change at, 0D 06H 00M (n=11, 11)	99999 (± 99999)	1.7 (± 4)		
Change at, 0D 08H 00M (n=11, 11)	99999 (± 99999)	0.8 (± 4.4)		
Change at, 0D 12H 00M (n=11, 11)	99999 (± 99999)	-0.5 (± 3.5)		
Change at, 1D 00H 00M (n=11, 11)	99999 (± 99999)	0.5 (± 6.5)		
Change at, 1D 06H 00M (n=11, 11)	99999 (± 99999)	1.4 (± 3)		
Change at, 1D 12H 00M (n=10, 10)	99999 (± 99999)	5.2 (± 4.3)		
Change at, 2D 00H 00M (n=11, 11)	99999 (± 99999)	1.7 (± 5.2)		
Change at, 5D 00H 00M (n=11, 11)	99999 (± 99999)	2.5 (± 6.5)		
Change at, 13D 00H 00M (n=11, 11)	99999 (± 99999)	1.9 (± 5.3)		

Notes:

[11] - SAF

[12] - SAF

Attachments (see zip file)	Statistical Analysis_Heart rate /16718_Statistical

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Findings

End point title	Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Findings[13]

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). Criteria for abnormal clinically significant findings in the ECG were such as a second or third degree atrio-ventricular (AV) block. The changes in the above parameters were considered as "clinically significant" at the discretion of the investigator.

End point type	Primary

End point timeframe:

From start of study drug administration until last follow-up (Day 22)

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.

End point values	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[14]	11[15]		
Units: Subjects	0	0		

Notes:

[14] - SAF

[15] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Blood Pressure at Specified Time Point

End point title	Change From Baseline in Blood Pressure at Specified Time Point[16]

End point description:

Blood pressure measured by central bedside monitoring system to record subject’s Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and mean arterial blood pressure (MAP). In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively. '99999' in the below table indicates that the data were not analysed for a respective reporting group at specified time-points.

End point type	Primary

End point timeframe:

From start of study drug administration until last follow-up (Day 22)

Notes:

[16] - 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: EudraCT database does auto-addition of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[17]	11[18]		
Units: Millimeters of mercury (mm of Hg)				
arithmetic mean (standard deviation)				

SBP: Baseline, -1D 00H 00M	116.5 (± 15.7)	99999 (± 99999)		
SBP: Change at, -0D 23H 30M	6.8 (± 14.9)	99999 (± 99999)		
SBP: Change at, -0D 23H 00M	-0.5 (± 4.7)	99999 (± 99999)		
SBP: Change at, -0D 22H 30M	-0.9 (± 6.9)	99999 (± 99999)		
SBP: Change at, -0D 22H 00M	0.1 (± 8.2)	99999 (± 99999)		
SBP: Change at, -0D 21H 00M	-1.8 (± 8.1)	99999 (± 99999)		
SBP: Change at, -0D 20H 00M	-2.5 (± 8.3)	99999 (± 99999)		
SBP: Change at, -0D 18H 00M	-11.7 (± 10.8)	99999 (± 99999)		
SBP: Change at, -0D 16H 00M	-4.9 (± 5.4)	99999 (± 99999)		
SBP: Change at, -0D 12H 00M	-4.4 (± 11.6)	99999 (± 99999)		
SBP: Baseline: 0D 00H 00M	99999 (± 99999)	113.8 (± 16.5)		
SBP: Change at, 0D 00H 30M	99999 (± 99999)	1.2 (± 9.3)		
SBP: Change at, 0D 01H 00M	99999 (± 99999)	-0.8 (± 10.2)		
SBP: Change at, 0D 01H 30M	99999 (± 99999)	-1.9 (± 7.4)		
SBP: Change at, 0D 02H 00M	99999 (± 99999)	-0.4 (± 8)		
SBP: Change at, 0D 03H 00M	99999 (± 99999)	-2.6 (± 9.9)		
SBP: Change at, 0D 04H 00M	99999 (± 99999)	-2.6 (± 8.6)		
SBP: Change at, 0D 06H 00M	99999 (± 99999)	-11.4 (± 13.7)		
SBP: Change at, 0D 08H 00M	99999 (± 99999)	-6.4 (± 8.9)		
SBP: Change at, 0D 12H 00M	99999 (± 99999)	-0.5 (± 15.1)		
SBP: Change at, 1D 00H 00M	99999 (± 99999)	-1.3 (± 8.2)		
SBP: Change at, 1D 06H 00M	99999 (± 99999)	-5.5 (± 10.1)		
SBP: Change at, 1D 12H 00M	99999 (± 99999)	0.5 (± 8.9)		
SBP: Change at, 2D 00H 00M	99999 (± 99999)	6.1 (± 19.9)		
SBP: Change at, 5D 00H 00M	99999 (± 99999)	1.3 (± 10.9)		
SBP: Change at, 13D 00H 00M	99999 (± 99999)	-1 (± 13)		
DBP: Baseline, -1D 00H 00M	68.5 (± 14)	99999 (± 99999)		
DBP: Change at, -0D 23H 30M	5 (± 6.6)	99999 (± 99999)		
DBP: Change at, -0D 23H 00M	4.5 (± 6.5)	99999 (± 99999)		
DBP: Change at, -0D 22H 30M	-0.5 (± 11.1)	99999 (± 99999)		
DBP: Change at, -0D 22H 00M	3 (± 9.3)	99999 (± 99999)		

DBP: Change at, -0D 21H 00M	1 (± 7.3)	99999 (± 99999)		
DBP: Change at, -0D 20H 00M	1.2 (± 8.2)	99999 (± 99999)		
DBP: Change at, -0D 18H 00M	-5.5 (± 11.1)	99999 (± 99999)		
DBP: Change at, -0D 16H 00M	-5.4 (± 10.3)	99999 (± 99999)		
DBP: Change at, -0D 12H 00M	-2.5 (± 10.6)	99999 (± 99999)		
DBP: Baseline: 0D 00H 00M	99999 (± 99999)	70.5 (± 9.1)		
DBP: Change at, 0D 00H 30M	99999 (± 99999)	0.2 (± 9.7)		
DBP: Change at, 0D 01H 00M	99999 (± 99999)	-1.7 (± 12.2)		
DBP: Change at, 0D 01H 30M	99999 (± 99999)	-1.2 (± 8.8)		
DBP: Change at, 0D 02H 00M	99999 (± 99999)	-1.6 (± 9.9)		
DBP: Change at, 0D 03H 00M	99999 (± 99999)	-2.9 (± 7)		
DBP: Change at, 0D 04H 00M	99999 (± 99999)	-3.2 (± 8.9)		
DBP: Change at, 0D 06H 00M	99999 (± 99999)	-8.6 (± 9.8)		
DBP: Change at, 0D 08H 00M	99999 (± 99999)	-5.8 (± 8.3)		
DBP: Change at, 0D 12H 00M	99999 (± 99999)	-2.5 (± 7.1)		
DBP: Change at, 1D 00H 00M	99999 (± 99999)	0.6 (± 9)		
DBP: Change at, 1D 06H 00M	99999 (± 99999)	-5.4 (± 6.2)		
DBP: Change at, 1D 12H 00M	99999 (± 99999)	-5.9 (± 10.1)		
DBP: Change at, 2D 00H 00M	99999 (± 99999)	-1.4 (± 12.5)		
DBP: Change at, 5D 00H 00M	99999 (± 99999)	1.4 (± 10)		
DBP: Change at, 13D 00H 00M	99999 (± 99999)	0.6 (± 10)		
MAP: Baseline, -1D 00H 00M	84.485 (± 13.458)	99999 (± 99999)		
MAP: Change at, -0D 23H 30M	5.606 (± 6.933)	99999 (± 99999)		
MAP: Change at, -0D 23H 00M	2.879 (± 4.595)	99999 (± 99999)		
MAP: Change at, -0D 22H 30M	-0.606 (± 8.692)	99999 (± 99999)		
MAP: Change at, -0D 22H 00M	2.03 (± 7.162)	99999 (± 99999)		
MAP: Change at, -0D 21H 00M	0.061 (± 5.652)	99999 (± 99999)		
MAP: Change at, -0D 20H 00M	-0.061 (± 7.122)	99999 (± 99999)		
MAP: Change at, -0D 18H 00M	-7.545 (± 9.407)	99999 (± 99999)		
MAP: Change at, -0D 16H 00M	-5.212 (± 7.816)	99999 (± 99999)		
MAP: Change at, -0D 12H 00M	-3.091 (± 8.533)	99999 (± 99999)		

MAP: Baseline: 0D 00H 00M	99999 (± 99999)	84.97 (± 10.951)		
MAP: Change at, 0D 00H 30M	99999 (± 99999)	0.515 (± 8.957)		
MAP: Change at, 0D 01H 00M	99999 (± 99999)	-1.424 (± 11.084)		
MAP: Change at, 0D 01H 30M	99999 (± 99999)	-1.424 (± 7.553)		
MAP: Change at, 0D 02H 00M	99999 (± 99999)	-1.212 (± 8.737)		
MAP: Change at, 0D 03H 00M	99999 (± 99999)	-2.818 (± 7.732)		
MAP: Change at, 0D 04H 00M	99999 (± 99999)	-3 (± 8.388)		
MAP: Change at, 0D 06H 00M	99999 (± 99999)	-9.546 (± 10.276)		
MAP: Change at, 0D 08H 00M	99999 (± 99999)	-6 (± 8.024)		
MAP: Change at, 0D 12H 00M	99999 (± 99999)	-1.849 (± 9.521)		
MAP: Change at, 1D 00H 00M	99999 (± 99999)	0 (± 8.121)		
MAP: Change at, 1D 06H 00M	99999 (± 99999)	-5.394 (± 6.865)		
MAP: Change at, 1D 12H 00M	99999 (± 99999)	-3.788 (± 9.512)		
MAP: Change at, 2D 00H 00M	99999 (± 99999)	1.121 (± 13.942)		
MAP: Change at, 5D 00H 00M	99999 (± 99999)	1.333 (± 9.663)		
MAP: Change at, 13D 00H 00M	99999 (± 99999)	0.091 (± 10.005)		

Notes:

[17] - SAF

[18] - SAF

Attachments (see zip file)	Statistical Analysis_Blood pressure/16718_Statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve From Zero to Infinity (AUC) of BAY84-3174 in Plasma After Single Dose of BAY1067197

End point title	Area Under the Concentration Versus Time Curve From Zero to Infinity (AUC) of BAY84-3174 in Plasma After Single Dose of BAY1067197

End point description:

Area under the concentration versus time curve from zero to infinity after single dose. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Pre-dose; 0 (0.5, 1, 2, 3, 4, 6 and 12 hours), 1, 2, 5, 13 and 21 days post-dose

End point values	BAY1067197 30 mg + Beta-blocker			
Subject group type	Subject analysis set			
Number of subjects analysed	11[19]			
Units: microgram*hours per liter				
geometric mean (geometric coefficient of variation)	4710.5 (± 45.21)			

Notes:

[19] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of BAY84-3174 from Time 0 to the Last Data Point Greater than (>) Lower Limit of Quantification (AUC[0-last]) After Single Dose of BAY1067197

End point title	AUC of BAY84-3174 from Time 0 to the Last Data Point Greater than (>) Lower Limit of Quantification (AUC[0-last]) After Single Dose of BAY1067197

End point description:

AUC from time 0 to the last data point >lower limit of quantification, calculated up by linear trapezoidal rule, down by logarithmic trapezoidal rule. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Pre-dose; 0 (0.5, 1, 2, 3, 4, 6 and 12 hours), 1, 2, 5, 13 and 21 days post-dose

End point values	BAY1067197 30 mg + Beta-blocker			
Subject group type	Subject analysis set			
Number of subjects analysed	11[20]			
Units: microgram*hours per liter				
geometric mean (geometric coefficient of variation)	4046.8 (± 40.72)			

Notes:

[20] - PKS

Statistical analyses

No statistical analyses for this end point

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

End point title	Maximum Observed BAY84-3174 Concentration in Plasma (Cmax) After Single Dose of BAY1067197

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	Secondary

End point timeframe:

Pre-dose; 0 (0.5, 1, 2, 3, 4, 6 and 12 hours), 1, 2, 5, 13 and 21 days post-dose

End point values	BAY1067197 30 mg + Beta-blocker			
Subject group type	Subject analysis set			
Number of subjects analysed	11[21]			
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	95.159 (± 36.29)			

Notes:

[21] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life (t1/2) Associated With the Terminal Slope of BAY84-3174 After Single Dose of BAY1067197

End point title	Half-Life (t1/2) Associated With the Terminal Slope of BAY84-3174 After Single Dose of BAY1067197

End point description:

Half-life associated with the terminal slope. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Pre-dose; 0 (0.5, 1, 2, 3, 4, 6 and 12 hours), 1, 2, 5, 13 and 21 days post-dose

End point values	BAY1067197 30 mg + Beta-blocker			
Subject group type	Subject analysis set			
Number of subjects analysed	11[22]			
Units: Hours				
geometric mean (geometric coefficient of variation)	210.85 (± 17.77)			

Notes:

[22] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Clearance (CL/F) of BAY84-3174 After Single Dose of BAY1067197

End point title	Apparent Oral Clearance (CL/F) of BAY84-3174 After Single Dose of BAY1067197

End point description:

Total body clearance of drug calculated after extra-vascular application.

End point type	Secondary

End point timeframe:

Pre-dose; 0 (0.5, 1, 2, 3, 4, 6 and 12 hours), 1, 2, 5, 13 and 21 days post-dose

End point values	BAY1067197 30 mg + Beta-blocker			
Subject group type	Subject analysis set			
Number of subjects analysed	11[23]			
Units: liter per hours				
geometric mean (geometric coefficient of variation)	5.1013 (± 45.21)			

Notes:

[23] - PKS

Statistical analyses

No statistical analyses for this end point

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

End point title	Time to Reach Maximum BAY84-3174 Concentration (tmax) in Plasma After Single Dose of BAY1067197

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:

Pre-dose; 0 (0.5, 1, 2, 3, 4, 6 and 12 hours), 1, 2, 5, 13 and 21 days post-dose

End point values	BAY1067197 30 mg + Beta-blocker			
Subject group type	Subject analysis set			
Number of subjects analysed	11[24]			
Units: Hours				
median (full range (min-max))	4 (1.83 to 4)			

Notes:

[24] - PKS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until last follow-up (Day 22)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo + Beta-blocker

Reporting group description:

Subject received a single oral dose of placebo under fasted condition (treatment 1) along with selected standard beta-blocker therapy (either >=95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol IR tablet or >=5 mg nebivolol IR tablet).

Reporting group title	BAY1067197 30 mg + Beta-blocker

Reporting group description:

Subjects received a single oral dose of 30 mg (3 X 10 mg) BAY1067197 tablet under fasted condition (treatment 2) along with selected standard beta-blocker therapy(either >=95 mg metoprolol succinate controlled release tablet, >=5 mg bisoprolol IR tablet or >=5 mg nebivolol IR tablet).

Serious adverse events	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo + Beta-blocker	BAY1067197 30 mg + Beta-blocker	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)	7 / 11 (63.64%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Implantable defibrillator replacement			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Paraesthesia oral			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2013	1. Status of the study was changed to pilot study 2. Deletion of leucine aminopeptidase as a laboratory parameter 3. Adverse events of special interest section was updated 4. Minor corrections to the protocol text.
19 November 2013	1. Exclusion of women of childbearing potential 2. Deletion of serum beta-human chorionic gonadotropin pregnancy test 3. Minor corrections to the protocol text.

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: