Clinical trial results:
A randomized, single-blind, threefold crossover, single-center study to assess the safety and the effects of 1 mg and 5 mg BAY 1193397 in comparison to placebo on skin capillary blood flow and transcutaneous oxygen pressure after single dose in type II diabetic patients

Summary

EudraCT number	2015-003799-63
Trial protocol	GB
Global end of trial date	28 October 2019

Results information

Result version number	v1 (current)
This version publication date	27 August 2020
First version publication date	27 August 2020

Trial information

Trial identification

Sponsor protocol code	BAY1193397/17500

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03128320
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
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	28 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were to: 1) Investigate the change in resting capillary blood flow velocity (CBV) before and after study drug administration; 2) Investigate the change in peak CBV during reactive hyperemia before and after study drug administration; 3) Investigate the change in time to peak CBV during reactive hyperemia before and after study drug administration; 4) Investigate the change in transcutaneous oxygen pressure (TcPO2) before and after study drug administration. The secondary objective was to analyze safety and tolerability of BAY1193397 after a single dose administration as evidenced by the incidence and severity of adverse events (AEs).

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. Only after the subject voluntarily signed the informed consent form was he/she able to enter the study. If the subject was not capable of providing a signature, an oral statement of consent could have been given in the presence of a witness. Each subject was assured of the right to 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	25 May 2017
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	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at one center in UK, between 25 May 2017 (first subject first visit) and 06 Sep 2019 (last subject last visit).

Pre-assignment

Screening details:

A total of 58 subjects were screened, of whom 23 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment sequence A-B-C

Arm description:

Subjects received a single oral dose of matching placebo (5*1 mg placebo IR tablet) in the first intervention period (Treatment A); followed by a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B); then a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) under fasted state in the third intervention period (Treatment C). A wash-out phase of approximately 5 to 15 days was maintained between each treatment.

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

Dosage and administration details:

Subjects received a single dose of matching placebo to BAY1193397 given in the fasted state.

Investigational medicinal product name	BAY1193397 (1 mg)
Investigational medicinal product code	BAY1193397
Other name	Treatment B
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of 1 mg BAY1193397 immediate release (IR) tablet given in the fasted state.

Investigational medicinal product name	BAY1193397 (5 mg)
Investigational medicinal product code	BAY1193397
Other name	Treatment C
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of 5 mg BAY1193397 (5*1 mg IR tablet) given in the fasted state.

Arm title	Treatment sequence B-A-C

Arm description:

Subjects received a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B) in the first intervention period; followed by a single oral dose of matching placebo

(5*1 mg placebo IR tablet) (Treatment A) in the second intervention period; then a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) (Treatment C) under fasted conditions in the third intervention period. A wash-out phase of approximately 5 to 15 days was maintained between each treatment.

Arm type	Experimental
Investigational medicinal product name	BAY1193397 (1 mg)
Investigational medicinal product code	BAY1193397
Other name	Treatment B
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of 1 mg BAY1193397 immediate release (IR) tablet given in the fasted state.

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

Dosage and administration details:

Subjects received a single dose of matching placebo to BAY1193397 given in the fasted state.

Investigational medicinal product name	BAY1193397 (5 mg)
Investigational medicinal product code	BAY1193397
Other name	Treatment C
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of 5 mg BAY1193397 (5*1 mg IR tablet) given in the fasted state.

Arm title	Treatment sequence B-C-A

Arm description:

Subjects received a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B) in the first intervention period; followed by a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) (Treatment C) in the second intervention period; then a single oral dose of matching placebo (5*1 mg placebo IR tablet) (Treatment A) under fasted conditions in the third intervention period. A wash-out phase of approximately 5 to 15 days was maintained between each treatment.

Arm type	Experimental
Investigational medicinal product name	BAY1193397 (1 mg)
Investigational medicinal product code	BAY1193397
Other name	Treatment B
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of 1 mg BAY1193397 immediate release (IR) tablet given in the fasted state.

Investigational medicinal product name	BAY1193397 (5 mg)
Investigational medicinal product code	BAY1193397
Other name	Treatment C
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of 5 mg BAY1193397 (5*1 mg IR tablet) given in the fasted state.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Treatment A
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of matching placebo to BAY1193397 given in the fasted state.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The sponsor’s early clinical leader and clinical pharmacology lead were unblinded to allow for additional safety monitoring.

Number of subjects in period 1	Treatment sequence A-B-C	Treatment sequence B-A-C	Treatment sequence B-C-A
Started	7	6	10
Treated	6	5	8
Completed	5	3	8
Not completed	2	3	2
Not treated, unable to find capillaries	1	1	2
drop out after treatment 1	-	1	-
miss schedule visits	1	-	-
withdrawn by sponsor	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment sequence A-B-C
Reporting group description:	
Subjects received a single oral dose of matching placebo (5*1 mg placebo IR tablet) in the first intervention period (Treatment A); followed by a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B); then a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) under fasted state in the third intervention period (Treatment C). A wash-out phase of approximately 5 to 15 days was maintained between each treatment.	
Reporting group title	Treatment sequence B-A-C
Reporting group description:	
Subjects received a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B) in the first intervention period; followed by a single oral dose of matching placebo (5*1 mg placebo IR tablet) (Treatment A) in the second intervention period; then a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) (Treatment C) under fasted conditions in the third intervention period. A wash-out phase of approximately 5 to 15 days was maintained between each treatment.	
Reporting group title	Treatment sequence B-C-A
Reporting group description:	
Subjects received a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B) in the first intervention period; followed by a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) (Treatment C) in the second intervention period; then a single oral dose of matching placebo (5*1 mg placebo IR tablet) (Treatment A) under fasted conditions in the third intervention period. A wash-out phase of approximately 5 to 15 days was maintained between each treatment.	

Reporting group values	Treatment sequence A-B-C	Treatment sequence B-A-C	Treatment sequence B-C-A
Number of subjects	7	6	10
Age Categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	70.6	67.0	68.9
standard deviation	± 3.6	± 6.1	± 7.4
Gender Categorical Units: Subjects			
Female	2	2	3
Male	5	4	7
Presence of Peripheral Neuropathy Units: Subjects			
No	3	3	6
Yes	4	3	4

Reporting group values	Total		
Number of subjects	23		
Age Categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	7		
Male	16		
Presence of Peripheral Neuropathy Units: Subjects			
No	12		
Yes	11		

End points

End points reporting groups

Reporting group title	Treatment sequence A-B-C

Reporting group description:

Subjects received a single oral dose of matching placebo (5*1 mg placebo IR tablet) in the first intervention period (Treatment A); followed by a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B); then a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) under fasted state in the third intervention period (Treatment C). A wash-out phase of approximately 5 to 15 days was maintained between each treatment.

Reporting group title	Treatment sequence B-A-C

Reporting group description:

Subjects received a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B) in the first intervention period; followed by a single oral dose of matching placebo (5*1 mg placebo IR tablet) (Treatment A) in the second intervention period; then a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) (Treatment C) under fasted conditions in the third intervention period. A wash-out phase of approximately 5 to 15 days was maintained between each treatment.

Reporting group title	Treatment sequence B-C-A

Reporting group description:

Subjects received a single oral dose of 1 mg BAY1193397 (1*1 mg IR tablet + 4*1 mg placebo IR tablet) (Treatment B) in the first intervention period; followed by a single oral dose of 5 mg BAY1193397 (5*1 mg IR tablet) (Treatment C) in the second intervention period; then a single oral dose of matching placebo (5*1 mg placebo IR tablet) (Treatment A) under fasted conditions in the third intervention period. A wash-out phase of approximately 5 to 15 days was maintained between each treatment.

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

Subject analysis set description:

All randomized subjects who received at least one dose of the study medication.

Subject analysis set title	Per-protocol analysis set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects of the SAF without validity findings who completed all three study periods with valid measurements for all four primary variables.

Subject analysis set title	BAY1193397 (1 mg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of 1 mg BAY1193397 immediate release (IR) tablet given in the fasted state.

Subject analysis set title	BAY1193397 (5 mg)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of 5 mg BAY1193397 (5*1 mg IR tablet) given in the fasted state.

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of matching placebo to BAY1193397 given in the fasted state.

Primary: Change in resting capillary blood flow velocity (CBV)

End point title	Change in resting capillary blood flow velocity (CBV)

End point description:

In each treatment period, capillaroscopy was performed twice – before and after study drug administration. Capillary images were recorded live and capillary blood flow velocity (CBV) was then analyzed offline. CBV was continuously computed during 2 min and the mean value during this period was termed resting CBV. Change in resting CBV = resting CBV after study drug administration – resting CBV before study drug administration.

End point type	Primary

End point timeframe:

Before and after treatment with study drug (within 1-3 hours after treatment with study drug)

End point values	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15[1]	15[2]	15[3]	
Units: µm/s				
arithmetic mean (standard deviation)	-94.73 (± 278.74)	-23.64 (± 249.52)	-63.28 (± 195.10)	

Notes:

[1] - PPS

[2] - PPS

[3] - PPS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The Holm procedure was applied on the 4 primary variables. This is a step-down procedure that starts with the hypothesis associated with the most significant p-value of the one-sided exact Page test and rejects it if the p-value is not greater than α/4 = 0.2/4 = 0.05. The overall α-level of this procedure is 0.20. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 15.

Comparison groups	BAY1193397 (1 mg) v BAY1193397 (5 mg) v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2634 [4]
Method	one-sided exact Page test

Notes:

[4] - Since this primary variable had the smallest one-sided p-value of the exact Page test and the p-value was larger than 0.05, the associated null hypothesis H was not rejected. The Holm procedure was therefore stopped.

Primary: Change in peak CBV during reactive hyperemia

End point title	Change in peak CBV during reactive hyperemia[5]

End point description:

In each treatment period, capillaroscopy was performed twice – before and after study drug administration. Peak CBV was measured following release of a 1-min arterial occlusion at the proximal phalanx of the great toe with a cuff pressure of 200 mmHg. Three 1-min arterial occlusions were performed at least 1 min apart. Results from the 3 independent measurements of peak CBV was entered in the eCRF and the mean was calculated by data management. Change in peak CBV during reactive hyperemia = peak CBV after study drug administration – peak CBV before study drug administration. During the study, the "no peak phenomenon" was observed in rare cases. The resulting missing quantitative data for peak CBV were replaced by imputed values to get semi quantitative information for the changes from baseline. In these cases, peak CBV was set to 0 which was considered as an approximation of infinity.

End point type	Primary

End point timeframe:

Before and after treatment with study drug (within 1-3 hours after treatment with study drug)

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: Since the p-value of the primary variable with the smallest one-sided p-value of the exact Page test was larger than 0.05, the associated null hypothesis H was not rejected. The Holm procedure was therefore stopped.

End point values	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15[6]	15[7]	15[8]	
Units: µm/s				
median (full range (min-max))	-27.80 (-1350.4 to 412.5)	144.50 (-1598.3 to 1153.1)	0.00 (-519.0 to 751.5)	

Notes:

[6] - PPS

[7] - PPS

[8] - PPS

Statistical analyses

No statistical analyses for this end point

Primary: Change in time to peak CBV during reactive hyperemia

End point title	Change in time to peak CBV during reactive hyperemia[9]

End point description:

In each treatment period, capillaroscopy was performed twice – before and after study drug administration. Time to peak CBV was measured following release of a 1-min arterial occlusion at the proximal phalanx of the great toe with a cuff pressure of 200 mmHg. Three 1-min arterial occlusions were performed at least 1 min apart. Results from the 3 independent measurements of time to peak was entered in the eCRF and the mean was calculated by data management. Change in time to peak CBV during reactive hyperemia = time to peak CBV after study drug administration – time to peak CBV before study drug administration. During the study, the "no peak phenomenon" was observed in rare cases. The resulting missing quantitative data for time to peak CBV were replaced by imputed values to get semi quantitative information for the changes from baseline. In these cases, time to peak was set to 100000 which was considered as an approximation of infinity.

End point type	Primary

End point timeframe:

Before and after treatment with study drug (within 1-3 hours after treatment with study drug)

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: Since the p-value of the primary variable with the smallest one-sided p-value of the exact Page test was larger than 0.05, the associated null hypothesis H was not rejected. The Holm procedure was therefore stopped.

End point values	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15[10]	15[11]	15[12]	
Units: second				
median (full range (min-max))	2.10 (-12.7 to 99992.4)	1.40 (-99992.8 to 99977.5)	0.00 (-3.9 to 4.6)	

Notes:

[10] - PPS

[11] - PPS

[12] - PPS

Statistical analyses

No statistical analyses for this end point

Primary: Change in transcutaneous oxygen pressure (TcPO2)

End point title	Change in transcutaneous oxygen pressure (TcPO2)[13]

End point description:

Local skin oxygenation was evaluated by measurement of transcutaneous oxygen pressure (TcPO2) at the dorsum of the foot in the first intermetatarsal space using the Periflux System 5000 (PF5040) and, as reference, at the left upper quadrant of the chest. TcPO2 is a non-invasive method reflecting local arterial skin blood flow and oxygenation. The same foot was used for capillaroscopy and TcPO2 measurements. For each TcPO2 determination, 3 measurements were performed at the foot and chest, 15, 17, and 19 min after heating, and documented in the eCRF. Means for foot and chest TcPO2 were calculated by data management. At least 2 out of 3 TcPO2 measurements had to be valid (as judged by skin temperature measurement) for mean calculation. Change in foot TcPO2 = TcPO2 after study drug administration – TcPO2 before study drug administration.

End point type	Primary

End point timeframe:

Before and after treatment with study drug (within 1-3 hours after treatment with study drug)

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: Since the p-value of the primary variable with the smallest one-sided p-value of the exact Page test was larger than 0.05, the associated null hypothesis H was not rejected. The Holm procedure was therefore stopped.

End point values	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15[14]	15[15]	15[16]	
Units: mmHg				
arithmetic mean (standard deviation)	-0.99 (± 11.27)	6.09 (± 21.19)	2.68 (± 10.01)	

Notes:

[14] - PPS

[15] - PPS

[16] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)

End point description:

An AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. An SAE was classified as any untoward medical occurrence that, at any dose, met any of the following criteria: Resulted in death; Was life-threatening; Required inpatient hospitalization or prolongation of existing hospitalization; Resulted in

persistent or significant disability/incapacity; Was a congenital anomaly/birth defect; Was another serious or important medical event as judged by the investigator. AEs were considered to be treatment-emergent if they had started or worsened after first application of study medication up to 2 days after end of treatment with study medication.

End point type	Secondary

End point timeframe:

From first application of study medication up to 2 days after end of treatment with study medication

End point values	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[17]	16[18]	18[19]	
Units: subjects				
number (not applicable)				
Any AE	9	6	5	
Any SAE	0	0	0	
Any study drug-related AE	5	6	3	
Related to protocol required procedures	3	3	1	
Leading to study drug discontinuation	0	0	0	

Notes:

[17] - SAF

[18] - SAF

[19] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with TEAEs in different severity

End point title	Number of subjects with TEAEs in different severity

End point description:

An AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. An SAE was classified as any untoward medical occurrence that, at any dose, met any of the following criteria: Resulted in death; Was life-threatening; Required inpatient hospitalization or prolongation of existing hospitalization; Resulted in persistent or significant disability/incapacity; Was a congenital anomaly/birth defect; Was another serious or important medical event as judged by the investigator. AEs were considered to be treatment-emergent if they had started or worsened after first application of study medication up to 2 days after end of treatment with study medication.

End point type	Secondary

End point timeframe:

From first application of study medication up to 2 days after end of treatment with study medication

End point values	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[20]	16[21]	18[22]	
Units: subjects				
number (not applicable)				
Any AE-Mild	8	6	5	
Any AE-Moderate	1	0	0	
Any study drug-related AE-Mild	4	6	3	
Any study drug-related AE-Moderate	1	0	0	

Notes:

[20] - SAF

[21] - SAF

[22] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first application of study medication up to 2 days after end of treatment with study medication

Adverse event reporting additional description:

In this cross-over study, some subjects could be experiencing the same adverse event in more than one period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	BAY1193397 (1 mg)

Reporting group description:

Subjects received a single dose of 1 mg BAY1193397 immediate release (IR) tablet given in the fasted state.

Reporting group title	BAY1193397 (5 mg)

Reporting group description:

Subjects received a single dose of 5 mg BAY1193397 (5*1 mg IR tablet) given in the fasted state.

Reporting group title	Placebo

Reporting group description:

Subjects received a single dose of matching placebo to BAY1193397 given in the fasted state.

Serious adverse events	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	BAY1193397 (1 mg)	BAY1193397 (5 mg)	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 18 (50.00%)	6 / 16 (37.50%)	5 / 18 (27.78%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			

subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Mean cell volume decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Reticulocyte count decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Head discomfort			
subjects affected / exposed	1 / 18 (5.56%)	3 / 16 (18.75%)	1 / 18 (5.56%)
occurrences (all)	1	3	1
Headache			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Tension headache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Medical device site erythema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Medical device site dryness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Medical device site scab			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	3 / 18 (16.67%)	0 / 16 (0.00%)	2 / 18 (11.11%)
occurrences (all)	3	0	2
Dry mouth			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Spontaneous penile erection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Skin discolouration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rhinitis			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 16 (0.00%) 0	0 / 18 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2017	This amendment was initiated to include restrictions for sunlight exposure of patients during study conduction.
24 August 2017	Modifications due to this amendment included the addition of inclusion criteria for diagnosis of PAD and the addition of exclusion criteria for patients with diabetes mellitus induced by immunosuppressive treatment, patients with renal replacement therapy, patients with organ transplants, and patients with a medical history of autoimmune disease.
12 July 2018	This amendment was issued to facilitate the enrollment of type II diabetes mellitus patients with impaired capillary microcirculation into the study. Modifications included the amendment of inclusion criteria to expand recruitment in type 2 diabetic patient populations also to individuals suffering from microangiopathy, the inclusion of final results from the multiple dose escalation study (EudraCT No. 2016-000038-23), and the amendment of the screening visit period from ‘‘Day -28 to Day -4’’ to “Day -28 to Day -1’’.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported