



## 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 (TcPO<sub>2</sub>) 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 <sup>[1]</sup>    |
| Roles blinded                | Investigator, Carer, Subject   |

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | 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.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | 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.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b>      | Treatment sequence<br>A-B-C | Treatment sequence<br>B-A-C | Treatment sequence<br>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<br>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<br>A-B-C | Treatment sequence<br>B-A-C | Treatment sequence<br>B-C-A |
|-------------------------------------------------------|-----------------------------|-----------------------------|-----------------------------|
| Number of subjects                                    | 7                           | 6                           | 10                          |
| Age Categorical<br>Units: Subjects                    |                             |                             |                             |
| In utero                                              |                             |                             |                             |
| Preterm newborn infants<br>(gestational age < 37 wks) |                             |                             |                             |
| Newborns (0-27 days)                                  |                             |                             |                             |
| Infants and toddlers (28 days-23<br>months)           |                             |                             |                             |
| Children (2-11 years)                                 |                             |                             |                             |
| Adolescents (12-17 years)                             |                             |                             |                             |
| Adults (18-64 years)                                  |                             |                             |                             |
| From 65-84 years                                      |                             |                             |                             |
| 85 years and over                                     |                             |                             |                             |
| Age Continuous<br>Units: years                        |                             |                             |                             |
| arithmetic mean                                       | 70.6                        | 67.0                        | 68.9                        |
| standard deviation                                    | ± 3.6                       | ± 6.1                       | ± 7.4                       |
| Gender Categorical<br>Units: Subjects                 |                             |                             |                             |
| Female                                                | 2                           | 2                           | 3                           |
| Male                                                  | 5                           | 4                           | 7                           |
| Presence of Peripheral Neuropathy<br>Units: Subjects  |                             |                             |                             |
| No                                                    | 3                           | 3                           | 6                           |
| Yes                                                   | 4                           | 3                           | 4                           |

|                                                                                                                                                                                                                                                              |       |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                                                                                                                                                                                                                                | Total |  |  |
| Number of subjects                                                                                                                                                                                                                                           | 23    |  |  |
| Age Categorical<br>Units: Subjects                                                                                                                                                                                                                           |       |  |  |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |       |  |  |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                      | -     |  |  |
| Gender Categorical<br>Units: Subjects                                                                                                                                                                                                                        |       |  |  |
| Female                                                                                                                                                                                                                                                       | 7     |  |  |
| Male                                                                                                                                                                                                                                                         | 16    |  |  |
| Presence of Peripheral Neuropathy<br>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 <sup>[1]</sup>    | 15 <sup>[2]</sup>    | 15 <sup>[3]</sup>    |  |
| 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  $\alpha/4 = 0.2/4 = 0.05$ . The overall  $\alpha$ -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 <sup>[4]</sup>                         |
| 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 <sup>[5]</sup> |
|-----------------|-------------------------------------------------------------|

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 <sup>[6]</sup>         | 15 <sup>[7]</sup>          | 15 <sup>[8]</sup>      |  |
| 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 <sup>[9]</sup> |
|-----------------|---------------------------------------------------------------------|

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 <sup>[10]</sup>      | 15 <sup>[11]</sup>         | 15 <sup>[12]</sup>   |  |
| 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

## 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) <sup>[13]</sup> |
|-----------------|------------------------------------------------------------------|

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 <sup>[14]</sup>   | 15 <sup>[15]</sup>   | 15 <sup>[16]</sup>   |  |
| 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 <sup>[17]</sup>   | 16 <sup>[18]</sup>   | 18 <sup>[19]</sup>   |  |
| 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                     |

| <b>End point values</b>            | BAY1193397 (1 mg)    | BAY1193397 (5 mg)    | Placebo              |  |
|------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                 | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed        | 18 <sup>[20]</sup>   | 16 <sup>[21]</sup>   | 18 <sup>[22]</sup>   |  |
| 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<br>occurrences (all)                                                                                         | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Mean cell volume decreased<br>subjects affected / exposed<br>occurrences (all)                                                           | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Reticulocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                                                         | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 |
| Injury, poisoning and procedural complications<br>Animal bite<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 18 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 0 / 18 (0.00%)<br>0 |
| Nervous system disorders<br>Head discomfort<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 18 (5.56%)<br>1  | 3 / 16 (18.75%)<br>3 | 1 / 18 (5.56%)<br>1 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                                             | 2 / 18 (11.11%)<br>2 | 1 / 16 (6.25%)<br>1  | 0 / 18 (0.00%)<br>0 |
| Tension headache<br>subjects affected / exposed<br>occurrences (all)                                                                     | 0 / 18 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 0 / 18 (0.00%)<br>0 |
| General disorders and administration site conditions<br>Medical device site erythema<br>subjects affected / exposed<br>occurrences (all) | 1 / 18 (5.56%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 |
| Medical device site dryness<br>subjects affected / exposed<br>occurrences (all)                                                          | 1 / 18 (5.56%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 |
| Medical device site scab<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 18 (5.56%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 |
| Eye disorders<br>Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 18 (5.56%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 18 (0.00%)<br>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 | 1 / 18 (5.56%) | 0 / 16 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all)           | 1              | 0              | 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported