



Clinical trial results:

Monocenter prospective open single-arm phase IV study of the effects of hawthorn extract WS® 1442 on arterial micro-vascular structure and macro-vascular function, persistence and erectile function of male patients with underlying cardiovascular disease and erectile dysfunction
Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-001319-38 |
| Trial protocol | DE |
| Global end of trial date | 09 September 2020 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 23 September 2021 |
| First version publication date | 23 September 2021 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | MW 051 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Dr. Willmar Schwabe GmbH & Co. KG |
| Sponsor organisation address | Willmar-Schwabe-Straße 4, Karlsruhe, Germany, 76227 |
| Public contact | Medical Affairs, Dr. Willmar Schwabe GmbH & Co. KG, 0049 7214093 573, ute.paulsen@schwabe.de |
| Scientific contact | Medical Affairs, Dr. Willmar Schwabe GmbH & Co. KG, 0049 7214093 573, ute.paulsen@schwabe.de |

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 | 23 June 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 September 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 September 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

- Description of the effects of hawthorn leaf and flower dry extract WS® 1442 on arterial micro-vascular structure and macro-vascular function and laboratory parameters of cardiac stress, endothelial function, oxidative stress and inflammation.
- Analysis of the correlations of these effects with improvements in clinical symptoms, endurance performance and erectile function.
- Description of the safety and tolerability of WS® 1442 in patients with underlying cardiovascular disease and erectile dysfunction.

Protection of trial subjects:

Safety monitoring (adverse events [AEs], serious adverse events [SAEs], adverse drug reactions [ADRs]), assessment of laboratory data (blood chemistry, hematology), physical examination, ECG and vital signs.

Background therapy:

Basic therapy of the underlying cardiovascular disease according to current guidelines.

Evidence for comparator:

Not applicable.

| | |
|---|----------------|
| Actual start date of recruitment | 18 August 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 35 |
| Worldwide total number of subjects | 35 |
| EEA total number of subjects | 35 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 19 |
| From 65 to 84 years | 16 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

35 subjects were enrolled at one study center in Germany. Patients were recruited by cooperating clinics and medical practices which referred the patients to the study center. The duration of the recruitment phase was about 3.5 years and terminated early.

First subject was screened on 18-Aug-2016, last patient completed on 25-Mar-2020.

Pre-assignment

Screening details:

Suitable subjects were selected by the investigator according to the eligibility criteria specified in the protocol.

Pre-assignment period milestones

| | |
|------------------------------|-------------------|
| Number of subjects started | 70 ^[1] |
| Number of subjects completed | 35 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | Failure meeting all inclusion criteria: 30 |
| Reason: Number of subjects | Meeting at least one exclusion criterion: 5 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The total number of patients in the pre-assignment period reflects the number of screened patients. The total number of enrolled patients is different from the number of screened patients.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable.

Arms

| | |
|-----------|----------|
| Arm title | WS® 1442 |
|-----------|----------|

Arm description:

Patients received hawthorn special extract WS® 1442, 450 mg p.o., b.i.d. (900 mg per day) for 8 weeks.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | hawthorn leaf and flower dry extract |
| Investigational medicinal product code | WS® 1442 |
| Other name | Crataegutt® 450 mg Herz-Kreislauf Tabletten |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

450 mg, p.o. (oral), b.i.d. (twice daily)

| | |
|---------------------------------------|----------|
| Number of subjects in period 1 | WS® 1442 |
| Started | 35 |
| Completed | 35 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Treatment |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|----------|
| Arm title | WS® 1442 |
|------------------|----------|

Arm description:

Patients received hawthorn special extract WS® 1442, 450 mg p.o., b.i.d. (900 mg per day) for 8 weeks.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | hawthorn leaf and flower dry extract |
| Investigational medicinal product code | WS® 1442 |
| Other name | Crataegutt® 450 mg Herz-Kreislauf Tabletten |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

450 mg, p.o. (oral), b.i.d. (twice daily)

| | |
|--|----------|
| Number of subjects in period 2 | WS® 1442 |
| Started | 35 |
| Completed | 31 |
| Not completed | 4 |
| Consent withdrawn by subject | 2 |
| Withdrawal due to rejection of study procedure | 1 |
| COVID-19 pandemic related reasons | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|----------|
| Reporting group title | Baseline |
| Reporting group description: - | |

| Reporting group values | Baseline | Total | |
|------------------------|----------|-------|--|
| Number of subjects | 35 | 35 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 19 | 19 | |
| From 65-84 years | 16 | 16 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.8 | | |
| standard deviation | ± 8.43 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 35 | 35 | |

Subject analysis sets

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59).

| | |
|----------------------------|------------------------|
| Subject analysis set title | Per Protocol Set (PPS) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation.

| | |
|----------------------------|---------------------|
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety Analysis Set (SAF) consists of all patients who received at least one dose of study medication.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Full Analysis Set (FAS) - Visit 2 |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59).

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Per Protocol Set (PPS) - Visit 2 |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Full Analysis Set (FAS) - Visit 3 |
|----------------------------|-----------------------------------|

| | |
|--|--|
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). | |
| Subject analysis set title | Per Protocol Set (PPS) - Visit 3 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. | |
| Subject analysis set title | Full Analysis Set (FAS) - Visit 4 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). | |
| Subject analysis set title | Per Protocol Set (PPS) - Visit 4 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. | |
| Subject analysis set title | Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). Subject analysis set for SEP analysis. | |
| Subject analysis set title | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. Subject analysis set for SEP analysis. | |
| Subject analysis set title | Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). Subject analysis set for SEP analysis. | |
| Subject analysis set title | Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. Subject analysis set for SEP analysis. | |
| Subject analysis set title | RigiScan Analysis Set - Visit 2 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: RigiScan Analysis Set comprises a subgroup of patients with optional RigiScan assessments at visit 2 (baseline, day 0) and visit 4 (completion, day 53-59). | |
| Subject analysis set title | RigiScan Analysis Set - Visit 4 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: RigiScan Analysis Set comprises a subgroup of patients with optional RigiScan assessments at visit 2 (baseline, day 0) and visit 4 (completion, day 53-59). | |

| Reporting group values | Full Analysis Set (FAS) | Per Protocol Set (PPS) | Safety Analysis Set |
|--|-------------------------|------------------------|---------------------|
| Number of subjects | 30 | 28 | 35 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) From 65-84 years | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 63.7 | 63.3 | 63.8 |
| standard deviation | ± 8.37 | ± 7.72 | ± 8.43 |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 30 | 28 | 35 |

| Reporting group values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 3 |
|--|-----------------------------------|----------------------------------|-----------------------------------|
| Number of subjects | 30 | 28 | 30 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) From 65-84 years | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 63.7 | 63.3 | 63.7 |
| standard deviation | ± 8.37 | ± 7.72 | ± 8.37 |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 30 | 28 | 30 |

| Reporting group values | Per Protocol Set (PPS) - Visit 3 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--|----------------------------------|-----------------------------------|----------------------------------|
| Number of subjects | 28 | 30 | 28 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) From 65-84 years | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 63.3 | 63.7 | 63.3 |
| standard deviation | ± 7.72 | ± 8.37 | ± 7.72 |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 28 | 30 | 28 |

| Reporting group values | Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] | Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] |
|------------------------|--|---|--|
| Number of subjects | 30 | 28 | 30 |

| | | | |
|----------------------|--------|--------|--------|
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.7 | 63.3 | 63.7 |
| standard deviation | ± 8.37 | ± 7.72 | ± 8.37 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 30 | 28 | 30 |

| Reporting group values | Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 |
|-------------------------------|---|---------------------------------|---------------------------------|
| Number of subjects | 28 | 4 | 4 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.3 | | |
| standard deviation | ± 7.72 | ± | ± |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | | |
| Male | 28 | | |

End points

End points reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | WS® 1442 |
| Reporting group description: Patients received hawthorn special extract WS® 1442, 450 mg p.o., b.i.d. (900 mg per day) for 8 weeks. | |
| Reporting group title | WS® 1442 |
| Reporting group description: Patients received hawthorn special extract WS® 1442, 450 mg p.o., b.i.d. (900 mg per day) for 8 weeks. | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). | |
| Subject analysis set title | Per Protocol Set (PPS) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The Safety Analysis Set (SAF) consists of all patients who received at least one dose of study medication. | |
| Subject analysis set title | Full Analysis Set (FAS) - Visit 2 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). | |
| Subject analysis set title | Per Protocol Set (PPS) - Visit 2 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. | |
| Subject analysis set title | Full Analysis Set (FAS) - Visit 3 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). | |
| Subject analysis set title | Per Protocol Set (PPS) - Visit 3 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. | |
| Subject analysis set title | Full Analysis Set (FAS) - Visit 4 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). | |

| | |
|---|---|
| Subject analysis set title | Per Protocol Set (PPS) - Visit 4 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. | |
| Subject analysis set title | Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). Subject analysis set for SEP analysis. | |
| Subject analysis set title | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. Subject analysis set for SEP analysis. | |
| Subject analysis set title | Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full Analysis Set (FAS) consists of all patients who received at least one dose of study medication and have results documented for the primary endpoint at visit 2 (baseline, Day 0) and visit 4 (completion, Day 53-59). Subject analysis set for SEP analysis. | |
| Subject analysis set title | Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The Per Protocol Set (PPS) consists of all patients in the Full Analysis Set with a study medication compliance of at least 80% and with no major protocol violation. Subject analysis set for SEP analysis. | |
| Subject analysis set title | RigiScan Analysis Set - Visit 2 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| RigiScan Analysis Set comprises a subgroup of patients with optional RigiScan assessments at visit 2 (baseline, day 0) and visit 4 (completion, day 53-59). | |
| Subject analysis set title | RigiScan Analysis Set - Visit 4 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| RigiScan Analysis Set comprises a subgroup of patients with optional RigiScan assessments at visit 2 (baseline, day 0) and visit 4 (completion, day 53-59). | |
| Primary: Primary Endpoint - Change in AVR (Retinal arteriolar to venous ratio) | |
| End point title | Primary Endpoint - Change in AVR (Retinal arteriolar to venous ratio) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Change from visit 2 (baseline, day 0) until visit 4 (completion, day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 28 | 30 | 28 |
| Units: AVR | | | | |
| arithmetic mean (standard deviation) | 0.813 (\pm 0.0607) | 0.812 (\pm 0.0620) | 0.814 (\pm 0.0620) | 0.811 (\pm 0.0624) |

Statistical analyses

| Statistical analysis title | Change in AVR (FAS) |
|--|---|
| Statistical analysis description: Change in AVR from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 4 v Full Analysis Set (FAS) - Visit 2 |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.008 |
| upper limit | 0.011 |
| Notes: | |
| [1] - N=30 | |

| Statistical analysis title | Change in AVR (PPS) |
|--|---|
| Statistical analysis description: Change in AVR from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 4 v Per Protocol Set (PPS) - Visit 2 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.011 |
| upper limit | 0.009 |
| Notes: | |
| [2] - N=28 | |

Secondary: SE | Microvascular structure| Central retinal arterial equivalent (CRAE)

| | |
|-----------------|--|
| End point title | SE Microvascular structure Central retinal arterial equivalent (CRAE) |
|-----------------|--|

End point description:

Three pictures of both eyes are taken at visits 2 and 4. CRAE was determined for each available picture. For each patient and visit, the arithmetic mean of all available CRAE values and the arithmetic mean of all CRAE values were calculated.

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 28 | 30 | 28 |
| Units: CRAE (µm) | | | | |
| arithmetic mean (standard deviation) | 146.8 (± 19.60) | 145.5 (± 17.53) | 148.2 (± 21.15) | 146.0 (± 15.91) |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Change in CRAE (FAS) |
|----------------------------|----------------------|

Statistical analysis description:

Change in CRAE from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 4 |

Notes:

[3] - N=30

| | |
|----------------------------|----------------------|
| Statistical analysis title | Change in CRAE (PPS) |
|----------------------------|----------------------|

Statistical analysis description:

Change in CRAE from baseline until visit 4 (week 8) for PPS.

| | |
|-------------------|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
|-------------------|---|

| | |
|---|----------------------|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 2.6 |

Notes:

[4] - N=28

Secondary: SE | Microvascular structure| Central retinal venous equivalent (CRVE)

| | |
|-----------------|--|
| End point title | SE Microvascular structure Central retinal venous equivalent (CRVE) |
|-----------------|--|

End point description:

Three pictures of both eyes are taken at visits 2 and 4. CRVE was determined for each available picture. For each patient and visit, the arithmetic mean of all available CRVE values and the arithmetic mean of all CRVE values were calculated.

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 28 | 30 | 28 |
| Units: CRVE (µm) | | | | |
| arithmetic mean (standard deviation) | 181.1 (± 22.89) | 179.7 (± 18.79) | 182.7 (± 26.40) | 180.9 (± 20.64) |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Change in CRVE (FAS) |
|----------------------------|----------------------|

Statistical analysis description:

Change in CRVE from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 3.8 |

Notes:

[5] - N=30

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Change in CRVE (PPS) |
|-----------------------------------|----------------------|

Statistical analysis description:

Change in CRVE from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 3 |

Notes:

[6] - N=28

Secondary: SE | Macrovascular function | Cardio-ankle pulse wave velocity

| | |
|-----------------|--|
| End point title | SE Macrovascular function Cardio-ankle pulse wave velocity |
|-----------------|--|

End point description:

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

End point timeframe:

Change from visit 2 (baseline, day 0) until visit 4 (completion, day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[7] | 27 ^[8] | 30 | 28 |
| Units: PWV (m/s) | | | | |
| arithmetic mean (standard deviation) | 13.52 (± 1.907) | 13.40 (± 1.906) | 14.18 (± 3.272) | 13.73 (± 2.173) |

Notes:

[7] - Data of one patient missing.

[8] - Data of one patient missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in PWV (FAS) |
| Statistical analysis description: Change in PWV from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 4 v Full Analysis Set (FAS) - Visit 2 |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 1.46 |

Notes:

[9] - N=29

| | |
|--|---|
| Statistical analysis title | Change in PWV (PPS) |
| Statistical analysis description: Change in PWV from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 0.65 |

Notes:

[10] - N=27

Secondary: SE | Macrovascular function | Cardio-ankle vascular index (CAVI)

| | |
|---|--|
| End point title | SE Macrovascular function Cardio-ankle vascular index (CAVI) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[11] | 27 ^[12] | 30 | 28 |
| Units: CAVI (m/s) | | | | |
| arithmetic mean (standard deviation) | 8.27 (± 1.079) | 8.19 (± 1.071) | 8.42 (± 1.352) | 8.28 (± 1.135) |

Notes:

[11] - Data of one patient missing.

[12] - Data of one patient missing.

Statistical analyses

| Statistical analysis title | Change in CAVI (FAS) |
|---|---|
| Statistical analysis description: Change in CAVI from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 0.39 |

Notes:

[13] - N=29

| Statistical analysis title | Change in CAVI (PPS) |
|---|---|
| Statistical analysis description: Change in CAVI from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 0.24 |

Notes:

[14] - N=27

Secondary: SE | Macrovascular function | Amplitude of the forward pulse wave (Pf)

| | |
|-----------------|--|
| End point title | SE Macrovascular function Amplitude of the forward pulse wave (Pf) |
|-----------------|--|

End point description:

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[15] | 26 ^[16] | 30 | 28 |
| Units: Pf (mmHg) | | | | |
| arithmetic mean (standard deviation) | 24.29 (± 8.063) | 24.49 (± 8.084) | 26.51 (± 9.237) | 26.75 (± 9.361) |

Notes:

[15] - Data of two patients missing.

[16] - Data of two patients missing.

Statistical analyses

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | Change in Pf (FAS) |
|-----------------------------------|--------------------|

Statistical analysis description:

Change in Amplitude of the forward pulse wave from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[17] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 4.56 |

Notes:

[17] - N=28

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | Change in Pf (PPS) |
|-----------------------------------|--------------------|

Statistical analysis description:

Change in Amplitude of the forward pulse wave from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[18] |
| Parameter estimate | Change from baseline |
| Point estimate | 2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.81 |
| upper limit | 4.81 |

Notes:

[18] - N=26

Secondary: SE | Macrovascular function | Amplitude of the backward pulse wave (Pb)

| | |
|-----------------|---|
| End point title | SE Macrovascular function Amplitude of the backward pulse wave (Pb) |
|-----------------|---|

End point description:

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

End point timeframe:

Change from visit 2 (baseline, day 0) until visit 4 (completion, day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[19] | 26 ^[20] | 30 | 28 |
| Units: Pb (mmHg) | | | | |
| arithmetic mean (standard deviation) | 14.35 (± 6.174) | 14.64 (± 6.267) | 16.15 (± 7.527) | 16.28 (± 7.711) |

Notes:

[19] - Data of two patients missing.

[20] - Data of two patients missing

Statistical analyses

| | |
|----------------------------|--------------------|
| Statistical analysis title | Change in Pb (FAS) |
|----------------------------|--------------------|

Statistical analysis description:

Change in Amplitude of the backward pulse wave from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 3.23 |

Notes:

[21] - N=28

| | |
|---|---|
| Statistical analysis title | Change in Pb (PPS) |
| Statistical analysis description: Change in Amplitude of the backward pulse wave from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 3.18 |

Notes:

[22] - N=26

Secondary: SE | Macrovascular function | Central arterial blood pressure (systolic, diastolic, mean)

| | |
|-----------------|---|
| End point title | SE Macrovascular function Central arterial blood pressure (systolic, diastolic, mean) |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[23] | 26 ^[24] | 30 | 28 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic | 125.96 (± 16.262) | 126.02 (± 16.787) | 127.04 (± 19.051) | 127.83 (± 19.245) |
| Diastolic | 89.54 (± 8.252) | 89.06 (± 8.372) | 87.38 (± 8.591) | 87.89 (± 8.661) |
| Mean | 101.68 (± 9.789) | 101.38 (± 10.105) | 100.60 (± 10.823) | 101.20 (± 10.877) |

Notes:

[23] - Data of two patients missing.

[24] - Data of two patients missing.

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Change in central arterial BP - mean (FAS) |
|-----------------------------------|--|

Statistical analysis description:

Change in central arterial blood pressure from baseline until visit 4 (week 8) for FAS.

| | |
|-------------------|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
|-------------------|---|

| | |
|---|-----------------------|
| | 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| Parameter estimate | Change from baseline |
| Point estimate | -1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.37 |
| upper limit | 1.59 |

Notes:

[25] - N=28

| | |
|--|---|
| Statistical analysis title | Change in central arterial BP - mean (PPS) |
| Statistical analysis description: Change in central arterial blood pressure from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[26] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.33 |
| upper limit | 2.39 |

Notes:

[26] - N=26

| | |
|--|--|
| Secondary: SE Macrovascular function Aortic pulse wave velocity (aoPWV) | |
| End point title | SE Macrovascular function Aortic pulse wave velocity (aoPWV) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[27] | 26 ^[28] | 30 | 28 |
| Units: aoPWV (m/s) | | | | |
| arithmetic mean (standard deviation) | 9.466 (± 1.4017) | 9.364 (± 1.2446) | 9.624 (± 1.5530) | 9.577 (± 1.4559) |

Notes:

[27] - Data of two patients missing.

[28] - Data of two patients missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in aoPWV (FAS) |
| Statistical analysis description: Change in aoPWV from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[29] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.117 |
| upper limit | 0.148 |

Notes:

[29] - N=28

| | |
|--|---|
| Statistical analysis title | Change in aoPWV (PPS) |
| Statistical analysis description: Change in aoPWV from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[30] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.073 |
| upper limit | 0.184 |

Notes:

[30] - N=26

Secondary: SE | Macrovascular function | Aortic pulse pressure (aoPP)

| | |
|---|--|
| End point title | SE Macrovascular function Aortic pulse pressure (aoPP) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[31] | 26 ^[32] | 30 | 28 |
| Units: aoPP (mm Hg) | | | | |
| arithmetic mean (standard deviation) | 36.33 (\pm 12.955) | 36.90 (\pm 13.063) | 39.70 (\pm 15.406) | 39.96 (\pm 15.698) |

Notes:

[31] - Data of two patients missing.

[32] - Data of two patients missing.

Statistical analyses

| Statistical analysis title | Change in aoPP (FAS) |
|---|---|
| Statistical analysis description: Change in aoPP from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[33] |
| Parameter estimate | Change from baseline |
| Point estimate | 2.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 6.22 |

Notes:

[33] - N=28

| Statistical analysis title | Change in aoPP (PPS) |
|---|---|
| Statistical analysis description: Change in aoPP from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[34] |
| Parameter estimate | Change from baseline |
| Point estimate | 2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.45 |
| upper limit | 6.12 |

Notes:

[34] - N=26

Secondary: SE | Macrovascular function | Augmentation pressure (AP)

End point title SE | Macrovascular function | Augmentation pressure (AP)

End point description:

End point type Secondary

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[35] | 26 ^[36] | 30 | 28 |
| Units: AP (mmHg) | | | | |
| arithmetic mean (standard deviation) | 13.26 (\pm 10.448) | 13.85 (\pm 10.625) | 14.13 (\pm 11.242) | 14.46 (\pm 11.564) |

Notes:

[35] - Data of two patients missing.

[36] - Data of two patients missing.

Statistical analyses

Statistical analysis title Change in AP (FAS)

Statistical analysis description:

Change in AP from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[37] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.48 |
| upper limit | 3.59 |

Notes:

[37] - N=28

Statistical analysis title Change in AP (PPS)

Statistical analysis description:

Change in AP from baseline until visit 4 (week 8) for PPS.

| | |
|-------------------|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
|-------------------|---|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[38] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.03 |
| upper limit | 3.57 |

Notes:

[38] - N=26

Secondary: SE | Macrovascular function | Peripheral arterial blood pressure (systolic and diastolic)

| | |
|-----------------|---|
| End point title | SE Macrovascular function Peripheral arterial blood pressure (systolic and diastolic) |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[39] | 27 ^[40] | 30 | 28 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic | 135.59 (± 12.758) | 135.32 (± 13.196) | 136.15 (± 15.330) | 136.95 (± 15.408) |
| Diastolic | 86.84 (± 7.986) | 86.38 (± 8.070) | 85.07 (± 8.443) | 85.46 (± 8.609) |

Notes:

[39] - Data of one patient missing.

[40] - Data of one patient missing.

Statistical analyses

| | |
|----------------------------|-------------------------------|
| Statistical analysis title | Change in systolic PABP (FAS) |
|----------------------------|-------------------------------|

Statistical analysis description:

Change in systolic PABP from baseline until visit 4 (week 8) for FAS.

| | |
|-------------------|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
|-------------------|---|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[41] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.7 |
| upper limit | 3.32 |

Notes:

[41] - N=29

| | |
|--|---|
| Statistical analysis title | Change in systolic PABP (PPS) |
| Statistical analysis description: Change in systolic PABP from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[42] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.43 |
| upper limit | 4.13 |

Notes:

[42] - N=27

| | |
|---|---|
| Statistical analysis title | Change in diastolic PABP (FAS) |
| Statistical analysis description: Change in diastolic PABP from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[43] |
| Parameter estimate | Change from baseline |
| Point estimate | -2.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.47 |
| upper limit | 0.28 |

Notes:

[43] - N=29

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Change in diastolic PABP (PPS) |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Change in diastolic PABP from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[44] |
| Parameter estimate | Change from baseline |
| Point estimate | -1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.43 |
| upper limit | 0.94 |

Notes:

[44] - N=27

Secondary: SE | Macrovascular function | Cardiac ejection time

| | |
|-----------------|---|
| End point title | SE Macrovascular function Cardiac ejection time |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[45] | 27 ^[46] | 30 | 28 |
| Units: Cardiac ejection time (sec.) | | | | |
| arithmetic mean (standard deviation) | 302.82 (± 29.379) | 305.31 (± 28.402) | 306.41 (± 26.444) | 304.98 (± 26.266) |

Notes:

[45] - Data of one patient missing.

[46] - Data of one patient missing.

Statistical analyses

| | |
|----------------------------|---------------------------------------|
| Statistical analysis title | Change in cardiac ejection time (FAS) |
|----------------------------|---------------------------------------|

Statistical analysis description:

Change in cardiac ejection time from baseline until visit 4 (week 8) for FAS.

| | |
|-------------------|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
|-------------------|---|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[47] |
| Parameter estimate | Change from baseline |
| Point estimate | 3.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.03 |
| upper limit | 12.58 |

Notes:

[47] - N=29

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Change in cardiac ejection time (PPS) |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Change in cardiac ejection time from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[48] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.07 |
| upper limit | 5.69 |

Notes:

[48] - N=27

Secondary: SE | Endurance performance in bicycle spiroergometry | Oxygen uptake at maximum burden (VO2 peak [ml/min])

| | |
|-----------------|--|
| End point title | SE Endurance performance in bicycle spiroergometry Oxygen uptake at maximum burden (VO2 peak [ml/min]) |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[49] | 27 ^[50] | 25 ^[51] | 25 ^[52] |
| Units: ml/min. | | | | |
| arithmetic mean (standard deviation) | 1988.8 (± 581.06) | 2048.6 (± 556.54) | 2128.5 (± 476.52) | 2128.5 (± 476.52) |

Notes:

[49] - Data of one patient missing.

[50] - Data of one patient missing

[51] - Data of five patients missing.

[52] - Data of three patients missing

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in oxygen uptake (FAS) |
| Statistical analysis description: Change in oxygen uptake at maximum burden from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[53] |
| Parameter estimate | Change from baseline |
| Point estimate | 18.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -107.6 |
| upper limit | 144.6 |

Notes:

[53] - N=24

| | |
|---|---|
| Statistical analysis title | Change in oxygen uptake (PPS) |
| Statistical analysis description: Change in oxygen uptake at maximum burden from baseline until visit 4 (week 8) for PPS | |
| Comparison groups | Per Protocol Set (PPS) - Visit 4 v Per Protocol Set (PPS) - Visit 2 |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[54] |
| Parameter estimate | Change from baseline |
| Point estimate | 18.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -107.6 |
| upper limit | 144.6 |

Notes:

[54] - N=24

Secondary: SE | Endurance performance in bicycle spiroergometry | Power at maximum burden [watts]

| | |
|------------------------|--|
| End point title | SE Endurance performance in bicycle spiroergometry Power at maximum burden [watts] |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[55] | 27 ^[56] | 25 ^[57] | 25 ^[58] |
| Units: watt | | | | |
| arithmetic mean (standard deviation) | 153.4 (± 54.07) | 158.9 (± 51.99) | 165.2 (± 52.77) | 165.2 (± 52.77) |

Notes:

[55] - Data of one patient missing.

[56] - Data of one patient missing

[57] - Data of five patients missing.

[58] - Data of three patients missing

Statistical analyses

| Statistical analysis title | Change in power at maximum burden (FAS) |
|--|---|
| Statistical analysis description: Change in power at maximum burden at maximum burden from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[59] |
| Parameter estimate | Change from baseline |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16 |
| upper limit | 22.7 |

Notes:

[59] - N=24

| Statistical analysis title | Change in power at maximum burden (PPS) |
|---|---|
| Statistical analysis description: Change in power at maximum burden at maximum burden from baseline until visit 4 (week 8) for PPS | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[60] |
| Parameter estimate | Change from baseline |
| Point estimate | 3.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16 |
| upper limit | 22.7 |

Notes:

[60] - N=24

Secondary: SE | Endurance performance in bicycle spiroergometry | Increase of the product of systolic arterial blood pressure and heart rate between rest and 50 watts load

| | |
|-----------------|--|
| End point title | SE Endurance performance in bicycle spiroergometry Increase of the product of systolic arterial blood pressure and heart rate between rest and 50 watts load |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[61] | 26 ^[62] | 24 ^[63] | 24 ^[64] |
| Units: Increase in rate pressure (mmHg/sec.) | | | | |
| arithmetic mean (standard deviation) | 3550.3 (± 2623.53) | 3234.6 (± 2248.69) | 2529.6 (± 1361.56) | 2529.6 (± 1361.6) |

Notes:

[61] - Data of two patients missing.

[62] - Data of two patients missing

[63] - Data of six patients missing.

[64] - Data of four patients missing

Statistical analyses

| | |
|----------------------------|-------------------------------|
| Statistical analysis title | Change in rate pressure (FAS) |
|----------------------------|-------------------------------|

Statistical analysis description:

Change in increase of the product of systolic arterial blood pressure and heart rate between rest and 50 watts load from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[65] |
| Parameter estimate | Change from baseline |
| Point estimate | -767.8 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1609.8 |
| upper limit | 74.2 |

Notes:

[65] - N=22

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Change in rate pressure (PPS) |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Change in increase of the product of systolic arterial blood pressure and heart rate between rest and 50 watts load from baseline until visit 4 (week 8) for PPS

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[66] |
| Parameter estimate | Change from baseline |
| Point estimate | -767.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1609.8 |
| upper limit | 74.2 |

Notes:

[66] - N=22

Secondary: SE | Endurance performance in bicycle spiroergometry | Increase in blood lactate between rest and 50 watts load

| | |
|-----------------|---|
| End point title | SE Endurance performance in bicycle spiroergometry Increase in blood lactate between rest and 50 watts load |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|---|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 28 | 26 ^[67] | 26 ^[68] |
| Units: Increase of blood lactate (mmol/L) | | | | |
| arithmetic mean (standard deviation) | 0.141 (± 0.2434) | 0.127 (± 0.2453) | 0.053 (± 0.1757) | 0.053 (± 0.1757) |

Notes:

[67] - Data of four patients missing.

[68] - Data of two patients missing

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in increase of blood lactate (FAS) |
| Statistical analysis description: Change in increase of in blood lactate between rest and 50 watts load from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[69] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.079 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.168 |
| upper limit | 0.011 |

Notes:

[69] - N=26

| | |
|--|---|
| Statistical analysis title | Change in increase of blood lactate (PPS) |
| Statistical analysis description: Change in increase of blood lactate between rest and 50 watts load from baseline until visit 4 (week 8) for PPS | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[70] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.079 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.168 |
| upper limit | 0.011 |

Notes:

[70] - N=26

Secondary: SE | Clinical Symptomatology | Sum Score in MLHFQ

| | |
|---|---|
| End point title | SE Clinical Symptomatology Sum Score in MLHFQ |
| End point description: The MLHFQ is scored according to MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE Instructions for Data Collection and Scoring. | |
| End point type | Secondary |
| End point timeframe: Measured at visit 2 (baseline), visit 3 (day 26-30) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 3 | Per Protocol Set (PPS) - Visit 3 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 ^[71] | 25 ^[72] | 30 | 28 |
| Units: MLHFQ Sum Score | | | | |
| arithmetic mean (standard deviation) | 18.6 (± 16.33) | 15.4 (± 12.09) | 16.6 (± 17.18) | 13.8 (± 13.97) |

Notes:

[71] - Data of three patients missing.

[72] - Data of three patients missing.

| End point values | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 | | |
|--------------------------------------|-----------------------------------|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 ^[73] | 27 ^[74] | | |
| Units: MLHFQ Sum Score | | | | |
| arithmetic mean (standard deviation) | 17.0 (± 18.96) | 13.8 (± 15.12) | | |

Notes:

[73] - Data of one patient missing.

[74] - Data of one patient missing.

Statistical analyses

| Statistical analysis title | Change from BL to Visit 3 in MLHFQ (FAS) |
|--|---|
| Statistical analysis description: Change in MLHFQ Sum Score from baseline until visit 3 (week 4) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 3 |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[75] |
| Parameter estimate | Change from baseline |
| Point estimate | -3.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | -0.4 |

Notes:

[75] - N=27

| Statistical analysis title | Change from BL to Visit 4 in MLHFQ (FAS) |
|--|---|
| Statistical analysis description: Change in MLHFQ Sum Score from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[76] |
| Parameter estimate | Change from baseline |
| Point estimate | -2.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7 |
| upper limit | 1.8 |

Notes:

[76] - N=26

| | |
|--|---|
| Statistical analysis title | Change from BL to Visit 3 in MLHFQ (PPS) |
| Statistical analysis description: Change in MLHFQ Sum Score from baseline until visit 3 (week 4) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 3 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[77] |
| Parameter estimate | Change from baseline |
| Point estimate | -3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.2 |
| upper limit | -0.2 |

Notes:

[77] - N=25

| | |
|--|---|
| Statistical analysis title | Change from BL to Visit 4 in MLHFQ (PPS) |
| Statistical analysis description: Change in MLHFQ Sum Score from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[78] |
| Parameter estimate | Change from baseline |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.8 |
| upper limit | 1.7 |

Notes:

[78] - N=24

Secondary: SE | Erectile function | Total Score in IIEF

| | |
|---|--|
| End point title | SE Erectile function Total Score in IIEF |
| End point description: | |
| The IIEF is scored according to Rosen R: SCALING AND SCORING OF THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF), Final version October, 2004 revised Sept 2007 and July 2008. | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline), visit 3 (day 26-30) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 3 | Per Protocol Set (PPS) - Visit 3 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 28 | 26 ^[79] | 25 ^[80] |
| Units: IIEF Total Score | | | | |
| arithmetic mean (standard deviation) | 27.8 (± 13.89) | 29.2 (± 13.32) | 30.8 (± 15.67) | 31.8 (± 15.13) |

Notes:

[79] - Data of four patients missing.

[80] - Data of three patients missing.

| End point values | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 | | |
|--------------------------------------|-----------------------------------|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 ^[81] | 23 ^[82] | | |
| Units: IIEF Total Score | | | | |
| arithmetic mean (standard deviation) | 38.5 (± 18.52) | 40.9 (± 17.20) | | |

Notes:

[81] - Data of five patients missing.

[82] - Data of five patients missing.

Statistical analyses

| Statistical analysis title | Change from BL to V3 in IIEF Total (FAS) |
|--|---|
| Statistical analysis description: | |
| Change in IIEF total score from baseline until visit 3 (week 4) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 3 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[83] |
| Parameter estimate | Change from baseline |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 7.3 |

Notes:

[83] - N=26

| | |
|--|--|
| | Change from BL to V4 in IIEF Total (FAS) |
|--|--|

| | |
|--|---|
| Statistical analysis title | |
| Statistical analysis description: | |
| Change in IIEF total score from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[84] |
| Parameter estimate | Change from baseline |
| Point estimate | 8.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.1 |
| upper limit | 13.7 |
| Notes: | |
| [84] - N=25 | |

| | |
|--|---|
| Statistical analysis title | Change from BL to V3 in IIEF Total (PPS) |
| Statistical analysis description: | |
| Change in IIEF total score from baseline until visit 3 (week 4) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 3 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[85] |
| Parameter estimate | Change from baseline |
| Point estimate | 3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 7.6 |
| Notes: | |
| [85] - N=25 | |

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in IIEF Total (PPS) |
| Statistical analysis description: | |
| Change in IIEF total score from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 4 v Per Protocol Set (PPS) - Visit 2 |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[86] |
| Parameter estimate | Change from baseline |
| Point estimate | 9.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.3 |
| upper limit | 14.6 |

Notes:

[86] - N=23

Secondary: SE | Erectile function | Value for erectile function in IIEF

| | |
|-----------------|--|
| End point title | SE Erectile function Value for erectile function in IIEF |
|-----------------|--|

End point description:

The IIEF is scored according to Rosen R: SCALING AND SCORING OF THE INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF), Final version October, 2004 revised Sept 2007 and July 2008.

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

End point timeframe:

Measured at visit 2 (baseline), visit 3 (day 26-30) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 3 | Per Protocol Set (PPS) - Visit 3 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 28 | 28 ^[87] | 26 ^[88] |
| Units: IIEF Domain Score | | | | |
| arithmetic mean (standard deviation) | 9.3 (± 6.46) | 9.8 (± 6.40) | 10.4 (± 6.37) | 10.9 (± 6.35) |

Notes:

[87] - Data of two patients missing.

[88] - Data of two patients missing.

| End point values | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 | | |
|--------------------------------------|-----------------------------------|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 28 ^[89] | 26 ^[90] | | |
| Units: IIEF Domain Score | | | | |
| arithmetic mean (standard deviation) | 13.9 (± 8.39) | 14.7 (± 8.14) | | |

Notes:

[89] - Data of two patients missing.

[90] - Data of two patients missing.

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change from BL to V3 in IIEF Erectile Func (FAS) |
|----------------------------|--|

Statistical analysis description:

Change in IIEF subscore erectile function from baseline until visit 3 (week 4) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 3 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[91] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 3.3 |

Notes:

[91] - N=28

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in IIEF Erectile Func (FAS) |
| Statistical analysis description: Change in IIEF subscore erectile function from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[92] |
| Parameter estimate | Change from baseline |
| Point estimate | 4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.4 |
| upper limit | 6.6 |

Notes:

[92] - N=28

| | |
|--|---|
| Statistical analysis title | Change from BL to V3 in IIEF Erectile Func (PPS) |
| Statistical analysis description: Change in IIEF subscore erectile function from baseline until visit 3 (week 4) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 3 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[93] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 3.4 |

Notes:

[93] - N=26

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in IIEF Erectile Func (PPS) |
| Statistical analysis description: Change in IIEF subscore erectile function from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[94] |
| Parameter estimate | Change from baseline |
| Point estimate | 4.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.5 |
| upper limit | 7.1 |

Notes:

[94] - N=26

Secondary: SE | Erectile function | Question 1 in the SEP – proportion of positive responses to any responses for question 1

| | |
|-----------------|---|
| End point title | SE Erectile function Question 1 in the SEP – proportion of positive responses to any responses for question 1 |
|-----------------|---|

End point description:

(1) Sexual Encounter Profile (SEP) Proportion of positive responses to any responses for question 1 at a particular visit; (2) SEP Change from [visit 2 to visit 3 (excluded)] to [visit 3 (included) to visit 4]

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

End point timeframe:

Measured at visit 2 (baseline), visit 3 (day 26-30) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] | Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] | Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] |
|--|--|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 16 ^[95] | 16 ^[96] | 16 ^[97] | 16 ^[98] |
| Units: Proportion of positive responses (Q1) | | | | |
| arithmetic mean (standard deviation) | 0.588 (± 0.4055) | 0.588 (± 0.4055) | 0.802 (± 0.2995) | 0.802 (± 0.2995) |

Notes:

[95] - Data of 14 patients missing.

[96] - Data of twelve patients missing.

[97] - Data of 14 patients missing.

[98] - Data of twelve patients missing.

Statistical analyses

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | SEP1 - Change between periods FAS |
|----------------------------|-------------------------------------|

Statistical analysis description:

Change in proportion of positive responses to SEP Q1 from [V2-V3 (excl.)] to [V3 (incl.)-V4] for FAS

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] v Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[99] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.139 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.107 |
| upper limit | 0.384 |

Notes:

[99] - N=13

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | SEP1 - Change between periods PPS |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Change in proportion of positive responses to SEP Q1 from [V2-V3 (excl.)] to [V3 (incl.)-V4] for PPS

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] v Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[100] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.139 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.107 |
| upper limit | 0.384 |

Notes:

[100] - N=13

Secondary: SE | Erectile function | Question 2 in the SEP – proportion of positive responses for question 2 to any responses for question 1

| | |
|-----------------|--|
| End point title | SE Erectile function Question 2 in the SEP – proportion of positive responses for question 2 to any responses for question 1 |
|-----------------|--|

End point description:

(1) Sexual Encounter Profile (SEP) Proportion of positive responses to any responses for question 2 at a particular visit; (2) SEP Change from [visit 2 to visit 3 (excluded)] to [visit 3 (included) to visit 4]

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

End point timeframe:

Measured at visit 2 (baseline), visit 3 (day 26-30) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] | Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] | Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] |
|--|--|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 16 ^[101] | 16 ^[102] | 16 ^[103] | 16 ^[104] |
| Units: Proportion of positive responses (Q2) | | | | |
| arithmetic mean (standard deviation) | 0.440 (± 0.3545) | 0.440 (± 0.3545) | 0.463 (± 0.4155) | 0.463 (± 0.4155) |

Notes:

[101] - Data of 14 patients missing.

[102] - Data of twelve patients missing.

[103] - Data of 14 patients missing.

[104] - Data of twelve patients missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | SEP2 - Change between periods FAS |
| Statistical analysis description: Change in proportion of positive responses to SEP Q2 from [V2-V3 (excl.)] to [V3 (incl.)-V4] for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - [Visit 2 to Visit 3 (excl.)] v Full Analysis Set (FAS) - [Visit 3 (incl.) to Visit 4] |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[105] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.313 |
| upper limit | 0.293 |

Notes:

[105] - N=13

| | |
|--|---|
| Statistical analysis title | SEP2 - Change between periods PPS |
| Statistical analysis description: Change in proportion of positive responses to SEP Q2 from [V2-V3 (excl.)] to [V3 (incl.)-V4] for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - [Visit 2 to Visit 3 (excl.)] v Per Protocol Set (PPS) - [Visit 3 (incl.) to Visit 4] |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[106] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.313 |
| upper limit | 0.293 |

Notes:

[106] - N=13

Secondary: SE | Erectile function | Event time per session

| | |
|--|---|
| End point title | SE Erectile function Event time per session |
| End point description: As only parameters that were independent from the duration of measurement were analyzed, 'event time per session' instead of 'number of nocturnal erections' was analyzed. | |
| End point type | Secondary |

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|-----------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4 | 4 | | |
| Units: Event time per session [%] | | | | |
| Patient 020 | 39 | 9 | | |
| Patient 045 | 21 | 21 | | |
| Patient 050 | 57 | 18 | | |
| Patient 057 | 42 | 37 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | Average event rigidity penis base

| | |
|-----------------|--|
| End point title | SE Erectile function Average event rigidity penis base |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|-----------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4 | 4 | | |
| Units: RIGidity base [%] | | | | |
| Patient 020 | 39 | 36 | | |
| Patient 045 | 27 | 29 | | |
| Patient 050 | 27 | 38 | | |
| Patient 057 | 24 | 39 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | Average event rigidity penis tip

| | |
|---|---|
| End point title | SE Erectile function Average event rigidity penis tip |
| End point description: Analysis was waived due to insufficient data (measurements from the penis tip are missing in at least one of the visits). | |
| End point type | Secondary |
| End point timeframe: Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|-----------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[107] | 0 ^[108] | | |
| Units: Rigidity tip [%] | | | | |
| Patient 020 | | | | |
| Patient 045 | | | | |
| Patient 050 | | | | |
| Patient 057 | | | | |

Notes:

[107] - For all patients measurements from the penis tip are missing in at least one of the visits.

[108] - For all patients measurements from the penis tip are missing in at least one of the visits.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | Average tumescence increase penis base

| | |
|---|---|
| End point title | SE Erectile function Average tumescence increase penis base |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|--------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4 | 4 | | |
| Units: Tumescence increase [%] | | | | |
| Patient 020 | 30 | 45 | | |
| Patient 045 | 25 | 25 | | |
| Patient 050 | 26 | 28 | | |
| Patient 057 | 28 | 29 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | Average tumescence increase penis tip

| | |
|-----------------|--|
| End point title | SE Erectile function Average tumescence increase penis tip |
|-----------------|--|

End point description:

Analysis was waived due to insufficient data (measurements from the penis tip are missing in at least one of the visits).

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|--------------------------------|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[109] | 0 ^[110] | | |
| Units: Tumescence increase [%] | | | | |
| Patient 020 | | | | |
| Patient 045 | | | | |
| Patient 050 | | | | |
| Patient 057 | | | | |

Notes:

[109] - For all patients measurements from the penis tip are missing in at least one of the visits.

[110] - For all patients measurements from the penis tip are missing in at least one of the visits.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | AUC for rigidity penis base

| | |
|-----------------|--|
| End point title | SE Erectile function AUC for rigidity penis base |
|-----------------|--|

End point description:

Analysis was waived due to insufficient data.

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|--------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[111] | 0 ^[112] | | |
| Units: AUC | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[111] - Analysis was waived due to insufficient data.

[112] - Analysis was waived due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | AUC for rigidity penis tip

| | |
|---|---|
| End point title | SE Erectile function AUC for rigidity penis tip |
| End point description: | |
| Analysis was waived due to insufficient data. | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|--------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[113] | 0 ^[114] | | |
| Units: AUC | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[113] - Analysis was waived due to insufficient data.

[114] - Analysis was waived due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | AUC for tumescence penis base

| | |
|---|--|
| End point title | SE Erectile function AUC for tumescence penis base |
| End point description: | |
| Analysis was waived due to insufficient data. | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|--------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[115] | 0 ^[116] | | |
| Units: AUC | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[115] - Analysis was waived due to insufficient data.

[116] - Analysis was waived due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Erectile function | AUC for tumescence penis tip

| | |
|------------------------|---|
| End point title | SE Erectile function AUC for tumescence penis tip |
| End point description: | Analysis was waived due to insufficient data. |
| End point type | Secondary |
| End point timeframe: | Measured at visit 2 (baseline) and visit 4 (day 53-59). |

| End point values | RigiScan Analysis Set - Visit 2 | RigiScan Analysis Set - Visit 4 | | |
|--------------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[117] | 0 ^[118] | | |
| Units: AUC | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[117] - Analysis was waived due to insufficient data.

[118] - Analysis was waived due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Laboratory Parameters | NT-proBNP at rest

| | |
|------------------------|---|
| End point title | SE Laboratory Parameters NT-proBNP at rest |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | Measured at visit 2 (baseline) and visit 4 (day 53-59). |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 ^[119] | 23 ^[120] | 28 ^[121] | 27 ^[122] |
| Units: ng/l | | | | |
| arithmetic mean (standard deviation) | 158.6 (± 256.26) | 127.4 (± 197.58) | 149.6 (± 187.56) | 133.3 (± 169.69) |

Notes:

[119] - Data of five patients missing.

[120] - Data of five patients missing.

[121] - Data of two patients missing.

[122] - Data of one patient missing.

Statistical analyses

| Statistical analysis title | Change from BL to V4 in NT-ProBNP at rest (FAS) |
|--|---|
| Statistical analysis description: Change in S-NT-ProBNP at rest from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[123] |
| Parameter estimate | Change from baseline |
| Point estimate | -23.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -68.4 |
| upper limit | 21.5 |

Notes:

[123] - N=24

| Statistical analysis title | Change from BL to V4 in NT-ProBNP at rest (PPS) |
|--|---|
| Statistical analysis description: Change in S-NT-ProBNP at rest from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[124] |
| Parameter estimate | Change from baseline |
| Point estimate | -7.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.7 |
| upper limit | 24.2 |

Notes:

[124] - N=23

Secondary: SE | Laboratory Parameters | NT-proBNP increase after spiroergometry

| | |
|---|--|
| End point title | SE Laboratory Parameters NT-proBNP increase after spiroergometry |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 ^[125] | 21 ^[126] | 25 ^[127] | 25 ^[128] |
| Units: ng/l | | | | |
| arithmetic mean (standard deviation) | 23.7 (± 40.16) | 24.6 (± 40.95) | 23.5 (± 32.35) | 23.5 (± 32.35) |

Notes:

[125] - Data of eight patients missing.

[126] - Data of seven patients missing.

[127] - Data of five patients missing.

[128] - Data of three patients missing.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in increase from BL to V4 NT-ProBNP (FAS) |
| Statistical analysis description: | |
| Change in increase of S-NT-ProBNP from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[129] |
| Parameter estimate | Change from baseline |
| Point estimate | -3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.8 |
| upper limit | 3.5 |

Notes:

[129] - N=20

| | |
|---|---|
| Statistical analysis title | Change in increase from BL to V4 NT-ProBNP (PPS) |
| Statistical analysis description: | |
| Change in increase of S-NT-ProBNP from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |

| | |
|---|------------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[130] |
| Parameter estimate | Change from baseline |
| Point estimate | -3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.8 |
| upper limit | 3.5 |

Notes:

[130] - N=20

Secondary: SE | Laboratory Parameters | ADMA at rest

| | |
|---|---|
| End point title | SE Laboratory Parameters ADMA at rest |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[131] | 27 ^[132] | 28 ^[133] | 27 ^[134] |
| Units: umol/L | | | | |
| arithmetic mean (standard deviation) | 0.509 (± 0.0890) | 0.511 (± 0.0913) | 0.511 (± 0.0829) | 0.513 (± 0.0840) |

Notes:

[131] - Data of one patient missing.

[132] - Data of one patient missing.

[133] - Data of two patients missing.

[134] - Data of one patient missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in ADMA at rest (FAS) |
| Statistical analysis description: | |
| Change in ADMA at rest from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[135] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.007 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.025 |
| upper limit | 0.04 |

Notes:

[135] - N=27

| | |
|-----------------------------------|--|
| Statistical analysis title | Change from BL to V4 in ADMA at rest (PPS) |
|-----------------------------------|--|

Statistical analysis description:

Change in ADMA at rest from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[136] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.01 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.024 |
| upper limit | 0.043 |

Notes:

[136] - N=26

Secondary: SE | Laboratory Parameters | BH4/BH2 at rest

| | |
|-----------------|--|
| End point title | SE Laboratory Parameters BH4/BH2 at rest |
|-----------------|--|

End point description:

Not analysed as none of the two analytes BH2 and BH4 could be detected in the blood samples.

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[137] | 0 ^[138] | 0 ^[139] | 0 ^[140] |
| Units: Ratio BH4/BH2 | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[137] - Not analysed as none of the two analytes BH2 and BH4 could be detected in the blood samples.

[138] - Not analysed as none of the two analytes BH2 and BH4 could be detected in the blood samples.

[139] - Not analysed as none of the two analytes BH2 and BH4 could be detected in the blood samples.

[140] - Not analysed as none of the two analytes BH2 and BH4 could be detected in the blood samples.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Laboratory Parameters | oxLDL/LDL at rest

End point title SE | Laboratory Parameters | oxLDL/LDL at rest

End point description:

End point type Secondary

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 ^[141] | 21 ^[142] | 26 ^[143] | 25 ^[144] |
| Units: oxLDL/LDL ratio | | | | |
| arithmetic mean (standard deviation) | 18.43 (± 7.391) | 18.51 (± 7.565) | 19.61 (± 10.436) | 19.75 (± 10.626) |

Notes:

[141] - Data of eight patients missing.

[142] - Data of seven patients missing.

[143] - Data of four patients missing.

[144] - Data of three patients missing.

Statistical analyses

Statistical analysis title Change from BL to V4 in oxLDL/LDL at rest (FAS)

Statistical analysis description:

Change in oxLDL/LDL ratio from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[145] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.13 |
| upper limit | 3.7 |

Notes:

[145] - N=20

Statistical analysis title Change from BL to V4 oxLDL/LDL at rest (PPS)

Statistical analysis description:

Change in oxLDL/LDL ratio from baseline until visit 4 (week 8) for PPS.

| | |
|-------------------|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
|-------------------|---|

| | |
|---|------------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[146] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.15 |
| upper limit | 3.94 |

Notes:

[146] - N=19

Secondary: SE | Laboratory Parameters | MDA at rest

| | |
|---|--|
| End point title | SE Laboratory Parameters MDA at rest |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[147] | 27 ^[148] | 28 ^[149] | 27 ^[150] |
| Units: umol/L | | | | |
| arithmetic mean (standard deviation) | 0.580 (± 0.2251) | 0.587 (± 0.2307) | 0.543 (± 0.3864) | 0.553 (± 0.3901) |

Notes:

[147] - Data of one patient missing.

[148] - Data of one patient missing.

[149] - Data of two patients missing.

[150] - Data of one patient missing.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL to V4 in MDA at rest (FAS) |
| Statistical analysis description: | |
| Change in MDA at rest from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[151] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.084 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.237 |
| upper limit | 0.068 |

Notes:

[151] - N=27

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from BL to V4 in MDA at rest (PPS) |
|-----------------------------------|---|

Statistical analysis description:

Change in MDA at rest from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[152] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.076 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.233 |
| upper limit | 0.082 |

Notes:

[152] - N=26

Secondary: SE | Laboratory Parameters | MDA increase after spiroergometry

| | |
|-----------------|--|
| End point title | SE Laboratory Parameters MDA increase after spiroergometry |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 ^[153] | 24 ^[154] | 23 ^[155] | 23 ^[156] |
| Units: umol/L | | | | |
| arithmetic mean (standard deviation) | 0.006 (± 0.3402) | -0.032 (± 0.2884) | -0.060 (± 0.3699) | -0.060 (± 0.3699) |

Notes:

[153] - Data of five patients missing.

[154] - Data of four patients missing.

[155] - Data of seven patients missing.

[156] - Data of five patients missing.

Statistical analyses

| Statistical analysis title | Change in increase from BL to V4 MDA (FAS) |
|---|---|
| Statistical analysis description: Change in increase of MDA after spiroergometry from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[157] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.162 |
| upper limit | 0.17 |

Notes:

[157] - N=22

| Statistical analysis title | Change in increase from BL to V4 MDA (PPS) |
|---|---|
| Statistical analysis description: Change in increase of MDA after spiroergometry from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[158] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.162 |
| upper limit | 0.17 |

Notes:

[158] - N=22

Secondary: SE | Laboratory Parameters | Nitrate/Nitrite at rest

| | |
|---|--|
| End point title | SE Laboratory Parameters Nitrate/Nitrite at rest |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[159] | 27 ^[160] | 28 ^[161] | 27 ^[162] |
| Units: Nitrate/Nitrite ratio | | | | |
| arithmetic mean (standard deviation) | 43.54 (± 25.732) | 43.54 (± 26.538) | 37.36 (± 16.612) | 37.89 (± 16.689) |

Notes:

[159] - Data of one patient missing.

[160] - Data of one patient missing.

[161] - Data of two patients missing.

[162] - Data of one patient missing.

Statistical analyses

| Statistical analysis title | Change (BL to V4) in Nitrate/Nitrite at rest (FAS) |
|--|---|
| Statistical analysis description: Change in Nitrate/Nitrite ratio at rest from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[163] |
| Parameter estimate | Change from baseline |
| Point estimate | -7.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.07 |
| upper limit | 3.88 |

Notes:

[163] - N=27

| Statistical analysis title | Change (BL to V4) in Nitrate/Nitrite at rest (PPS) |
|--|---|
| Statistical analysis description: Change in Nitrate/Nitrite ratio at rest from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[164] |
| Parameter estimate | Change from baseline |
| Point estimate | -7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.42 |
| upper limit | 4.43 |

Notes:

[164] - N=26

Secondary: SE | Laboratory Parameters | Nitrate/Nitrite increase after spiroergometry

| | |
|-----------------|--|
| End point title | SE Laboratory Parameters Nitrate/Nitrite increase after spiroergometry |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 ^[165] | 24 ^[166] | 23 ^[167] | 23 ^[168] |
| Units: Nitrate/Nitrite ratio | | | | |
| arithmetic mean (standard deviation) | 2.83 (± 5.434) | 2.54 (± 5.362) | 4.55 (± 8.550) | 4.55 (± 8.550) |

Notes:

[165] - Data of five patients missing.

[166] - Data of four patients missing.

[167] - Data of seven patients missing.

[168] - Data of five patients missing.

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Change in increase from BL to V4 NO3-/NO2- (FAS) |
|----------------------------|--|

Statistical analysis description:

Change of increase in Nitrate/Nitrite ratio from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[169] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.71 |
| upper limit | 5.65 |

Notes:

[169] - N=22

| | |
|----------------------------|--|
| Statistical analysis title | Change in increase from BL to V4 NO3-/NO2- (PPS) |
|----------------------------|--|

Statistical analysis description:

Change of increase in Nitrate/Nitrite ratio from baseline until visit 4 (week 8) for PPS.

| | |
|-------------------|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
|-------------------|---|

| | |
|---|------------------------|
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[170] |
| Parameter estimate | Change from baseline |
| Point estimate | 1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.71 |
| upper limit | 5.65 |

Notes:

[170] - N=22

Secondary: SE | Laboratory Parameters | Plasma-F2-Isoprostane at rest

| | |
|---|--|
| End point title | SE Laboratory Parameters Plasma-F2-Isoprostane at rest |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 ^[171] | 27 ^[172] | 28 ^[173] | 27 ^[174] |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 0.607 (± 0.3825) | 0.607 (± 0.3968) | 0.776 (± 0.5027) | 0.785 (± 0.5099) |

Notes:

[171] - Data of one patient missing.

[172] - Data of one patient missing.

[173] - Data of two patients missing.

[174] - Data of one patient missing.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change (BL to V4) in F2-Isoprostane at rest (FAS) |
| Statistical analysis description: | |
| Change in plasma F2-Isoprostane at rest from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[175] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.147 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.057 |
| upper limit | 0.351 |

Notes:

[175] - N=27

| | |
|-----------------------------------|---|
| Statistical analysis title | Change (BL to V4) in F2-Isoprostane at rest (PPS) |
|-----------------------------------|---|

Statistical analysis description:

Change in plasma F2-Isoprostane at rest from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[176] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.155 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.057 |
| upper limit | 0.366 |

Notes:

[176] - N=26

Secondary: SE | Laboratory Parameters | Plasma-F2-Isoprostane increase after spiroergometry

| | |
|-----------------|--|
| End point title | SE Laboratory Parameters Plasma-F2-Isoprostane increase after spiroergometry |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 ^[177] | 24 ^[178] | 23 ^[179] | 23 ^[180] |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 0.122 (± 0.6947) | 0.125 (± 0.7095) | 0.162 (± 0.7229) | 0.162 (± 0.7229) |

Notes:

[177] - Data of five patients missing.

[178] - Data of four patients missing.

[179] - Data of seven patients missing.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change in increase from BL to V4 F2-Isopro (FAS) |
| Statistical analysis description: Change in increase of plasma F2 Isoprostane after spiroergometry from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 4 v Full Analysis Set (FAS) - Visit 2 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[181] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 0.45 |

Notes:

[181] - N=22

| | |
|---|---|
| Statistical analysis title | Change in increase from BL to V4 F2-Isopro (PPS) |
| Statistical analysis description: Change in increase of plasma F2 Isoprostane after spiroergometry from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 4 v Per Protocol Set (PPS) - Visit 2 |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[182] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 0.45 |

Notes:

[182] - N=22

Secondary: SE | Laboratory Parameters | hs-CRP at rest

| | |
|------------------------|---|
| End point title | SE Laboratory Parameters hs-CRP at rest |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 ^[183] | 23 ^[184] | 28 ^[185] | 27 ^[186] |
| Units: mg/L | | | | |
| arithmetic mean (standard deviation) | 2.56 (± 3.214) | 2.49 (± 3.335) | 2.30 (± 3.503) | 2.30 (± 3.570) |

Notes:

[183] - Data of five patients missing.

[184] - Data of five patients missing.

[185] - Data of two patients missing.

[186] - Data of one patient missing.

Statistical analyses

| Statistical analysis title | Change from BL to V4 in hs-CRP at rest (FAS) |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Change in S-CRP from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[187] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.72 |
| upper limit | 0.89 |

Notes:

[187] - N=24

| Statistical analysis title | Change from BL to V4 in hs-CRP at rest (PPS) |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Change in S-CRP from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[188] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.11 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 0.95 |

Notes:

[188] - N=23

Secondary: SE | Laboratory Parameters | hs-CRP increase after spiroergometry

| | |
|-----------------|---|
| End point title | SE Laboratory Parameters hs-CRP increase after spiroergometry |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 ^[189] | 21 ^[190] | 25 ^[191] | 25 ^[192] |
| Units: mg/L | | | | |
| arithmetic mean (standard deviation) | 0.35 (± 0.705) | 0.36 (± 0.721) | 0.36 (± 0.819) | 0.36 (± 0.819) |

Notes:

[189] - Data of eight patients missing.

[190] - Data of seven patients missing.

[191] - Data of five patients missing.

[192] - Data of three patients missing.

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Change in increase from BL to V4 hs-CRP (FAS) |
|----------------------------|---|

Statistical analysis description:

Change in increase of S-CRP after spiroergometry from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[193] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.45 |

Notes:

[193] - N=20

| | |
|---|---|
| Statistical analysis title | Change in increase from BL to V4 hs-CRP (PPS) |
| Statistical analysis description: Change in increase of S-CRP after spiroergometry from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[194] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.45 |

Notes:

[194] - N=20

Secondary: SE | Laboratory Parameters | IL-6 at rest

| | |
|---|---|
| End point title | SE Laboratory Parameters IL-6 at rest |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 ^[195] | 22 ^[196] | 23 ^[197] | 22 ^[198] |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | 4.2 (± 3.73) | 4.1 (± 3.80) | 4.0 (± 2.79) | 3.9 (± 2.84) |

Notes:

[195] - Data of seven patients missing.

[196] - Data of six patients missing.

[197] - Data of seven patients missing.

[198] - Data of six patients missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in IL-6 at rest (FAS) |
| Statistical analysis description: Change in S-Interleukin-6 at rest from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 4 v Full Analysis Set (FAS) - Visit 2 |

| | |
|---|------------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[199] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 1 |

Notes:

[199] - N=18

| | |
|-----------------------------------|--|
| Statistical analysis title | Change from BL to V4 in IL-6 at rest (PPS) |
|-----------------------------------|--|

Statistical analysis description:

Change in S-Interleukin-6 at rest from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[200] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | 1.2 |

Notes:

[200] - N=17

Secondary: SE | Laboratory Parameters | IL-6 increase after spiroergometry

| | |
|-----------------|---|
| End point title | SE Laboratory Parameters IL-6 increase after spiroergometry |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at visit 2 (baseline) and visit 4 (day 53-59).

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 ^[201] | 19 ^[202] | 20 ^[203] | 20 ^[204] |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | 0.9 (± 1.65) | 0.9 (± 1.65) | 0.7 (± 1.26) | 0.7 (± 1.26) |

Notes:

[201] - Data of eleven patients missing.

[202] - Data of nine patients missing.

[203] - Data of ten patients missing.

[204] - Data of eight patients missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change in increase from BL to V4 IL-6 (FAS) |
| Statistical analysis description: | |
| Change in increase of S-Interleukin-6 after spiroergometry from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[205] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.2 |

Notes:

[205] - N=14

| | |
|--|---|
| Statistical analysis title | Change in increase from BL to V4 IL-6 (PPS) |
| Statistical analysis description: | |
| Change in increase of S-Interleukin-6 after spiroergometry from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[206] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.2 |

Notes:

[206] - N=14

Secondary: SE | Laboratory Parameters | Plasma-Microparticles at rest

| | |
|---|--|
| End point title | SE Laboratory Parameters Plasma-Microparticles at rest |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Measured at visit 2 (baseline) and visit 4 (day 53-59). | |

| End point values | Full Analysis Set (FAS) - Visit 2 | Per Protocol Set (PPS) - Visit 2 | Full Analysis Set (FAS) - Visit 4 | Per Protocol Set (PPS) - Visit 4 |
|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 ^[207] | 26 ^[208] | 28 ^[209] | 27 ^[210] |
| Units: per uL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AV+ | 7.00 (± 2.397) | 7.04 (± 2.405) | 6.41 (± 1.773) | 6.49 (± 1.757) |
| CD105+ | 0.55 (± 0.243) | 0.51 (± 0.193) | 0.55 (± 0.203) | 0.53 (± 0.194) |
| GP1b+ | 3.61 (± 2.152) | 3.70 (± 2.212) | 3.79 (± 1.985) | 3.81 (± 2.019) |
| Glyco.A+ | 1.68 (± 0.985) | 1.60 (± 0.906) | 1.49 (± 0.898) | 1.49 (± 0.915) |
| CD11a+ | 3.35 (± 0.669) | 3.28 (± 0.641) | 3.40 (± 0.827) | 3.37 (± 0.819) |
| CD31+ | 0.06 (± 0.084) | 0.06 (± 0.085) | 0.06 (± 0.088) | 0.06 (± 0.089) |

Notes:

[207] - Data of two patients missing.

[208] - Data of two patients missing.

[209] - Data of two patients missing.

[210] - Data of one patient missing.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in AV+ (FAS) |
| Statistical analysis description: Change in AV+ from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[211] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.65 |
| upper limit | 0.55 |

Notes:

[211] - N=26

| | |
|--|---|
| Statistical analysis title | Change from BL to V4 in AV+ (PPS) |
| Statistical analysis description: Change in AV+ from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |

| | |
|---|------------------------|
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[212] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 0.71 |

Notes:

[212] - N=25

| | |
|---|---|
| Statistical analysis title | Change from BL to V4 in CD105+ (FAS) |
| Statistical analysis description: Change in CD105+ from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 4 v Full Analysis Set (FAS) - Visit 2 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[213] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.07 |

Notes:

[213] - N=26

| | |
|---|---|
| Statistical analysis title | Change from BL to V4 in CD105+ (PPS) |
| Statistical analysis description: Change in CD105+ from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[214] |
| Parameter estimate | Change from baseline |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.08 |

Notes:

[214] - N=25

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Change from BL to V4 in GP1b+ (FAS) |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Change in Gp1b+ from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[215] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.67 |
| upper limit | 1.06 |

Notes:

[215] - N=26

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Change from BL to V4 in GP1b+ (PPS) |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Change in Gp1b+ from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[216] |
| Parameter estimate | Change from baseline |
| Point estimate | 0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.72 |
| upper limit | 1.08 |

Notes:

[216] - N=25

| | |
|-----------------------------------|--|
| Statistical analysis title | Change from BL to V4 in Glyco.A+ (FAS) |
|-----------------------------------|--|

Statistical analysis description:

Change in Glyco.A+ from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[217] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 0.11 |

Notes:

[217] - N=26

| | |
|---|---|
| Statistical analysis title | Change from BL to V4 in Glyco.A+ (PPS) |
| Statistical analysis description: Change in Glyco.A+ from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[218] |
| Parameter estimate | Change from baseline |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | 0.14 |

Notes:

[218] - N=25

| | |
|---|---|
| Statistical analysis title | Change from BL to V4 in CD11a+ (FAS) |
| Statistical analysis description: Change in CD11a+ from baseline until visit 4 (week 8) for FAS. | |
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[219] |
| Parameter estimate | Change from baseline |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.19 |
| upper limit | 0.2 |

Notes:

[219] - N=26

| | |
|---|---|
| Statistical analysis title | Change from BL to V4 in CD11a+ (PPS) |
| Statistical analysis description: Change in CD11a+ from baseline until visit 4 (week 8) for PPS. | |
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[220] |
| Parameter estimate | Change from baseline |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.21 |

Notes:

[220] - N=25

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Change from BL to V4 in CD31+ (FAS) |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Change in CD31+ from baseline until visit 4 (week 8) for FAS.

| | |
|---|---|
| Comparison groups | Full Analysis Set (FAS) - Visit 2 v Full Analysis Set (FAS) - Visit 4 |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[221] |
| Parameter estimate | Change from baseline |
| Point estimate | 0 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.05 |

Notes:

[221] - N=26

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Change from BL to V4 in CD31+ (PPS) |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Change in CD31+ from baseline until visit 4 (week 8) for PPS.

| | |
|---|---|
| Comparison groups | Per Protocol Set (PPS) - Visit 2 v Per Protocol Set (PPS) - Visit 4 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[222] |
| Parameter estimate | Change from baseline |
| Point estimate | 0 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.05 |

Notes:

[222] - N=25

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first intake of study medication until last visit.

Adverse event reporting additional description:

Adverse events (AE) were defined as any undesirable event occurring between first intake of study medication and last visit. Events occurring between study enrollment and first intake of study medication are classified as health related events (HRE) and were not reported as AEs.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Safety Analysis Set |
|-----------------------|---------------------|

Reporting group description:

The Safety Analysis Set (SAF) consists of all patients who received at least one dose of study medication.

| Serious adverse events | Safety Analysis Set | | |
|--|---------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Safety Analysis Set | | |
|---|---------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 35 (31.43%) | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Sleep disorder | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) | 4 / 35 (11.43%) 4 1 / 35 (2.86%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 02 November 2015 | Non-substantial protocol amendment: change in the responsibility for suspected unexpected serious adverse reactions (SUSAR) reporting from CRO to sponsor; clarification of wording. |
| 24 May 2016 | Non-substantial protocol amendment: change in responsibilities of responsible Biometrician; adjustment of study duration, changed number of measurements for arterial stiffness, determination of erectile function by determining the average (instead of maximum) rigidity and tumescence at the base and tip of the penis. |
| 28 June 2017 | Substantial protocol amendment: modification of inclusion and exclusion criteria based on results of screening failure analyses: too low values in the IIEF and MLHF with regard to heart failure symptoms: inclusion criterion 3 omitted; inclusion criterion 7 adjusted: IIEF changed from 11-21 points to less than 22 points; quality assurance measures adapted to ICH E6 (R2); change of responsible biometrician. |
| 16 May 2018 | Substantial protocol amendment: change of approval status and application of the active substance by the competent authority: Active substance is now registered as a traditional herbal medicinal product for support of cardiovascular function: Change of title and inclusion criteria. |
| 25 June 2018 | Substantial amendment of Patient information and Informed Consent Form: adaption of Patient information and Informed Consent form due to data protection regulation that came in to force in May 2018. |
| 19 November 2019 | Substantial protocol amendment: change of the contracted CRO and resulting responsibilities in monitoring, data management, statistical analysis and medical writing; adaption of the absolute and relative discontinuation criteria of bicycle spiroergometry; adjustment of the recruitment and study duration; introduction of a questionnaire for improved interpretation of the measurement results; new information on side effects of the IMP (hypersensitivity reactions). |
| 02 March 2020 | Non-substantial amendment of Patient information and Informed Consent Form: adaption of the privacy statement in patient information due to Data Protection Amendment and Implementation 2019, adaption of IB (version Oct. 2019) |
| 02 April 2020 | Substantial amendment trial level: suspension of the clinical trial as an urgent safety measure to protect participants, as the population under study is one of the groups most at risk from COVID-19 due to several factors. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|---------------|--|---|
| 01 March 2020 | <p>The start of the study was in Q3/2016 with the inclusion of the first patient. The last visit of the last patient and thus the end of the study was expected by the end of 2020. Due to COVID-19 pandemic the study was interrupted in March-2020.</p> <p>Due to delayed patient recruitment, which was also adversely affected by the COVID 19 pandemic, the study was not restarted. The decision to terminate the entire study prematurely was made in compliance with the protocol by the sponsor in consultation with the investigator on 09-Sep-2020, representing the official end of study.</p> <p>Thus, the total duration of the study was 49 months.</p> | - |
|---------------|--|---|

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The significance of the study and results is limited by the reduced number of recruited and analyzed patients.

Notes: