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, persistance 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 standard deviation	 63.7 ± 8.37	 63.3 ± 7.72	 63.8 ± 8.43
Gender categorical Units: Subjects			
Female Male	0 30	0 28	0 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 standard deviation	 63.7 ± 8.37	 63.3 ± 7.72	 63.7 ± 8.37
Gender categorical Units: Subjects			
Female Male	0 30	0 28	0 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 standard deviation	 63.3 ± 7.72	 63.7 ± 8.37	 63.3 ± 7.72
Gender categorical Units: Subjects			
Female Male	0 28	0 30	0 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 standard deviation	 63.7 ± 8.37	 63.3 ± 7.72	 63.7 ± 8.37
Gender categorical Units: Subjects			
Female Male	0 30	0 28	0 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 standard deviation	 63.3 ± 7.72	 ±	 ±
Gender categorical Units: Subjects			
Female Male	0 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 (± 0.0607)	0.812 (± 0.0620)	0.814 (± 0.0620)	0.811 (± 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) undtil 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
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 (± 12.955)	36.90 (± 13.063)	39.70 (± 15.406)	39.96 (± 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 (± 10.448)	13.85 (± 10.625)	14.13 (± 11.242)	14.46 (± 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 (basleline), 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 (basleline) 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.

[180] - Data of five 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 occuring between first intake of study medication and last visit. Events occuring 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	1 / 35 (2.86%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	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 resonsible 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	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. 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. Thus, the total duration of the study was 49 months.	-

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: