Clinical trial results:
Early Treatment of Borderline Pulmonary Arterial Hypertension Associated with Systemic Sclerosis (SSc-APAH)

Summary

EudraCT number	2014-001882-28
Trial protocol	DE
Global end of trial date	21 December 2018

Results information

Result version number	v1 (current)
This version publication date	08 April 2020
First version publication date	08 April 2020
Summary attachment (see zip file)	Clinical Study Report (EDITA Ergebnisbericht PharmNetBund.pdf)

Trial information

Trial identification

Sponsor protocol code	2014-05ED

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02290613
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Thoraxklinik Heidelberg gGmbH
Sponsor organisation address	Röntgenstraße 1, Heidelberg, Germany,
Public contact	Director of the clinic, Thoraxklinik am Universitätsklinikum Heidelberg, +49 6221 396 2100,
Scientific contact	Director of the clinic, Thoraxklinik am Universitätsklinikum Heidelberg, +49 6221 396 2100,

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	21 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2017
Global end of trial reached?	Yes
Global end of trial date	21 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine whether mPAP of SSc patients with borderline - PAH (mPAP 21 24 mmHg, TPG >11 mmHg) can be reduced by 15% following treatment with ambrisentan 10 mg/die (initiated with 5 mg/die and elevated up to 10 mg/die) over 6 months compared to baseline and placebo.

Protection of trial subjects:

Annual development safety update reports were submitted to the Ethics committee.

Patient safety was ensured by regular safety assessments. In case of clinical Deterioration, measures and Treatment according to clinical routine were taken.

Serious adverse Events (SAEs) were described in Detail including severity, expectedness and relation to study drug.
In case the investigator who primarily reported the SAE classified the SAE as ‘suspected’ (i.e. either definitely or probable or possible related to the IMP or not assessable) and the SAE was unexpected, a drug safety officer as second Assessor was asked to classify the SAE. All SUSARs were subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority, i.e. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), and to all participating investigators. No SUSARs occurred during the study.

Trial findings stored on a computer were stored in accordance with local data protection law and were handled in strictest confidence. For protection of these data, organizational procedures were implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation were fulfilled in its entirety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2014
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: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	32
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients from the in- and outpatient clinic were recruited. In patients who already underwent a screening with right heart catheterization assessment due to clinical routine within the preceding 6 months, this assessment served as baseline.

Pre-assignment

Screening details:

Patients were screened by clinical examinations and right heart catheterization. If patients were eligible for the study, the baseline assessment was performed within 28 days from Screening.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Randomization to one of the groups was performed by block randomization. Randomization lists were created by the data management using a computer to generate random numbers. Medication was packed with sequential patient numbers. The randomization list were kept in safe and confidential custody. Emergency envelopes were collected at the end of the Trial by the Trial Monitor and were only to be opened in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	ambrisentan

Arm description:

Ambrisentan once daily starting at 5 mg/die in the beginning of the study. Dosage was up-titrated to 10 mg/die after 1-4 weeks according to the physician’s and the patient’s estimation.
Study medication was provided orally with or without food. Treatment effect was controlled at each study visit and the dose was adapted. The patient took one or two tablets of ambrisentan 5 mg once daily.

Arm type	Experimental
Investigational medicinal product name	Ambrisentan
Investigational medicinal product code	
Other name	Volibris
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Titration
As to common practice of the clinic, the patient adapted the dose from 5 mg to 10 mg after 1 to 4 weeks according to tolerability and after consultation (by phone or personally) with one of the investigators. Additionally, at each study visit the investigator needed to decide, based on the patient’s well-being, patients´ assessment, safety parameters, and tolerance of ambrisentan, if the study medication should be modified. The respective decision (increase, maintain or decrease dose) were documented.
Maximum dose allowed: not to exceed 10 mg/die.

Administration
Ambrisentan and placebo was administered orally with or without food intake.

Arm title	Placebo

Arm description:

Placebo tablets with the same treatment regimen (once daily) as the verum therapy were provided. One

pill a day were given. Treatment effect was controlled at each study visit and the sham dose was adapted. The patient took one or two tablets once daily.

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

Dosage and administration details:

Sham Titration in accordance with the protocol with 1 tablet at the beginning and up to 2 tablets after up-titration (4 weeks) with regard to 5 to 10 mg in the Intervention Group.

Number of subjects in period 1	ambrisentan	Placebo
Started	19	19
Completed	19	19

Period 2

Period 2 title	6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ambrisentan

Arm description:

Ambrisentan once daily starting at 5 mg/die in the beginning of the study. Dosage was up-titrated to 10 mg/die after 1-4 weeks according to the physician’s and the patient’s estimation.
Study medication was provided orally with or without food. Treatment effect was controlled at each study visit and the dose was adapted. The patient took one or two tablets of ambrisentan 5 mg once daily.

Arm type	Experimental
Investigational medicinal product name	Ambrisentan
Investigational medicinal product code	
Other name	Volibris
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Titration
As to common practice of the clinic, the patient adapted the dose from 5 mg to 10 mg after 1 to 4 weeks according to tolerability and after consultation (by phone or personally) with one of the investigators. Additionally, at each study visit the investigator needed to decide, based on the patient’s well-being,

patients´ assessment, safety parameters, and tolerance of ambrisentan, if the study medication should be modified. The respective decision (increase, maintain or decrease dose) were documented. Maximum dose allowed: not to exceed 10 mg/die.

Administration
Ambrisentan and placebo was administered orally with or without food intake.

Arm title	Placebo

Arm description:

Placebo tablets with the same treatment regimen (once daily) as the verum therapy were provided. One pill a day were given. Treatment effect was controlled at each study visit and the sham dose was adapted. The patient took one or two tablets once daily.

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

Dosage and administration details:

Sham Titration in accordance with the protocol with 1 tablet at the beginning and up to 2 tablets after up-titration (4 weeks) with regard to 5 to 10 mg in the Intervention Group.

Number of subjects in period 2	ambrisentan	Placebo
Started	19	19
Completed	17	15
Not completed	2	4
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ambrisentan

Reporting group description:

Ambrisentan once daily starting at 5 mg/die in the beginning of the study. Dosage was up-titrated to 10 mg/die after 1-4 weeks according to the physician's and the patient's estimation.
Study medication was provided orally with or without food. Treatment effect was controlled at each study visit and the dose was adapted. The patient took one or two tablets of ambrisentan 5 mg once daily.

Reporting group title	Placebo

Reporting group description:

Placebo tablets with the same treatment regimen (once daily) as the verum therapy were provided. One pill a day were given. Treatment effect was controlled at each study visit and the sham dose was adapted. The patient took one or two tablets once daily.

Reporting group values	ambrisentan	Placebo	Total
Number of subjects	19	19	38
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	58.79	54.89	
standard deviation	± 10.75	± 11.23	-
Gender categorical Units: Subjects			
Female	16	14	30
Male	3	5	8
WHO functional class			
WHO functional classification I : no symptoms II: no symptoms at rest but during normal activity (climbing stairs), slight Limitation of normal activity III: no symptoms at rest but during normal activity, marked limitation of normal activity IV: symptoms at rest and during any activity			
Units: Subjects			
II	17	15	32
III	2	4	6
Systemic sclerosis subgroup Units: Subjects			
diffuse	4	11	15
limited	15	8	23

Hemodynamic characteristic according to inclusion criteria Units: Subjects			
mPAP rest 21-24mmHg, mPAP exercise >30mmHg	10	12	22
mPAP rest 21-24mmHg, mPAP exercise ≤30mmHg	1	3	4
mPAP rest <21mmHg, mPAP exercise >30mmHg	8	4	12
Mean pulmonary arterial pressure Units: mmHg			
arithmetic mean	19.84	21.32	
standard deviation	± 3.58	± 2.43	-
Height Units: cm			
arithmetic mean	166.05	166.21	
standard deviation	± 5.59	± 10.19	-
Weight Units: kg			
arithmetic mean	71.45	74.81	
standard deviation	± 15.83	± 17.25	-
Systolic blood pressure Units: mmHg			
arithmetic mean	116.32	121.32	
standard deviation	± 11.53	± 14.99	-
Diastolic blood pressure Units: mmHg			
arithmetic mean	73.68	73.42	
standard deviation	± 8.95	± 9.14	-
Heart rate Units: beats/min			
arithmetic mean	73.05	77.58	
standard deviation	± 11.12	± 9.85	-
Modified Rodnan Skin score Units: points			
arithmetic mean	11.47	11.47	
standard deviation	± 5.71	± 5.22	-
Systemic sclerosis disease duration Units: years			
arithmetic mean	6.63	13.28	
standard deviation	± 4.80	± 10.85	-
Pulmonary arterial wedge pressure Units: mmHg			
arithmetic mean	9.42	9.58	
standard deviation	± 2.32	± 2.97	-
Cardiac Output Units: l/min			
arithmetic mean	5.04	5.66	
standard deviation	± 1.26	± 1.48	-
Cardiac Index Units: l/min/m2			
arithmetic mean	2.84	3.20	
standard deviation	± 0.64	± 0.85	-

SvO2			
Units: percent			
arithmetic mean	73.13	73.94	
standard deviation	± 4.60	± 8.58	-
Pulmonary vascular resistance			
Units: Wood Units			
arithmetic mean	2.22	2.09	
standard deviation	± 0.93	± 0.61	-
mean pulmonary arterial pressure at peak exercise			
Units: mmHg			
arithmetic mean	37.78	36.94	
standard deviation	± 3.61	± 6.08	-
Pulmonary arterial wedge pressure at peak exercise			
Units: mmHg			
arithmetic mean	16.78	15.24	
standard deviation	± 6.42	± 5.43	-
Cardiac Output at peak exercise			
Units: l/min			
arithmetic mean	9.67	11.03	
standard deviation	± 2.67	± 3.62	-
Cardiac index at peak exercise			
Units: l/min/m2			
arithmetic mean	5.41	6.04	
standard deviation	± 1.32	± 1.79	-
SvO2 at peak exercise			
Units: percent			
arithmetic mean	42.77	38.27	
standard deviation	± 11.56	± 6.10	-
Workload at peak exercise			
Units: watt			
arithmetic mean	75.00	75.00	
standard deviation	± 27.12	± 34.23	-
Heart rate at peak exercise			
Units: beats/min			
arithmetic mean	111.39	117.65	
standard deviation	± 23.06	± 21.37	-
Pulmonary vascular resistance at peak exercise			
Units: Wood Units			
arithmetic mean	2.29	2.07	
standard deviation	± 0.85	± 0.61	-
Total pulmonary resistance			
Units: mmHg*min*l-1			
arithmetic mean	4.28	3.65	
standard deviation	± 1.65	± 1.18	-
6-minute walking distance			
Units: meter			
arithmetic mean	470.21	448.11	
standard deviation	± 77.03	± 82.64	-
Borg dyspnea score			
Units: score			

arithmetic mean	2.41	2.93	
standard deviation	± 1.32	± 1.97	-
Oxygen saturation after 6-minute walking distance			
Units: percent			
arithmetic mean	91.71	91.87	
standard deviation	± 4.79	± 4.63	-
Heart rate after 6-minute walking distance			
Units: beats/minute			
arithmetic mean	107	99	
standard deviation	± 19.64	± 21.27	-
Systolic pulmonary arterial pressure (echocardiography)			
Units: mmHg			
arithmetic mean	28.58	29.21	
standard deviation	± 6.57	± 5.16	-
Right atrial area			
Units: cm2			
arithmetic mean	11.68	12.05	
standard deviation	± 3.28	± 4.24	-
Right ventricular area			
Units: cm2			
arithmetic mean	14.13	14.89	
standard deviation	± 4.74	± 4.56	-
Tricuspid annular plane systolic excursion			
Units: cm			
arithmetic mean	2.41	2.50	
standard deviation	± 0.33	± 0.51	-
Forced Vital Capacity			
Units: percent			
arithmetic mean	70.51	69.17	
standard deviation	± 17.61	± 13.72	-
Forced Expiratory Volume in 1 second			
Units: litre(s)			
arithmetic mean	2.26	2.40	
standard deviation	± 0.63	± 0.77	-
FEV1 % Vital capacity max			
Units: percent			
arithmetic mean	81.44	79.31	
standard deviation	± 15.38	± 6.98	-
PEF			
Units: litre/second			
arithmetic mean	5.17	5.46	
standard deviation	± 1.72	± 2.32	-
Total lung capacity			
Units: litre(s)			
arithmetic mean	5.08	4.96	
standard deviation	± 1.25	± 1.07	-
Residual volume			
Units: litre(s)			
arithmetic mean	2.18	1.94	

standard deviation	± 0.70	± 0.55	-
Diffusion capacity of the lung			
Units: mmol/min/kPa			
arithmetic mean	5.03	5.28	
standard deviation	± 1.33	± 1.52	-
Diffusion capacity of the lung percent predicted			
Units: percent			
arithmetic mean	84.16	84.73	
standard deviation	± 1.89	± 2.61	-
SaO2			
Units: percent			
arithmetic mean	96.82	96.13	
standard deviation	± 0.77	± 1.80	-
PaO2			
Units: mmHg			
arithmetic mean	81.22	78.78	
standard deviation	± 5.91	± 9.42	-
PaCO2			
Units: mmHg			
arithmetic mean	37.23	39.01	
standard deviation	± 2.57	± 3.63	-
Hemoglobin			
Units: g/dl			
arithmetic mean	13.62	13.54	
standard deviation	± 1.13	± 1.26	-
Hematocrit			
Units: 1/l			
arithmetic mean	0.41	0.42	
standard deviation	± 0.03	± 0.03	-
Platelet			
Units: 100/nl			
arithmetic mean	2.62	2.53	
standard deviation	± 0.63	± 0.94	-
Creatinine			
Units: mg/dl			
arithmetic mean	0.86	0.83	
standard deviation	± 0.12	± 0.16	-
Potassium			
Units: mmol/l			
arithmetic mean	4.20	4.05	
standard deviation	± 0.48	± 0.38	-
AST			
Units: U/l			
arithmetic mean	19.79	24.11	
standard deviation	± 7.06	± 21.78	-
ALT			
Units: U/l			
arithmetic mean	24.68	29.68	
standard deviation	± 9.85	± 24.93	-
LDH			
Units: U/l			

arithmetic mean	197.53	197.63	
standard deviation	± 35.59	± 54.74	-
CRP			
Units: mg/l			
arithmetic mean	5.28	5.18	
standard deviation	± 11.60	± 5.17	-
NTproBNP			
Units: pg/ml			
arithmetic mean	267.83	123.42	
standard deviation	± 303.11	± 142.96	-
Physical functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	64.21	50.26	
standard deviation	± 25.83	± 25.95	-
Physical role functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	51.32	35.53	
standard deviation	± 41.23	± 40.24	-
Bodily pain (SF-36 questionnaire)			
Units: score			
arithmetic mean	62.00	49.79	
standard deviation	± 29.16	± 28.96	-
General health perception			
Units: score			
arithmetic mean	54.42	41.74	
standard deviation	± 19.47	± 13.07	-
Vitality (SF-36 questionnaire)			
Units: score			
arithmetic mean	50.53	42.89	
standard deviation	± 20.94	± 19.32	-
Social role functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	74.47	58.05	
standard deviation	± 24.45	± 25.99	-
Emotional role functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	63.16	49.16	
standard deviation	± 47.02	± 46.33	-
Mental health (SF-36 questionnaire)			
Units: score			
arithmetic mean	64.42	59.58	
standard deviation	± 18.03	± 18.85	-
Physical summation score (SF-36 questionnaire)			
Units: score			
arithmetic mean	56.47	43.89	
standard deviation	± 23.87	± 21.26	-
Mental summation score (SF-36 questionnaire)			
Units: score			

arithmetic mean	61.42	50.26	
standard deviation	± 21.45	± 20.70	-

Subject analysis sets	
Subject analysis set title	All patients randomised
Subject analysis set type	Full analysis
Subject analysis set description:	
Includes all patients that were randomised into the study	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Efficacy analysis set of all patients who completed the study	
Subject analysis set title	Ambrisentan
Subject analysis set type	Full analysis
Subject analysis set description:	
Efficacy analysis of all patients who completed the study	

Reporting group values	All patients randomised	Placebo	Ambrisentan
Number of subjects	38	15	17
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
WHO functional class			
WHO functional classification I : no symptoms II: no symptoms at rest but during normal activity (climbing stairs), slight Limitation of normal activity III: no symptoms at rest but during normal activity, marked limitation of normal activity IV: symptoms at rest and during any activity			
Units: Subjects			
II III			
Systemic sclerosis subgroup			

Units: Subjects			
diffuse	15		
limited	23		
Hemodynamic characteristic according to inclusion criteria Units: Subjects			
mPAP rest 21-24mmHg, mPAP exercise >30mmHg	22		
mPAP rest 21-24mmHg, mPAP exercise ≤30mmHg	4		
mPAP rest <21mmHg, mPAP exercise >30mmHg	12		
Mean pulmonary arterial pressure Units: mmHg			
arithmetic mean	20.58		
standard deviation	± 3.11	±	±
Height Units: cm			
arithmetic mean	166.13		
standard deviation	± 8.11	±	±
Weight Units: kg			
arithmetic mean	73.13		
standard deviation	± 16.42	±	±
Systolic blood pressure Units: mmHg			
arithmetic mean	118.82		
standard deviation	± 13.43	±	±
Diastolic blood pressure Units: mmHg			
arithmetic mean	73.55		
standard deviation	± 8.92	±	±
Heart rate Units: beats/min			
arithmetic mean	75.32		
standard deviation	± 10.61	±	±
Modified Rodnan Skin score Units: points			
arithmetic mean	11.47		
standard deviation	± 5.40	±	±
Systemic sclerosis disease duration Units: years			
arithmetic mean	9.96		
standard deviation	± 8.93	±	±
Pulmonary arterial wedge pressure Units: mmHg			
arithmetic mean	9.50		
standard deviation	± 2.63	±	±
Cardiac Output Units: l/min			
arithmetic mean	5.35		
standard deviation	± 1.39	±	±
Cardiac Index			

Units: l/min/m2			
arithmetic mean	3.02		
standard deviation	± 0.76	±	±
SvO2			
Units: percent			
arithmetic mean	73.53		
standard deviation	± 6.85	±	±
Pulmonary vascular resistance			
Units: Wood Units			
arithmetic mean	2.16		
standard deviation	± 0.78	±	±
mean pulmonary arterial pressure at peak exercise			
Units: mmHg			
arithmetic mean	37.37		
standard deviation	± 4.91	±	±
Pulmonary arterial wedge pressure at peak exercise			
Units: mmHg			
arithmetic mean	16.03		
standard deviation	± 5.92	±	±
Cardiac Output at peak exercise			
Units: l/min			
arithmetic mean	10.33		
standard deviation	± 3.19	±	±
Cardiac index at peak exercise			
Units: l/min/m2			
arithmetic mean	5.71		
standard deviation	± 1.58	±	±
SvO2 at peak exercise			
Units: percent			
arithmetic mean	40.52		
standard deviation	± 9.37	±	±
Workload at peak exercise			
Units: watt			
arithmetic mean	75.00		
standard deviation	± 30.32	±	±
Heart rate at peak exercise			
Units: beats/min			
arithmetic mean	114.43		
standard deviation	± 22.15	±	±
Pulmonary vascular resistance at peak exercise			
Units: Wood Units			
arithmetic mean	2.18		
standard deviation	± 0.74	±	±
Total pulmonary resistance			
Units: mmHg*min*l-1			
arithmetic mean	3.97		
standard deviation	± 1.46	±	±
6-minute walking distance			
Units: meter			
arithmetic mean	459.16		

standard deviation	± 79.59	±	±
Borg dyspnea score			
Units: score			
arithmetic mean	2.67		
standard deviation	± 1.68	±	±
Oxygen saturation after 6-minute walking distance			
Units: percent			
arithmetic mean	91.78		
standard deviation	± 4.64	±	±
Heart rate after 6-minute walking distance			
Units: beats/minute			
arithmetic mean	103		
standard deviation	± 20.56	±	±
Systolic pulmonary arterial pressure (echocardiography)			
Units: mmHg			
arithmetic mean	28.89		
standard deviation	± 5.83	±	±
Right atrial area			
Units: cm2			
arithmetic mean	11.87		
standard deviation	± 3.74	±	±
Right ventricular area			
Units: cm2			
arithmetic mean	14.51		
standard deviation	± 4.60	±	±
Tricuspid annular plane systolic excursion			
Units: cm			
arithmetic mean	2.48		
standard deviation	± 0.47	±	±
Forced Vital Capacity			
Units: percent			
arithmetic mean	69.84		
standard deviation	± 15.58	±	±
Forced Expiratory Volume in 1 second			
Units: litre(s)			
arithmetic mean	2.33		
standard deviation	± 0.70	±	±
FEV1 % Vital capacity max			
Units: percent			
arithmetic mean	80.38		
standard deviation	± 11.83	±	±
PEF			
Units: litre/second			
arithmetic mean	5.31		
standard deviation	± 2.02	±	±
Total lung capacity			
Units: litre(s)			
arithmetic mean	5.02		
standard deviation	± 1.15	±	±

Residual volume			
Units: litre(s)			
arithmetic mean	2.06		
standard deviation	± 0.63	±	±
Diffusion capacity of the lung			
Units: mmol/min/kPa			
arithmetic mean	5.16		
standard deviation	± 1.42	±	±
Diffusion capacity of the lung percent predicted			
Units: percent			
arithmetic mean	84.45		
standard deviation	± 2.27	±	±
SaO2			
Units: percent			
arithmetic mean	96.47		
standard deviation	± 1.41	±	±
PaO2			
Units: mmHg			
arithmetic mean	80.00		
standard deviation	± 7.85	±	±
PaCO2			
Units: mmHg			
arithmetic mean	38.12		
standard deviation	± 3.23	±	±
Hemoglobin			
Units: g/dl			
arithmetic mean	13.58		
standard deviation	± 1.18	±	±
Hematocrit			
Units: 1/l			
arithmetic mean	0.41		
standard deviation	± 0.03	±	±
Platelet			
Units: 100/nl			
arithmetic mean	2.58		
standard deviation	± 0.79	±	±
Creatinine			
Units: mg/dl			
arithmetic mean	0.85		
standard deviation	± 0.14	±	±
Potassium			
Units: mmol/l			
arithmetic mean	4.12		
standard deviation	± 0.43	±	±
AST			
Units: U/l			
arithmetic mean	21.95		
standard deviation	± 16.12	±	±
ALT			
Units: U/l			
arithmetic mean	27.18		

standard deviation	± 18.87	±	±
LDH			
Units: U/l			
arithmetic mean	197.58		
standard deviation	±	±	±
CRP			
Units: mg/l			
arithmetic mean	5.23		
standard deviation	± 8.77	±	±
NTproBNP			
Units: pg/ml			
arithmetic mean	193.68		
standard deviation	± 242.81	±	±
Physical functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	57.24		
standard deviation	± 26.50	±	±
Physical role functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	43.42		
standard deviation	± 40.97	±	±
Bodily pain (SF-36 questionnaire)			
Units: score			
arithmetic mean	55.89		
standard deviation	± 29.33	±	±
General health perception			
Units: score			
arithmetic mean	48.08		
standard deviation	± 17.58	±	±
Vitality (SF-36 questionnaire)			
Units: score			
arithmetic mean	46.71		
standard deviation	± 20.24	±	±
Social role functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	66.26		
standard deviation	± 26.24	±	±
Emotional role functioning (SF-36 questionnaire)			
Units: score			
arithmetic mean	56.16		
standard deviation	± 46.58	±	±
Mental health (SF-36 questionnaire)			
Units: score			
arithmetic mean	62.00		
standard deviation	± 18.36	±	±
Physical summation score (SF-36 questionnaire)			
Units: score			
arithmetic mean	50.18		

standard deviation	± 23.19	±	±
Mental summation score (SF-36 questionnaire)			
Units: score			
arithmetic mean	55.84		
standard deviation	± 21.55	±	±

End points

End points reporting groups

Reporting group title	ambrisentan

Reporting group description:

Ambrisentan once daily starting at 5 mg/die in the beginning of the study. Dosage was up-titrated to 10 mg/die after 1-4 weeks according to the physician's and the patient's estimation.
Study medication was provided orally with or without food. Treatment effect was controlled at each study visit and the dose was adapted. The patient took one or two tablets of ambrisentan 5 mg once daily.

Reporting group title	Placebo

Reporting group description:

Placebo tablets with the same treatment regimen (once daily) as the verum therapy were provided. One pill a day were given. Treatment effect was controlled at each study visit and the sham dose was adapted. The patient took one or two tablets once daily.

Reporting group title	ambrisentan

Reporting group description:

Ambrisentan once daily starting at 5 mg/die in the beginning of the study. Dosage was up-titrated to 10 mg/die after 1-4 weeks according to the physician's and the patient's estimation.
Study medication was provided orally with or without food. Treatment effect was controlled at each study visit and the dose was adapted. The patient took one or two tablets of ambrisentan 5 mg once daily.

Reporting group title	Placebo

Reporting group description:

Placebo tablets with the same treatment regimen (once daily) as the verum therapy were provided. One pill a day were given. Treatment effect was controlled at each study visit and the sham dose was adapted. The patient took one or two tablets once daily.

Subject analysis set title	All patients randomised
Subject analysis set type	Full analysis

Subject analysis set description:

Includes all patients that were randomised into the study

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Efficacy analysis set of all patients who completed the study

Subject analysis set title	Ambrisentan
Subject analysis set type	Full analysis

Subject analysis set description:

Efficacy analysis of all patients who completed the study

Primary: mean pulmonary arterial pressure

End point title	mean pulmonary arterial pressure

End point description:

End point type	Primary

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: mmHg				
arithmetic mean (standard deviation)	-0.73 (± 3.59)	-1.0 (± 6.40)		

Statistical analyses

Statistical analysis title	t-test with unequal variances (Welch-Test)
Comparison groups	Placebo v Ambrisentan
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.884
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.09
upper limit	3.56

Secondary: Cardiac index

End point title	Cardiac index

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: l/min				
arithmetic mean (standard deviation)	-0.31 (± 0.71)	0.66 (± 1.17)		

Statistical analyses

Statistical analysis title	T-test with unequal variances (Welch-test)
Comparison groups	Placebo v Ambrisentan

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.18

Secondary: Pulmonary vascular resistance

End point title	Pulmonary vascular resistance

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: Wood Units				
arithmetic mean (standard deviation)	0.02 (± 0.76)	-0.59 (± 0.79)		

Statistical analyses

Statistical analysis title	T-test with unequal variances
Comparison groups	Placebo v Ambrisentan
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.17

Secondary: 6-minute walking distance

End point title	6-minute walking distance

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: meter				
arithmetic mean (standard deviation)	-16.53 (± 77.21)	21.53 (± 34.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diffusion capacity of the lung

End point title	Diffusion capacity of the lung

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	17		
Units: percent predicted				
arithmetic mean (standard deviation)	-0.44 (± 1.84)	1.19 (± 1.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin

End point title	Hemoglobin

End point description:

End point type	Secondary

End point timeframe:

Change form baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: g/dl				
arithmetic mean (standard deviation)	0.19 (± 0.68)	-0.59 (± 0.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: NTproBNP

End point title	NTproBNP

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	16		
Units: pg/ml				
arithmetic mean (standard deviation)	31.00 (± 85.83)	-15.63 (± 207.48)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: mean pulmonary arterial pressure at peak exercise

End point title	mean pulmonary arterial pressure at peak exercise

End point description:

End point type	Other pre-specified

End point timeframe:
Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: mmHg				
arithmetic mean (standard deviation)	1.08 (± 7.39)	-0.73 (± 6.23)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: pulmonary arterial wedge pressure at peak exercise

End point title	pulmonary arterial wedge pressure at peak exercise

End point description:

End point type	Other pre-specified

End point timeframe:
Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: mmHg				
arithmetic mean (standard deviation)	0.85 (± 6.3)	4.93 (± 6.52)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cardiac index at peak exercise

End point title	Cardiac index at peak exercise

End point description:

End point type	Other pre-specified

End point timeframe: Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: l/min/m^2				
arithmetic mean (standard deviation)	-0.45 (± 1.36)	0.70 (± 0.81)		

Statistical analyses

Statistical analysis title	t-test with unequal variances (Welch test)
Comparison groups	Ambrisentan v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2

Other pre-specified: Workload at peak exercise	
End point title	Workload at peak exercise
End point description:	

End point type	Other pre-specified
End point timeframe: Change form baseline to 6 months	

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: watt				
arithmetic mean (standard deviation)	1.92 (± 16.01)	5.00 (± 16.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Heart rate at peak exercise

End point title	Heart rate at peak exercise

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: beats/min				
arithmetic mean (standard deviation)	6.00 (± 18.74)	7.47 (± 12.01)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pulmonary vascular resistance at peak exercise

End point title	Pulmonary vascular resistance at peak exercise

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: Wood Units				
arithmetic mean (standard deviation)	0.003 (± 0.34)	-0.84 (± 0.48)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total pulmonary resistance at peak exercise

End point title	Total pulmonary resistance at peak exercise

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: mmHg*min*l^-1				
arithmetic mean (standard deviation)	0.16 (± 0.63)	-0.56 (± 0.48)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Modified rodnan skin score

End point title	Modified rodnan skin score

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: Score				
arithmetic mean (standard deviation)	0.73 (± 2.15)	0.24 (± 0.97)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Physical functioning (SF-36 questionnaire)

End point title	Physical functioning (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	-2.00 (± 25.20)	-7.65 (± 21.66)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Physical role functioning (SF-36 questionnaire)

End point title	Physical role functioning (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	13.33 (± 38.81)	-10.29 (± 42.44)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Bodily Pain (SF-36 questionnaire)

End point title	Bodily Pain (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	-2.47 (± 28.19)	-9.29 (± 23.87)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: General health perception (SF-36 questionnaire)

End point title	General health perception (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	0.20 (± 19.39)	-2.71 (± 10.62)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vitality (SF-36 questionnaire)

End point title	Vitality (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	-5.00 (± 16.37)	-3.53 (± 12.34)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Social role functioning (SF-36 questionnaire)

End point title	Social role functioning (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	0.87 (± 27.69)	-2.18 (± 19.21)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Emotional role functioning (SF-36 questionnaire)

End point title	Emotional role functioning (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	8.80 (± 49.68)	-9.82 (± 36.76)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mental health (SF-36 questionnaire)

End point title	Mental health (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	-3.73 (± 11.85)	-4.47 (± 10.94)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Physical summation score (SF-36 questionnaire)

End point title	Physical summation score (SF-36 questionnaire)

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	0.87 (± 16.01)	-6.71 (± 12.17)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mental health score

End point title	Mental health score

End point description:

End point type	Other pre-specified

End point timeframe:

Change from baseline to 6 months

End point values	Placebo	Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	17		
Units: score				
arithmetic mean (standard deviation)	0.27 (± 19.77)	-4.65 (± 9.47)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline until 6 month visit + 30 days follow-up after last study drug intake	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ambrisentan
Reporting group description: -	

Serious adverse events	Placebo	Ambrisentan	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)	1 / 19 (5.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphangitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal infection			

subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lower jaw fracture			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raynaud's phenomenon			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Ambrisentan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 19 (89.47%)	17 / 19 (89.47%)	
Vascular disorders			
Dizziness			
subjects affected / exposed	6 / 19 (31.58%)	0 / 19 (0.00%)	
occurrences (all)	6	0	
Hypotension			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	3 / 19 (15.79%)	
occurrences (all)	1	3	
Raynaud's phenomenon			
subjects affected / exposed	2 / 19 (10.53%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	3 / 19 (15.79%)	1 / 19 (5.26%)	
occurrences (all)	3	1	

Tachycardia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 19 (31.58%)	6 / 19 (31.58%)	
occurrences (all)	6	6	
Paraesthesia			
subjects affected / exposed	0 / 19 (0.00%)	4 / 19 (21.05%)	
occurrences (all)	0	4	
Tinnitus			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
edema			
subjects affected / exposed	4 / 19 (21.05%)	8 / 19 (42.11%)	
occurrences (all)	4	8	
sweating			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)	4 / 19 (21.05%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	3 / 19 (15.79%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Gastrointestinal infection			
subjects affected / exposed	3 / 19 (15.79%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Gingival bleeding			

subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Infection			
subjects affected / exposed	0 / 19 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	2 / 19 (10.53%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Infection	Additional description: urinary infection		
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Rheumatic disorder	Additional description: worsening of Underlying condition		
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 19 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2015	Change of site address due to relocation of main entrance of clinic
29 April 2016	Amendment 2 includes: • Clarification of exclusion criteria • Clarification of optional assessment of right atrial pressure by right heart catheterization during exercise • Change of packaging of the study drug (second batch of study drug was packed in modified blister sizes) • Change of the paragraph regarding the tear-off portions on the labels of study medication as labels with tear-off portions were not provided. • Adaptation of the timelines for the study according to the recruitment status and anticipated recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31655622