Clinical trial results:
An Exploratory Study to Investigate the Haemodynamic Effects of Serelaxin (RLX030) in Patients With Compensated Cirrhosis and Portal Hypertension

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-000236-26
Trial protocol	GB
Global end of trial date	19 December 2014

Results information

Result version number	v1 (current)
This version publication date	28 March 2016
First version publication date	28 March 2016

Trial information

Trial identification

Sponsor protocol code	CRLX030X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01640964
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, trialandresults.registries@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, trialandresults.registries@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Part A (Magnetic resonance angiography (MRA))

To investigate whether serelaxin increases the total renal arterial blood flow in patients with cirrhosis and PHT after at least 120 min of infusion (60 min at 80 µg/kg/day and at least 60 min at 30 µg/kg/day).

- Part B (direct venous pressure measurement)

To investigate whether serelaxin reduces the PPG in patients with cirrhosis, PHT and a TIPSS in situ after at least 120 min of infusion (60 min at 80 µg/kg/day and at least 60 min at 30 µg/kg/day).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.
Rescue medication to treat severe or serious condition in the opinion of the investigator was allowed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	38
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 47 enrolled patients, 1 patient did not get randomized to Part A serelaxin arm ; patient withdrew consent due to failure of meeting an exclusion criterion for Part A prior to receiving the dose of study medication.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Terlipressin acetate

Arm description:

Patients received terlipressin acetate 2 mg intravenous (IV) bolus injection.

Arm type	Active comparator
Investigational medicinal product name	Terlipressin acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

2 mg IV bolus injection

Arm title	Part A: Serelaxin (RLX030)

Arm description:

Randomized patients received an intravenous serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min.; duration of infusion depends on time required for completion of magnetic resonance angiography (MRA) data acquisition

Arm type	Experimental
Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion for 2-3 hours; duration of infusion depends on time required for completion of MRA data acquisition;

Arm title	Part B: Serelaxin (RLX030)

Arm description:

The patients enrolled in this part of the study received an intravenous (iv) serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min; duration of infusion depends on time required for completion of the Portal pressure gradient (PPG) data acquisition.

Arm type	Experimental

Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion for approximately 2 hours

Number of subjects in period 1	Part A: Terlipressin acetate	Part A: Serelaxin (RLX030)	Part B: Serelaxin (RLX030)
Started	20	20	6
Completed	19	19	3
Not completed	1	1	3
Protocol Deviation	1	1	2
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Part A: Terlipressin acetate

Reporting group description:

Patients received terlipressin acetate 2 mg intravenous (IV) bolus injection.

Reporting group title	Part A: Serelaxin (RLX030)

Reporting group description:

Randomized patients received an intravenous serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min.; duration of infusion depends on time required for completion of magnetic resonance angiography (MRA) data acquisition

Reporting group title	Part B: Serelaxin (RLX030)

Reporting group description:

The patients enrolled in this part of the study received an intravenous (iv) serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min; duration of infusion depends on time required for completion of the Portal pressure gradient (PPG) data acquisition.

Reporting group values	Part A: Terlipressin acetate	Part A: Serelaxin (RLX030)	Part B: Serelaxin (RLX030)
Number of subjects	20	20	6
Age categorical Units: Subjects			
Adults (18-64 years)	17	15	6
From 65-84 years	3	5	0
Gender, Male/Female Units: Patients			
Female	4	4	3
Male	16	16	3

Reporting group values	Total		
Number of subjects	46		
Age categorical Units: Subjects			
Adults (18-64 years)	38		
From 65-84 years	8		
Gender, Male/Female Units: Patients			
Female	11		
Male	35		

End points

End points reporting groups

Reporting group title	Part A: Terlipressin acetate

Reporting group description:

Patients received terlipressin acetate 2 mg intravenous (IV) bolus injection.

Reporting group title	Part A: Serelaxin (RLX030)

Reporting group description:

Randomized patients received an intravenous serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min.; duration of infusion depends on time required for completion of magnetic resonance angiography (MRA) data acquisition

Reporting group title	Part B: Serelaxin (RLX030)

Reporting group description:

The patients enrolled in this part of the study received an intravenous (iv) serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min; duration of infusion depends on time required for completion of the Portal pressure gradient (PPG) data acquisition.

Primary: Change from baseline of the blood flow for the total renal arteries (Study Part A (Serelaxin treatment group only))

End point title	Change from baseline of the blood flow for the total renal arteries (Study Part A (Serelaxin treatment group only))[1][2]

End point description:

The flow is the average flow over the cardiac cycle. Total renal artery flow = left renal artery flow + right renal artery flow. These measurements were collected through magnetic resonance angiography (MRA) scans. Baseline blood flow for total renal artery is measured at pre-dose (Day 1, 0 min post-treatment)

End point type	Primary

End point timeframe:

Baseline, 120 min post serelaxin infusion

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical hypothesis testing for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: L/min				
arithmetic mean (confidence interval 95%)	0.438 (0.274 to 0.601)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline of the portal pressure gradient (PPG) (Study Part B)

End point title	Change from baseline of the portal pressure gradient (PPG) (Study Part B)[3][4]

End point description:

Direct venous pressure was measured by portal pressure gradient (PPG). PPG = portal vein pressure (PVP) - inferior vena cava pressure (IVCP). Baseline blood flow for PPG was measured at pre-dose (Day 1, 0 min post-treatment). PVP was measured at 15 min intervals (i.e. prior to and at 15, 30, 45, 60, 75, 90, 105, and 120 min of serelaxin infusion).

End point type	Primary

End point timeframe:

Baseline, 120 min post-infusion start

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical hypothesis testing for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part B: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (confidence interval 95%)	-1.2 (-6.1 to 3.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the blood flow for the total renal arteries (Study Part A (Terlipressin Acetate group only))

End point title	Change from baseline of the blood flow for the total renal arteries (Study Part A (Terlipressin Acetate group only))[5]

End point description:

The flow is the average flow over the cardiac cycle. Total renal artery flow = left renal artery flow + right renal artery flow. These measurements were collected through magnetic resonance angiography (MRA) scans. Baseline blood flow for total renal artery is measured at pre-dose (Day 1, 0 min post-treatment)

End point type	Secondary

End point timeframe:

Baseline, 120 min post infusion

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Terlipressin acetate			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: L/min				
arithmetic mean (confidence interval 95%)	0.059 (-0.045 to 0.164)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the blood flow for the hepatic artery (Study Part A (Serelaxin treatment group only))

End point title	Change from baseline of the blood flow for the hepatic artery (Study Part A (Serelaxin treatment group only))[6]

End point description:

A non-contrast magnetic resonance angiography (MRA) sequence was performed to acquire phase contrast blood flow measurements from vessels of interest such as hepatic artery. The flow is the average flow over the cardiac cycle. Baseline blood flow measurements are measured at pre-dose (Day 1, 0 min post-treatment).

End point type	Secondary

End point timeframe:

Baseline, 120 min post-infusion

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: L/min				
arithmetic mean (confidence interval 95%)	0.084 (-0.02 to 0.187)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the blood flow for the superior mesenteric artery (Study Part A (Serelaxin treatment group only))

End point title	Change from baseline of the blood flow for the superior mesenteric artery (Study Part A (Serelaxin treatment group only))[7]

End point description:

A non-contrast magnetic resonance angiography (MRA) sequence was performed to acquire phase contrast blood flow measurements from vessels of interest such as superior mesenteric artery. The flow is the average flow over the cardiac cycle. Baseline blood flow measurements are measured at pre-dose (Day 1, 0 min post-treatment).

End point type	Secondary

End point timeframe:

Baseline, 120 min post-infusion

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: L/min				
arithmetic mean (confidence interval 95%)	0.002 (-0.087 to 0.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the blood flow for the descending thoracic aorta (Study Part A (Serelaxin treatment group only))

End point title	Change from baseline of the blood flow for the descending thoracic aorta (Study Part A (Serelaxin treatment group only))[8]

End point description:

A non-contrast magnetic resonance angiography (MRA) sequence was performed to acquire phase contrast blood flow measurements from vessels of interest such as descending thoracic aorta. The flow is the average flow over the cardiac cycle. Baseline blood flow measurements are measured at pre-dose (Day 1, 0 min post-treatment).

End point type	Secondary

End point timeframe:

Baseline, 120 min post-infusion

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: L/min				
arithmetic mean (confidence interval 95%)	0.293 (0.059 to 0.527)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the blood flow for the portal vein (Study Part A (Serelaxin treatment group only))

End point title	Change from baseline of the blood flow for the portal vein (Study Part A (Serelaxin treatment group only))[9]

End point description:

A non-contrast magnetic resonance angiography (MRA) sequence was performed to acquire phase contrast blood flow measurements from vessels of interest such as the portal vein. The flow is the average flow over the cardiac cycle. Baseline blood flow measurements are measured at pre-dose (Day 1, 0 min post-treatment).

End point type	Secondary

End point timeframe:

Baseline, 120 min post-infusion

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: L/min				
arithmetic mean (confidence interval 95%)	-0.091 (-0.204 to 0.023)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the portal vein pressure (PVP) (Study Part B)

End point title	Change from baseline of the portal vein pressure (PVP) (Study Part B)[10]

End point description:

Portal vein pressure was measured at 15 min intervals (i.e. prior to and at 15, 30, 45, 60, 75, 90, 105, and 120 min of serelaxin infusion).

End point type	Secondary

End point timeframe:

Baseline, 120 min post infusion

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part B: Serelaxin (RLX030)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (confidence interval 95%)	-3.7 (-8.8 to 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with total adverse events, serious adverse and death as assessment of safety and tolerability of serelaxin

End point title	Number of patients with total adverse events, serious adverse and death as assessment of safety and tolerability of serelaxin[11]

End point description:

This endpoint reports patients with any adverse event, serious adverse event and death for the serelaxin group of Part A and Part B of the study.

End point type	Secondary

End point timeframe:

4 weeks

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

End point values	Part A: Serelaxin (RLX030)	Part B: Serelaxin (RLX030)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	6		
Units: Patients				
Any adverse event	3	3		
Serious Adverse Events	1	2		
Death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Part A - Serelaxin (RLX030)
Reporting group description:	
Randomized patients received an intravenous serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min.; duration of infusion depends on time required for completion of magnetic resonance angiography (MRA) data acquisition	
Reporting group title	Part B - Serelaxin (RLX030)
Reporting group description:	
The patients enrolled in this part of the study received an intravenous (iv) serelaxin infusion at two different infusion rates: 80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min; duration of infusion depends on time required for completion of the Portal pressure gradient (PPG) data acquisition.	
Reporting group title	Part A - Terlipressin acetate
Reporting group description:	
Patients received terlipressin acetate 2 mg intravenous (IV) bolus injection.	

Serious adverse events	Part A - Serelaxin (RLX030)	Part B - Serelaxin (RLX030)	Part A - Terlipressin acetate
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	2 / 6 (33.33%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Hepatic encephalopathy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 20 (5.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part A - Serelaxin (RLX030)	Part B - Serelaxin (RLX030)	Part A - Terlipressin acetate
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	2 / 6 (33.33%)	11 / 20 (55.00%)
Investigations			

Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 20 (5.00%)	2 / 6 (33.33%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Electrocardiogram T wave biphasic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	4 / 20 (20.00%)
occurrences (all)	0	0	4
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	6 / 20 (30.00%)
occurrences (all)	0	0	6
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2014	The reasons for this amendment were to correct the minimum number of patients required for Part A and to modify the number of patients that would be enrolled into Part B. For Part A, the changes to the minimum values did not affect the statistical rationale as these minimum numbers were well below the number currently enrolled in Part A. For Part B, 10 patients had originally been planned (above the minimum of six required), as they were expected to have been enrolled within a reasonable time frame. However, during the course of the trial, it became apparent that a significant number of patient candidates for Part B had advanced to a disease stage where certain exclusion criteria were then limiting factors for recruitment, including low blood pressure (SBP <110 mmHg) and requirement for diuretics. Additionally, the PPG 'window' for treatment (between 5 and 12 mmHg in most patients) had proven to be rather narrow. Thus, for clinical enrollment reasons, the decision was made to reduce the number of patients enrolled in Part B from ten to six. The statistical rationale was not affected; six patients represented the minimum required for the 90% CI on mean change from Baseline to exclude zero for each endpoint (PPG gradient, PVP, RAP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported