Clinical trial results:
COMbination therapy for PulmonAry hypertension using RacEcadotril (COMPARE).

Summary

EudraCT number	2012-003921-13
Trial protocol	GB
Global end of trial date	05 April 2017

Results information

Result version number	v1 (current)
This version publication date	13 June 2019
First version publication date	13 June 2019

Trial information

Trial identification

Sponsor protocol code	12/0368

Additional study identifiers

ISRCTN number	ISRCTN96717546
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Comprehensive Clinical Trials Unit at UCL
Sponsor organisation address	Institute of Clinical Trials and Methodology, 90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk
Scientific contact	CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL, CCTU-enquiries@ucl.ac.uk

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	01 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2016
Global end of trial reached?	Yes
Global end of trial date	05 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial aims to generate data on the efficacy and safety of racecadotril in patients with pulmonary hypertension (PH) taking sildenafil or tadalafil.

Step 1 (Step 1A and 1B) was carried out to identify a safe dose of racecadotril on pulmonary and systemic haemodynamics. The aim was to confirm that a single dose of racecadotril effectively inhibits the enzyme neutral endopeptidase (NEP) without causing unacceptable adverse effects.

The aim of Step 2 was to investigate the safety and pharmacological effects of racecadotril on the six minute walk test, haemodynamics and biomarkers over a 12-14 day repeat-dosing study.

The hypothesis to be tested: racecadotril, administered in single and repeat dosing, will increase plasma atrial natriuretic peptide (ANP) concentration in patients with PH.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

Protocol pre-defined reasons for discontinuation of trial medication were in place in the event of participants experiencing: unacceptable toxicity or adverse event; inter-current illness that prevents further treatment; any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion; inadequate compliance with the protocol treatment in the judgement of the treating physician; withdrawal of consent for treatment by the patient; complications of right heart catheterisation (step 1 only) or pregnancy.

All participants could choose to discontinue trial treatment at any time, without giving a reason and without medical care or legal rights being affected.
Investigation and treatment of adverse events were as per NHS standard of care.

Specific clinical measures that were put in place to protect trial subjects:

During the extension to the routine Right Heart Catheterisation in step 1 to minimise the risk of thrombosis formation, the access sheath placed during the routine catheterisation was left in situ for approximately 2 hours and a small bolus of heparin (or another anti-thrombin agent) administered to ensure that no thrombus formation occurs.

Patients with PH have higher concentrations of NP in their plasma. It is possible that they might be more sensitive to the vasodilator effects of racecadotril and might experience a fall in systemic blood pressure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	10
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	21
Number of subjects completed	21

Period 1

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

Blinding implementation details:

All trial medication dispensed will have identical outer packaging to preserve the blind. The outer packaging will be labelled in compliance with clinical trial regulations, and will also contain a patient identification code which is given when the patient is randomised. On completion of the trial prescription, only the patient trial identification code will be used to identify the medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Racecadotril repeat dose

Arm description:

Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1.

Arm type	Experimental
Investigational medicinal product name	Racecadotril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1. 42 or 84 capsules will be dispensed either directly to the patient or to a member of the trial team to then pass on to the patient. The number of capsules dispensed per patient will depend on the dosing recommendation of the IDMC.

Arm title	Placebo repeat dose

Arm description:

Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. 42 or 84 capsules will be dispensed either directly to the patient or to a member of the trial team to then pass on to the patient. The number of capsules dispensed per patient will depend on the dosing recommendation of the IDMC.

Arm title	Racecadotril single dose

Arm description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

Arm type	Experimental
Investigational medicinal product name	Racecadotril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In Step1a patients will receive a single dose of racecadotril 100 mg p.o. Racecadotril will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).
After 6 patients have been randomised and completed step 1a, the IDMC will review their results and decide if the dose can be escalated to 200 mg. In Step1b patients will receive a single dose of racecadotril, either 100 mg or 200mg p.o. Racecadotril will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).

Arm title	Placebo single dose

Arm description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

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

Dosage and administration details:

In Step1a patients will receive a single dose of Placebo. Placebo will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After 6 patients have been randomised and completed step 1a, the IDMC will review their results. In Step1b patients will receive a single dose of Placebo. Placebo will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).

Number of subjects in period 1	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose
Started	5	3	9
Completed	5	3	9

Number of subjects in period 1	Placebo single dose
Started	4
Completed	4

Period 2

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

Blinding implementation details:

Blinding will be maintained using a placebo matched in appearance to racecadotril. All trial medication dispensed will have identical outer packaging to preserve the blind. The outer packaging will be labelled in compliance with clinical trial regulations, and will also contain a patient identification code which is given when the patient is randomised. On completion of the trial prescription, only the patient trial identification code will be used to identify the medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Racecadotril repeat dose

Arm description:

This step will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1.

Arm type	Experimental
Investigational medicinal product name	Racecadotril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

This step will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1. 42 or 84 capsules will be dispensed either directly to the patient or to a member of the trial team to then pass on to the patient. The number of capsules dispensed per patient will depend on the dosing recommendation of the IDMC.

Arm title	Placebo repeat dose

Arm description:

This step will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days.

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

Dosage and administration details:

This step will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. 42 or 84 capsules will be dispensed either directly to the patient or to a member of the trial team to then pass on to the patient. The number of capsules dispensed per patient will depend on the dosing recommendation of the IDMC.

Arm title	Racecadotril single dose

Arm description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

Arm type	Experimental
Investigational medicinal product name	Racecadotril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In Step1a patients will receive a single dose of racecadotril 100 mg p.o. Racecadotril will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).
After 6 patients have been randomised and completed step 1a, the IDMC will review their results and decide if the dose can be escalated to 200 mg. In Step1b patients will receive a single dose of racecadotril, either 100 mg or 200mg p.o. Racecadotril will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).

Arm title	Placebo single dose

Arm description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

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

Dosage and administration details:

In Step1a patients will receive a single dose of Placebo. Placebo will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).
After 6 patients have been randomised and completed step 1a, the IDMC will review their results. In Step1b patients will receive a single dose of Placebo. Placebo will be co-administered concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.).

Number of subjects in period 2	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose
Started	5	3	9
Completed	5	3	9

Number of subjects in period 2	Placebo single dose
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Racecadotril repeat dose
Reporting group description:	
Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1.	
Reporting group title	Placebo repeat dose
Reporting group description:	
Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days.	
Reporting group title	Racecadotril single dose
Reporting group description:	
Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.	
Reporting group title	Placebo single dose
Reporting group description:	
Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.	

Reporting group values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose
Number of subjects	5	3	9
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	0	6
From 65-84 years	3	3	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	69	67	57
standard deviation	± 7	± 3	± 14
Gender categorical Units: Subjects			
Female	5	2	6
Male	0	1	3

Plasma atrial natriuretic peptide (ANP)(nM)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: nM			
geometric mean	0.16	0.2	0.076
standard deviation	± 1.79	± 1.08	± 1.90
Diastolic blood pressure (DBP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	70	73	72
standard deviation	± 1.22	± 1.36	± 1.17
Systolic blood pressure (SBP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	121	115	122
standard deviation	± 1.13	± 1.17	± 1.13
Mean arterial pressure (MAP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	88	87	89
standard deviation	± 1.17	± 1.27	± 1.13
Pulmonary vascular resistance (PVR)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: dynes.sec/cm^5			
geometric mean	0	0	469
standard deviation	± 0	± 0	± 1.38
Mean Pulmonary artery wedge pressure (PAWP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	0	0	11.2
standard deviation	± 0	± 0	± 1.17
Cyclic guanosine-3',5'-monophosphate (cGMP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: nM			
geometric mean	13	58	16.8
standard deviation	± 4.55	± 1.62	± 2.66

Reporting group values	Placebo single dose	Total	
Number of subjects	4	21	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	10	
From 65-84 years	2	11	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	58		
standard deviation	± 10	-	
Gender categorical Units: Subjects			
Female	4	17	
Male	0	4	
Plasma atrial natriuretic peptide (ANP)(nM)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: nM			
geometric mean	0.114		
standard deviation	± 1.45	-	
Diastolic blood pressure (DBP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	76		
standard deviation	± 1.15	-	
Systolic blood pressure (SBP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	133		
standard deviation	± 1.12	-	
Mean arterial pressure (MAP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	96		
standard deviation	± 1.13	-	
Pulmonary vascular resistance (PVR)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: dynes.sec/cm^5			
geometric mean	550		

standard deviation	± 1.39	-	
Mean Pulmonary artery wedge pressure (PAWP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: mmHg			
geometric mean	10.2		
standard deviation	± 1.46	-	
Cyclic guanosine-3',5'-monophosphate (cGMP)			
Here we report the geometric standard deviation, the exponent of the estimated standard deviation of the log-quantity, as the confidence intervals reported for this study were based on the assumption that the quantity was log-normally distributed.			
Units: nM			
geometric mean	41.3		
standard deviation	± 1.93	-	

End points

End points reporting groups

Reporting group title	Racecadotril repeat dose

Reporting group description:

Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1.

Reporting group title	Placebo repeat dose

Reporting group description:

Step 2 will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days.

Reporting group title	Racecadotril single dose

Reporting group description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

Reporting group title	Placebo single dose

Reporting group description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

Reporting group title	Racecadotril repeat dose

Reporting group description:

This step will be 12-14 day repeat-dosing. Patients will receive a dose of racecadotril either 100 mg or 200mg p.o. t.i.d. concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days. The dose of racecadotril for step 2 will be determined by the IDMC following step 1.

Reporting group title	Placebo repeat dose

Reporting group description:

This step will be 12-14 day repeat-dosing. Patients will receive a dose of Placebo concurrently with sildenafil (20-100 mg; p.o.; t.i.d.), or tadalafil (20-40 mg; p.o./o.d.), for 12 or 13 or 14 days.

Reporting group title	Racecadotril single dose

Reporting group description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

Reporting group title	Placebo single dose

Reporting group description:

Six patients will be randomised 2:1 100mg racecadotril to placebo, concurrently with sildenafil (20-100 mg; p.o.) or tadalafil (20-40 mg; p.o./o.d.). After six patients have been recruited to and completed step 1a data will be reviewed by the IDMC to determine the dose to be used in step 1b. Six patients will be randomised 2:1 to either 100 mg or 200 mg p.o. racecadotril to placebo, concurrently with sildenafil (20-100mg; p.o) or tadalafil (20-40 mg; p.o./o.d.). The dose will depend on the results of the IDMC review in step 1a.

Primary: Step 1 - Maximum percentage change from baseline in ANP

End point title	Step 1 - Maximum percentage change from baseline in ANP

End point description:

The maximum percentage change in the log transformed ANP post baseline between the two treatments (racecadotril - placebo).

End point type	Primary

End point timeframe:

Value at the time of the maximum change from baseline

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[1]	0[2]	9	4
Units: nM				
geometric mean (confidence interval 95%)	(to)	(to)	79 (6 to 203)	-9 (-63 to 121)

Notes:

[1] - N/A

[2] - N/A

End point values	Racecadotril single dose	Placebo single dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: nM				
geometric mean (confidence interval 95%)	(to)	(to)		

Notes:

[3] - N/A

[4] - N/A

Statistical analyses

Statistical analysis title	Primary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed ANP post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31
upper limit	235

Primary: Step 2 - Percentage change in ANP from baseline

End point title	Step 2 - Percentage change in ANP from baseline
End point description:	
The percentage change in log transformed ANP at end of treatment.	
End point type	Primary
End point timeframe:	
14 days from baseline.	

End point values	Racecadotril repeat dose	Placebo repeat dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: nM				
geometric mean (confidence interval 95%)	19 (-18 to 73)	-15 (-69 to 128)		

Statistical analyses

Statistical analysis title	Primary outcome analysis
Statistical analysis description:	
Linear regression model is used to estimate the difference in percentage change in ANP between the two treatments (Racecadotril - placebo) at the end of treatment, adjusting for baseline values.	
Comparison groups	Racecadotril repeat dose v Placebo repeat dose
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23
upper limit	187

Secondary: Step 1 - Maximum percentage change from baseline in DBP

End point title	Step 1 - Maximum percentage change from baseline in DBP[5]
End point description:	
The maximum percentage change in the log transformed DBP post baseline between the two treatments.	

End point type	Secondary

End point timeframe:

Value at the time of the maximum change from baseline.

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: For repeat dosing the end point is only measured at a single time hence no maximum percentage change.

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	9	4
Units: mmHg				
geometric mean (confidence interval 95%)	(to)	(to)	-24 (-37 to -9)	-16 (-60 to 74)

Notes:

[6] - N/A

[7] - N/A

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed DBP post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42
upper limit	29

Secondary: Step 1 - Maximum percentage change from baseline in SBP

End point title	Step 1 - Maximum percentage change from baseline in SBP[8]

End point description:

The maximum change in the log transformed SBP post baseline between the two treatments.

End point type	Secondary

End point timeframe:

Value at the time of the maximum change from baseline.

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: For repeat dosing the end point is only measured at a single time hence no maximum percentage change.

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[9]	0[10]	9	4
Units: mmHg				
geometric mean (confidence interval 95%)	(to)	(to)	-15 (-25 to -3)	-6 (-54 to 94)

Notes:

[9] - N/A

[10] - N/A

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed SBP post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	-20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43
upper limit	13

Secondary: Step 1 - Maximum percentage change from baseline in MAP

End point title	Step 1 - Maximum percentage change from baseline in MAP[11]

End point description:

The maximum percentage change in the log transformed MAP post baseline between the two treatments.

End point type	Secondary

End point timeframe:

Value at the time of the maximum change from baseline.

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: For repeat dosing the end point is only measured at a single time hence no maximum percentage change.

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[12]	0[13]	9	4
Units: mmHg				
geometric mean (confidence interval 95%)	(to)	(to)	-20 (-29 to -10)	-14 (-55 to 66)

Notes:

[12] - N/A

[13] - N/A

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed MAP post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	22

Secondary: Step 1 - Maximum percentage change from baseline in PVR

End point title	Step 1 - Maximum percentage change from baseline in PVR[14]

End point description:

The maximum percentage change in the log transformed PVR post baseline between the two treatments.

End point type	Secondary

End point timeframe:

Value at the time of the maximum change

Notes:

[14] - 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: For repeat dosing the end point is only measured at a single time hence no maximum percentage change.

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[15]	0[16]	9	4
Units: dynes.sec/cm5				
geometric mean (confidence interval 95%)	(to)	(to)	-14 (-23 to -3)	-7 (-31 to 24)

Notes:

[15] - N/A

[16] - N/A

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed PVR post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25
upper limit	17

Secondary: Step 1 - Maximum percentage change from baseline in PAWP

End point title	Step 1 - Maximum percentage change from baseline in

End point description:

The maximum percentage change in the log transformed PAWP post baseline between the two treatments.

End point type	Secondary

End point timeframe:

Value at the time of maximum change from baseline.

Notes:

[17] - 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: For repeat dosing the end point is only measured at a single time hence no maximum percentage change.

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[18]	0[19]	9	4
Units: mmHg				
geometric mean (confidence interval 95%)	(to)	(to)	-19 (-38 to 4)	24 (-25 to 105)

Notes:

[18] - N/A

[19] - N/A

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed PAWP post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model
adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	-33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55
upper limit	2

Secondary: Step 2 - Percentage change in DBP from baseline

End point title	Step 2 - Percentage change in DBP from baseline

End point description:

The percentage change in log transformed DBP at end of treatment.

End point type	Secondary

End point timeframe:

14 days from baseline.

End point values	Racecadotril repeat dose	Placebo repeat dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: mmHg				
geometric mean (confidence interval 95%)	-4 (-19 to 13)	-10 (-56 to 83)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression model is used to estimate the difference in the percentage change in DBP between the two treatments (Racecadotril - placebo) at the end of treatment, adjusting for baseline values.	
Comparison groups	Racecadotril repeat dose v Placebo repeat dose
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	28

Secondary: Step 2 - Percentage change in SBP from baseline

End point title	Step 2 - Percentage change in SBP from baseline
End point description:	
The percentage change in log transformed SBP at end of treatment.	
End point type	Secondary
End point timeframe:	
14 days from baseline.	

End point values	Racecadotril repeat dose	Placebo repeat dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: mmHg				
geometric mean (confidence interval 95%)	-4 (-24 to 19)	-10 (-42 to 41)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

Linear regression model is used to estimate the difference in the percentage change in SBP between the two treatments (Racecadotril - placebo) at the end of treatment, adjusting for baseline values.

Comparison groups	Racecadotril repeat dose v Placebo repeat dose
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	46

Secondary: Step 2 - Percentage change in HR from baseline

End point title	Step 2 - Percentage change in HR from baseline

End point description:

The percentage change in log HR at end of treatment.

End point type	Secondary

End point timeframe:

14 days from baseline.

End point values	Racecadotril repeat dose	Placebo repeat dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: BPM				
geometric mean (confidence interval 95%)	24 (5 to 46)	-7 (-38 to 40)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

Linear regression model is used to estimate the difference in the percentage change in HR between the two treatments (Racecadotril - placebo) at the end of treatment, adjusting for baseline values.

Comparison groups	Racecadotril repeat dose v Placebo repeat dose

Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	74

Secondary: Step 2 - Percentage change in MAP from baseline

End point title	Step 2 - Percentage change in MAP from baseline
End point description:	
The percentage change in log transformed MAP at end of treatment.	
End point type	Secondary
End point timeframe:	
14 days from baseline.	

End point values	Racecadotril repeat dose	Placebo repeat dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: mmHg				
geometric mean (confidence interval 95%)	-4 (-21 to 16)	-10 (-50 to 61)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression model is used to estimate the difference in the percentage change in MAP between the two treatments (Racecadotril - placebo) at the end of treatment, adjusting for baseline values.	
Comparison groups	Racecadotril repeat dose v Placebo repeat dose
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	31

Secondary: Step 2 - Percentage change in cGMP from baseline

End point title	Step 2 - Percentage change in cGMP from baseline
End point description:	
The percentage change in log transformed cGMP at the end of treatment.	
End point type	Secondary
End point timeframe:	
14 days from baseline.	

End point values	Racecadotril repeat dose	Placebo repeat dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: nM				
geometric mean (confidence interval 95%)	34 (-64 to 395)	-51 (-92 to 193)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression model is used to estimate the difference in the percentage change in cGMP between the two treatments (Racecadotril - placebo) at the end of treatment, adjusting for baseline values.	
Comparison groups	Racecadotril repeat dose v Placebo repeat dose
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-79
upper limit	871

Secondary: Step 1 - Maximum percentage change from baseline in cGMP

End point title	Step 1 - Maximum percentage change from baseline in cGMP[20]

End point description:

The maximum percentage change in the log transformed cGMP post baseline between the two treatments.

End point type	Secondary

End point timeframe:

Value at the time of the maximum change from baseline.

Notes:

[20] - 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: For repeat dosing the end point is only measured at a single time hence no maximum percentage change.

End point values	Racecadotril repeat dose	Placebo repeat dose	Racecadotril single dose	Placebo single dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[21]	0[22]	9	4
Units: nM				
geometric mean (confidence interval 95%)	(to)	(to)	98 (-4 to 308)	-53 (-89 to 110)

Notes:

[21] - N/A

[22] - N/A

Statistical analyses

Statistical analysis title	Secondary outcome analysis

Statistical analysis description:

The maximum percentage change in the log transformed cGMP post baseline between the two treatments (racecadotril - placebo) together with a two-sided 95% CI was estimated using a linear regression model adjusted for baseline values.

Comparison groups	Racecadotril single dose v Placebo single dose
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Regression, Linear
Parameter estimate	Geometric Mean Difference
Point estimate	166
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	861

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to end of treatment.	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4
Reporting groups	
Reporting group title	Racecadotril single dose
Reporting group description: -	
Reporting group title	Racecadotril repeat dose
Reporting group description: -	
Reporting group title	Placebo repeat dose
Reporting group description: -	
Reporting group title	Placebo single dose
Reporting group description: -	

Serious adverse events	Racecadotril single dose	Racecadotril repeat dose	Placebo repeat dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		

Serious adverse events	Placebo single dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Racecadotril single dose	Racecadotril repeat dose	Placebo repeat dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	4 / 5 (80.00%)	1 / 3 (33.33%)
Vascular disorders			

Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	0 / 9 (0.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
All over body cramps			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Stomach pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo single dose		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
Vascular disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
All over body cramps			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Stomach pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	 0 / 4 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2013	Protocol updated to v3.0 with the following: Tiorfan (racecadotril) becoming licensed in the UK (doses added); addition of Patients taking ACE inhibitors to the exclusion criteria; update to how the placebo is matched to racecadotril to maintain the blind; the investigator being able to unblind without the involvement of the sponsor; updates to the processing of SUSARs; allowance for not all IMP and/or containers being returned; clarification of assessment schedules.
15 August 2014	Protocol updated to v4.0 with the following: inclusion of patients on tadalafil (addition) or sildenafil (original); time window for the right heart catheter measurements increase; allowance for replacement participants if needed; updated SmPC for Tiorfan 100mg capsule and Adcirca 20 mg film coated tablets; clarifications throughout.
20 January 2015	Protocol updated to v5.0 with clarifications to possible study processes following the step 1a IDMC data review and the transition from step 1b to step 2 with other clarifications throughout.
27 May 2015	Protocol updated to v6.0 with the following: recruitment stop for the IDMC to review step 1a and step 1b data at the end of step 1b; an update to data review criteria; allowance for IMP to be allocated (but not administered) before eligibility is confirmed; clarifications throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

For repeat dosing the end point is only measured at a single time hence no maximum percentage change. Repeat dosing arms did not measure PVR and PAWP - '0' has been entered as summary measures.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30761523