Clinical trial results:
Serelaxin To Lower Portal Pressure in Patients with Cirrhosis and Portal Hypertension (STOPP)

Summary

EudraCT number	2015-004031-12
Trial protocol	GB
Global end of trial date	31 August 2018

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020
Summary attachment (see zip file)	Clinical Study Report (STOPP Clinical Study Report_27Feb2019.pdf)

Trial information

Trial identification

Sponsor protocol code	AC15007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02669875
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD (Academic and Clinical Central Office for Research and Development for NHS Lothian/University of Edinburgh)
Sponsor organisation address	Queen's Medical Research Institute, Edinburgh BioQuarter, 47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Professor Jonathan Fallowfield, University of Edinburgh, 44 01312426589, Jonathan.Fallowfield@ed.ac.uk
Scientific contact	Professor Jonathan Fallowfield, University of Edinburgh, 44 01312426589, Jonathan.Fallowfield@ed.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	31 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2018
Global end of trial reached?	Yes
Global end of trial date	31 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that 2 hours treatment with serelaxin through a drip reduces the portal pressure in patients with liver cirrhosis and high blood pressure in the portal vein.

Protection of trial subjects:

We offered participants the option of a small dose of sedative (midazolam) prior to insertion of the femoral venous catheter.
Fluoroscopic (x-ray) screening was kept to an absolute minimum (catheter positioning only).
We used a non-invasive method to measure cardiac output so did not need to pass a catheter into the heart, thus obviating the risk of cardiac arrhythmias associated with right atrial pressure measurement.

Background therapy: -

Evidence for comparator:

The small placebo control arm was included to allow double-blindness (not as a comparison group) and to help generate valuable information for designing a future larger randomised controlled trial.

Actual start date of recruitment	19 October 2017
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	15
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single-site study, undertaken at the Royal Infirmary of Edinburgh (Edinburgh, UK) between 19th October 2017 and 31st August 2018.

Pre-assignment

Screening details:

A total of 17 participants were screened. Of these, 2 had a screening failure and did not proceed to randomisation. Fifteen patients were randomised and 11 completed the trial (n=9 serelaxin, n=2 placebo). Reasons for withdrawal were baseline HVPG <10 mmHg (n=2) and technical failure (n=2).

Period 1

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

Blinding implementation details:

Both treatments were prepared to be similar in appearance, colour, and organoleptic properties. The procedures for emergency unblinding complied with the European Clinical Trials Directive 2001/20/EC (EUCTD).

Arms

Arm title	Serelaxin

Arm description:

Recombinant human relaxin-2 (serelaxin (Novartis Pharmaceuticals, UK)) administered via peripheral i.v. infusion.

Arm type	Experimental
Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	recombinant human relaxin-2
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

80 µg/kg/day for 60 min followed by 30 µg/kg/day for at least 60 min. This was achieved by a single infusion bag with a change in the administration rate.

Number of subjects in period 1[1]	Serelaxin
Started	11
Completed	9
Not completed	2
Technical failure with HVPG	1
Stop/go if HVPG < 10mmHg	1

Notes:

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

Justification: The primary outcome relates to the change at 2 hours in the treated group; the placebo group was included only to help maintain the blind (investigators could not be confident that a treatment had been received) and to provide a background rate of adverse events

Baseline characteristics

Reporting groups	
Reporting group title	Serelaxin
Reporting group description:	
Recombinant human relaxin-2 (serelaxin (Novartis Pharmaceuticals, UK)) administered via peripheral i.v. infusion.	

Reporting group values	Serelaxin	Total	
Number of subjects	11	11	
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			
Male or female adult subjects over 18 years of age			
Units: years			
arithmetic mean	56		
standard deviation	± 7.8	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	8	8	
MELD score Units: interger			
arithmetic mean	10		
full range (min-max)	6 to 14	-	

End points

End points reporting groups

Reporting group title	Serelaxin
Reporting group description:	
Recombinant human relaxin-2 (serelaxin (Novartis Pharmaceuticals, UK)) administered via peripheral i.v. infusion.	
Subject analysis set title	Baseline HVPG
Subject analysis set type	Per protocol
Subject analysis set description:	
The primary endpoint was the change from baseline in fasting hepatic venous pressure gradient (HVPG) after 2 hr serelaxin infusion. No formal comparison will be made between treatment and placebo.	
Subject analysis set title	2h HVPG following serelaxin
Subject analysis set type	Per protocol
Subject analysis set description:	
value at 2 hours	

Primary: HVPG

End point title	HVPG
End point description:	
End point type	Primary
End point timeframe:	
The primary outcome is to examine if the baseline to 2 hr change in fasting hepatic venous pressure gradient (HVPG) is a clinically significant one.	

End point values	Serelaxin	Baseline HVPG	2h HVPG following serelaxin	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[1]	9	9	
Units: mmHg				
arithmetic mean (standard deviation)	15.6 (± 4.3)	15.9 (± 3.3)	15.6 (± 4.3)	

Notes:

[1] - data for end of trial reported here

Attachments (see zip file)	Figure2HVPG.pdf

Statistical analyses

Statistical analysis title	paired t-test
Comparison groups	Baseline HVPG v 2h HVPG following serelaxin

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	3.1
Variability estimate	Standard deviation
Dispersion value	3.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Adverse event reporting additional description:

Safety assessments included collection of adverse events (AE), clinical examination, vital signs, laboratory tests and electrocardiograms (ECGs). Both the severity of AEs and relation to study medication treatment was collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Serelaxin

Reporting group description:

Recombinant human relaxin-2 (serelaxin (Novartis Pharmaceuticals, UK)) administered via peripheral i.v. infusion.

Reporting group title	Placebo

Reporting group description:

Placebo for serelaxin

Serious adverse events	Serelaxin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Serelaxin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	1 / 2 (50.00%)	
Vascular disorders			
Arterial puncture	Additional description: mild bruising; no serious sequelae		
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Syncope	Additional description: Syncopal episode on inserting venflons or catheters		

subjects affected / exposed	2 / 9 (22.22%)	0 / 2 (0.00%)	
occurrences (all)	5	0	
Hypotension	Additional description: diastolic - transient, asymptomatic, resolved spontaneously		
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Conduction disorder	Additional description: Prolonged QTc - transient, asymptomatic, resolved spontaneously		
subjects affected / exposed	2 / 9 (22.22%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea	Additional description: Non infectious, no bloody, spontaneously resolved		
subjects affected / exposed	0 / 9 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Abdominal discomfort	Additional description: mild right upper quadrant ache - resolved spontaneously		
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Liver function test increased	Additional description: bilirubin - mild, spontaneously resolved		
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess	Additional description: dental		
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2016	The amendment related to a protocol update. The PIS and consent were updated in-line with the changes. There was also the addition of new documents (Female Partner Information Sheet and Consent plus the GP letter).

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.

The study was terminated before the recruitment target was met due to a global drug supply issue (Novartis stopped manufacturing serelaxin and there was none available with a shelf-life beyond 31st August 2018). Therefore, the study was underpowered.

Notes: