Clinical trial results:
Single-center, randomized, double-blind, placebo-controlled clinical trial for the safety, tolerability and efficacy of ularitide in cirrhosis patients with refractory ascites.

Summary

EudraCT number	2019-002268-28
Trial protocol	DK
Global end of trial date	14 December 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2024
First version publication date	15 July 2024

Trial information

Trial identification

Sponsor protocol code	ULA04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04311489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Clinical Trials Information, Department of Hepatology and Gastroenterology, Aarhus University Hospital, henngroe@rm.dk
Scientific contact	Clinical Trials Information, Department of Hepatology and Gastroenterology, Aarhus University Hospital, henngroe@rm.dk

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	Interim
Date of interim/final analysis	28 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2022
Global end of trial reached?	Yes
Global end of trial date	14 December 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety, tolerability and efficacy of ularitide on the renal response in patients with liver cirrhosis and refractory ascites (as defined in this protocol) for a maximum exposure duration of 48 hours, through a randomized, placebo-controlled, double-blind, single-center clinical trial.

Protection of trial subjects:

Standard of care and treatment during hospitalization at a highly specialized hepatology department.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2020
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	Denmark: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	7
From 65 to 84 years	9
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Single-center study at the Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark. Participants were recruited from August 2020 to November 2022.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	19[1]
Intermediate milestone: Number of subjects	Included: 19
Intermediate milestone: Number of subjects	Randomized: 17
Number of subjects completed	17

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2 patients were included but failed to reach the stage of randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ularitide

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	Ularitide
Investigational medicinal product code	
Other name	Urodilatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The first eight participants were treated with a starting dose of 30 ng/kg/min with a possibility for a dose increase to 45 ng/kg/min or a reduction to 15 ng/kg/min. The last nine participants were treated with a dosing regimen reduced by one-third compared with the original regimen, i.e., a starting dose of 20 ng/kg/min, a possible dose increase to 30 ng/kg/min, and a safety dose reduction to 10 ng/kg/min.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	Ularitide
Investigational medicinal product code	
Other name	Urodilatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The first eight participants were treated with a starting dose of 30 ng/kg/min with a possibility for a dose increase to 45 ng/kg/min or a reduction to 15 ng/kg/min. The last nine participants were treated with a dosing regimen reduced by one-third compared with the original regimen, i.e., a starting dose of 20 ng/kg/min, a possible dose increase to 30 ng/kg/min, and a safety dose reduction to 10 ng/kg/min.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo consists of mannitol and is supplied as a lyophilized powder. Reconstitution and dissolution in sterile saline is identical to the active treatment.

Number of subjects in period 1	Ularitide	Placebo
Started	11	6
Baseline	11	6
2 hours treatment	11	6
4 hours treatment	11	6
24 hours treatment	10 [2]	6
48 hours treatment	1 [3]	3 [4]
4 hours post-treatment follow-up	11	6
Completed	11	6

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not an issue.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not an issue.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not an issue.

Period 2

Period 2 title	30 day follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ularitide

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	Ularitide
Investigational medicinal product code	
Other name	Urodilatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The first eight participants were treated with a starting dose of 30 ng/kg/min with a possibility for a dose increase to 45 ng/kg/min or a reduction to 15 ng/kg/min. The last nine participants were treated with a dosing regimen reduced by one-third compared with the original regimen, i.e., a starting dose of 20 ng/kg/min, a possible dose increase to 30 ng/kg/min, and a safety dose reduction to 10 ng/kg/min.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Ularitide
Investigational medicinal product code	
Other name	Urodilatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The first eight participants were treated with a starting dose of 30 ng/kg/min with a possibility for a dose increase to 45 ng/kg/min or a reduction to 15 ng/kg/min. The last nine participants were treated with a dosing regimen reduced by one-third compared with the original regimen, i.e., a starting dose of 20 ng/kg/min, a possible dose increase to 30 ng/kg/min, and a safety dose reduction to 10 ng/kg/min.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo consists of mannitol and is supplied as a lyophilized powder. Reconstitution and dissolution in sterile saline is identical to the active treatment.

Number of subjects in period 2	Ularitide	Placebo
Started	11	6
Completed	11	6

Baseline characteristics

Reporting groups	
Reporting group title	Ularitide
Reporting group description: Active treatment	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Ularitide	Placebo	Total
Number of subjects	11	6	17
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	70	55	
inter-quartile range (Q1-Q3)	60 to 77	53 to 68	-
Gender categorical Units: Subjects			
Female	4	2	6
Male	7	4	11
Cirrhosis etiologies Units: Subjects			
Alcohol	6	4	10
MAFLD	1	0	1
Alcohol + MAFLD	1	1	2
PSC	1	0	1
Toxic	1	0	1
Budd-Chiari	0	1	1
Cryptogenic	1	0	1
Refractory ascites characteristics Units: Subjects			
Diuretic-intractable	8	4	12
Diuretic-resistant	3	2	5
Height Units: centimetre			
median	174	174	

inter-quartile range (Q1-Q3)	163 to 178	170 to 174	-
Body weight			
Units: kilogram(s)			
median	78	73	
inter-quartile range (Q1-Q3)	63 to 85	68 to 83	-
Cirrhosis debut			
Time since debut of cirrhosis			
Units: months			
median	25	24	
inter-quartile range (Q1-Q3)	9 to 47	9 to 65	-
Ascites debut			
Time since debut of ascites			
Units: months			
median	20	27	
inter-quartile range (Q1-Q3)	4 to 47	9 to 65	-
Refractory ascites debut			
Time since debut of refractory ascites			
Units: months			
median	5	7	
inter-quartile range (Q1-Q3)	2 to 6	6 to 12	-
Systolic blood pressure			
Units: mmHg			
median	116	111	
inter-quartile range (Q1-Q3)	106 to 135	102 to 123	-
Diastolic blood pressure			
Units: mmHg			
median	66	69	
inter-quartile range (Q1-Q3)	54 to 79	62 to 78	-
Heart rate			
Units: beats/min			
median	85	82	
inter-quartile range (Q1-Q3)	66 to 93	76 to 94	-
P-albumin			
Units: gram(s)/litre			
median	30	27	
inter-quartile range (Q1-Q3)	29 to 30	22 to 30	-
P-bilirubin			
Units: micromole(s)/litre			
median	23	22	
inter-quartile range (Q1-Q3)	16 to 60	14 to 33	-
P-ALAT			
alanine aminotransferase			
Units: U/l			
median	24	30	
inter-quartile range (Q1-Q3)	18 to 62	14 to 45	-
P-alkaline phosphatase			
Units: U/l			
median	154	135	
inter-quartile range (Q1-Q3)	102 to 256	115 to 220	-
INR			
international normalized ratio			
Units: ratio			

median	1.3	1.3	
inter-quartile range (Q1-Q3)	1.3 to 1.5	1.2 to 1.6	-
P-sodium			
Units: millimole(s)/litre			
median	133	130	
inter-quartile range (Q1-Q3)	129 to 135	123 to 132	-
P-potassium			
Units: millimole(s)/litre			
median	4.2	4.6	
inter-quartile range (Q1-Q3)	3.9 to 4.4	3.8 to 5.2	-
P-creatinine			
Units: micromole(s)/litre			
median	103	100	
inter-quartile range (Q1-Q3)	77 to 118	61 to 117	-
B-platelets			
Units: x10^9			
median	97	227	
inter-quartile range (Q1-Q3)	85 to 186	74 to 326	-
B-hemoglobin			
Units: millimole(s)/litre			
median	6.9	6.8	
inter-quartile range (Q1-Q3)	6.2 to 8.1	6.4 to 7.0	-
Child-Pugh score			
Units: points			
median	8	9	
inter-quartile range (Q1-Q3)	8 to 10	8 to 10	-
MELD-Na			
Model for end-stage liver disease with sodium			
Units: points			
median	21	23	
inter-quartile range (Q1-Q3)	14 to 26	21 to 29	-
MELD 3.0			
model for end-stage liver disease version 3.0			
Units: points			
median	18	21	
inter-quartile range (Q1-Q3)	14 to 21	17 to 22	-
P-renin			
Units: x10^-3 IU/l			
median	550	550	
inter-quartile range (Q1-Q3)	183 to 550	240 to 550	-
P-aldosterone			
Units: pmol/l			
median	3432	8532	
inter-quartile range (Q1-Q3)	2388 to 9777	3533 to 9781	-
U-sodium			
urine			
Units: millimole(s)/litre			
median	16	13	
inter-quartile range (Q1-Q3)	10 to 27	9 to 17	-
U-sodium excretion rate			
urine			
Units: mmol/day			

median	24	11	
inter-quartile range (Q1-Q3)	9 to 37	9 to 35	-
U-potassium			
urine			
Units: millimole(s)/litre			
median	32	32	
inter-quartile range (Q1-Q3)	23 to 46	24 to 41	-
U-potassium excretion rate			
urine			
Units: mmol/day			
median	32	39	
inter-quartile range (Q1-Q3)	26 to 44	12 to 57	-
U-creatinine			
urine			
Units: millimole(s)/litre			
median	6.7	7.5	
inter-quartile range (Q1-Q3)	4.4 to 9.2	6.4 to 10.3	-
U-creatinine excretion rate			
urine			
Units: mmol/day			
median	7.1	7.0	
inter-quartile range (Q1-Q3)	4.6 to 8.3	6.2 to 7.7	-
GFR-24h-creatinine-clearance			
Units: millilitre(s)/minute			
median	40	49	
inter-quartile range (Q1-Q3)	27 to 69	39 to 75	-
U-albumin			
urine			
Units: mg/day			
median	3	3	
inter-quartile range (Q1-Q3)	2 to 7	2 to 4	-
P-copeptin			
Precursor of vasopressin			
Units: pmol/l			
median	27.1	24.4	
inter-quartile range (Q1-Q3)	14.1 to 35.6	19.6 to 52.5	-

End points

End points reporting groups	
Reporting group title	Ularitide
Reporting group description: Active treatment	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Ularitide
Reporting group description: Active treatment	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Absolute urine production	
End point title	Absolute urine production
End point description: Change in urine volume production at 24 hours post infusion start versus baseline	
End point type	Primary
End point timeframe: 24 hours	

End point values	Ularitide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: ml/h				
arithmetic mean (confidence interval 95%)	-24.7 (-52.3 to 3.0)	6.2 (-17.6 to 30.0)		

Attachments (see zip file)	Figure 1 - paper.jpg

Statistical analyses

Statistical analysis title	Between-group analyses
Comparison groups	Ularitide v Placebo

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	68.3
Variability estimate	Standard error of the mean
Dispersion value	17.5

Statistical analysis title	Within-group: Ularitide
Comparison groups	Ularitide v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.04
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-24.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.3
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	12.2

Notes:

[1] - paired t-test

Primary: Absolute renal sodium excretion rate	
End point title	Absolute renal sodium excretion rate
End point description:	
Change in renal sodium excretion rate at 24 hours post infusion start versus baseline	
End point type	Primary
End point timeframe:	
24 hours	

End point values	Ularitide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: micromoles/min				
arithmetic mean (confidence interval 95%)	-21.8 (-61.9 to 18.4)	3.3 (-7.0 to 13.7)		

Statistical analyses

Statistical analysis title	Between-group analyses
Comparison groups	Ularitide v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.1
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	25.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.5
upper limit	65.7
Variability estimate	Standard error of the mean
Dispersion value	18.2

Notes:

[2] - unequal variance

Statistical analysis title	Within-group: Ularitide
Comparison groups	Ularitide v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.13
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.9
upper limit	18.4
Variability estimate	Standard error of the mean
Dispersion value	17.8

Notes:

[3] - paired t-test

Primary: Absolute body weight reduction

End point title	Absolute body weight reduction
End point description:	
Change of absolute body weight at the end of treatment versus baseline	
End point type	Primary
End point timeframe:	
End of treatment; most patients recieved 24 hours of treatment.	

End point values	Ularitide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	6		
Units: kilogram(s)				
arithmetic mean (confidence interval 95%)	-0.98 (-1.61 to -0.35)	-1.28 (-2.74 to 0.17)		

Statistical analyses

Statistical analysis title	Between-group analyses
Comparison groups	Ularitide v Placebo
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.56

Primary: Number of treatment responders

End point title	Number of treatment responders[4]
End point description:	
Responder as predefined in the study protocol.	
End point type	Primary
End point timeframe:	
During the whole treatment course	

Notes:

[4] - 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: A statistical analysis is irrelevant here.

End point values	Ularitide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	6		
Units: number				
Responder	3	3		
Non-responder	8	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to post-treatment follow-up (de facto while hospitalized).
SAE's were collected from inclusion until the 30-day follow-up visit.

Adverse event reporting additional description:

All adverse events were collected and reported by study investigators.
The incidence of stopping criteria leading to a dose reduction was higher in ularitide than placebo (p = 0.043). The incidence rate of adverse reactions was higher in ularitide than placebo, with an IRR of 8.5 (95% CI: 2.0 – 35, p = 0.003).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Ularitide

Reporting group description:

Active treatment

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Ularitide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)	5 / 6 (83.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haemoconcentration	Additional description: Hemoconcentration (10019479)		
subjects affected / exposed	2 / 11 (18.18%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Hypotension (10021097)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Upper abdominal discomfort (10067000)		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis	Additional description: Hemoptysis (10019523)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Decompensated cirrhosis	Additional description: Decompensated cirrhosis (10064704)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Peritonitis bacterial	Additional description: Spontaneous bacterial peritonitis (10061135)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia (10035664)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection (10021789)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia	Additional description: Hyperkalaemia (10020646)		
subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ularitide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	3 / 6 (50.00%)	
Cardiac disorders			
Hypotension	Additional description: Blood pressure systolic low (10005763)		
subjects affected / exposed	2 / 11 (18.18%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Tachycardia	Additional description: Tachycardia (10043071)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Presyncope	Additional description: Pre-syncope (10036507)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Syncope	Additional description: Syncope (10042772)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Headache	Additional description: Headaches (10019231)		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemoglobin decreased	Additional description: Hemoglobin low (10055600)		
subjects affected / exposed	0 / 11 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Dizziness	Additional description: Dizziness (10013573)		

subjects affected / exposed	6 / 11 (54.55%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			
Vomiting	Additional description: Vomiting (10047700)		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 11 (54.55%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Nausea	Additional description: Nausea and vomiting symptoms (10028817)		
subjects affected / exposed	3 / 11 (27.27%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Appetite disorder	Additional description: Appetite suppressed (10003030)		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 11 (18.18%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Diarrhoea	Additional description: Diarrhoea (10012735)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic enzyme increased	Additional description: Hepatic enzyme increased (10060795)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Albuminuria	Additional description: Albuminuria (10001580)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Creatinine renal clearance increased	Additional description: Creatinine blood increased (10011361)		
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle pain	Additional description: Muscle pains (10028323)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Muscle spasms	Additional description: Muscle spasms (10028334)		
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 6 (0.00%) 0	
Metabolism and nutrition disorders			
Hyperkalaemia	Additional description: Hyperkalaemia (10020646)		
subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 6 (16.67%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2021	After treatment of the first eight participants: A high rate of hypotensive episodes was observed, likely influencing the renal efficacy measures. The overall treatment algorithm persisted but with all three dose steps reduced by one-third and incorporation of safety precautions at each status time point to supplement the efficacy criteria determining a dose increase.
21 November 2022	After treatment of the first 17 participants: The study investigators observed a persistent high level of adverse reactions and had a clinical impression of sparse renal effects regardless of the new dose regimen. Therefore, a hired external biostatistician performed an unblinded interim analysis to determine if further reduction of the dose scheme or trial termination should be performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 December 2022	After completing 17 participants, the interim analysis demonstrated that ularitide was neither safe nor better than placebo as a treatment of refractory cirrhotic ascites with the setup and doses used. Therefore, the trial was terminated and unblinded to permit further investigations of the efficacy endpoints and safety measures, as well as subgroup analysis on the different dose regimens.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38934679