



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