Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomized, Multicenter, Phase 2 Study Assessing the Safety, Tolerability and Efficacy of IONIS-AGT-LRX, an Antisense Inhibitor of Angiotensinogen Production, Administered Subcutaneously Over 12 Weeks in Patients With Chronic Heart Failure With Reduced Ejection Fraction

Summary

EudraCT number	2020-005878-10
Trial protocol	HU PL
Global end of trial date	11 January 2023

Results information

Result version number	v1 (current)
This version publication date	20 December 2023
First version publication date	20 December 2023

Trial information

Trial identification

Sponsor protocol code	ISIS 757456-CS5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04836182
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 (760) 931-9200, globalregulatoryaffairs@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 (760) 931-9200, globalregulatoryaffairs@ionisph.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of this study is to evaluate the effect of AGT-LRX weekly subcutaneous (SC) injection on plasma angiotensinogen (AGT) concentration from baseline to study day 85 (Week 13) in subjects with chronic heart failure (HF) with reduced ejection fraction (rEF).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Poland: 48
Worldwide total number of subjects	72
EEA total number of subjects	53

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)	21

From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 19 investigational sites in the United States, Hungary, and Poland from 21 May 2021 to 11 January 2023.

Pre-assignment

Screening details:

Subjects with Crohn's disease were randomised to receive placebo, ISIS 757456 40 mg, ISIS 757456 80 mg, or ISIS 757456 120 mg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received AGT-LRX-matching placebo, subcutaneous (SC) injection once every week up to Day 78.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 757456-matching placebo, administered subcutaneously.

Arm title	AGT-LRX 40 mg

Arm description:

Subjects received AGT-LRX 40 mg, SC injection once every week up to Day 78.

Arm type	Experimental
Investigational medicinal product name	AGT-LRX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AGT-LRX 40 mg, administered subcutaneously.

Arm title	AGT-LRX 80 mg

Arm description:

Subjects received AGT-LRX 80 mg, SC injection once every week up to Day 78.

Arm type	Experimental

Investigational medicinal product name	AGT-LRX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AGT-LRX 80 mg, administered subcutaneously.

Arm title	AGT-LRX 120 mg

Arm description:

Subjects received AGT-LRX 120 mg, SC injection once every week up to Day 78.

Arm type	Experimental
Investigational medicinal product name	AGT-LRX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

AGT-LRX 120 mg, administered subcutaneously.

Number of subjects in period 1	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg
Started	21	12	26
Pharmacokinetic Set	0	12	26
Safety Set	20	12	26
Full Analysis Set	20	12	26
Per Protocol Set	17	9	19
Completed	19	10	21
Not completed	2	2	5
Voluntary Withdrawal	1	1	-
Investigator Judgement	-	-	1
Significant Protocol Deviation	-	-	1
Adverse event or Serious Adverse Event (SAE)	1	1	3

Number of subjects in period 1	AGT-LRX 120 mg
Started	13
Pharmacokinetic Set	13
Safety Set	13
Full Analysis Set	13
Per Protocol Set	13
Completed	13
Not completed	0
Voluntary Withdrawal	-
Investigator Judgement	-

Significant Protocol Deviation	-
Adverse event or Serious Adverse Event (SAE)	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received AGT-LRX-matching placebo, subcutaneous (SC) injection once every week up to Day 78.	
Reporting group title	AGT-LRX 40 mg
Reporting group description:	
Subjects received AGT-LRX 40 mg, SC injection once every week up to Day 78.	
Reporting group title	AGT-LRX 80 mg
Reporting group description:	
Subjects received AGT-LRX 80 mg, SC injection once every week up to Day 78.	
Reporting group title	AGT-LRX 120 mg
Reporting group description:	
Subjects received AGT-LRX 120 mg, SC injection once every week up to Day 78.	

Reporting group values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg
Number of subjects	21	12	26
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 ±	 67 ± 6	 67 ± 7
Gender categorical Units: Subjects			
Male	17	9	25
Female	4	3	1

Reporting group values	AGT-LRX 120 mg	Total	
Number of subjects	13	72	
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 70 ± 7	 -	
Gender categorical Units: Subjects			
Male	9	60	
Female	4	12	

Subject analysis sets	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received AGT-LRX-matching placebo, subcutaneous (SC) injection once every week up to Day 78.

Reporting group values	Placebo		
Number of subjects	20		
Age Categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	69		
standard deviation	± 8		
Gender categorical Units: Subjects			
Male			
Female			

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received AGT-LRX-matching placebo, subcutaneous (SC) injection once every week up to Day 78.	
Reporting group title	AGT-LRX 40 mg
Reporting group description:	
Subjects received AGT-LRX 40 mg, SC injection once every week up to Day 78.	
Reporting group title	AGT-LRX 80 mg
Reporting group description:	
Subjects received AGT-LRX 80 mg, SC injection once every week up to Day 78.	
Reporting group title	AGT-LRX 120 mg
Reporting group description:	
Subjects received AGT-LRX 120 mg, SC injection once every week up to Day 78.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received AGT-LRX-matching placebo, subcutaneous (SC) injection once every week up to Day 78.	

Primary: Percent Change in Plasma AGT Concentration From Baseline to Day 85

End point title	Percent Change in Plasma AGT Concentration From Baseline to Day 85
End point description:	
PPS consisted of all FAS subjects who received at least 10 of the 12 doses of study drug, did not have major changes of screening life-saving HF medications during the treatment period and prior to study day 85, and had no significant protocol deviations that would have been expected to affect efficacy or exploratory assessments. Analysis of covariance (ANCOVA) was used for the analyses.	
End point type	Primary
End point timeframe:	
Baseline to Day 85	

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	9	19	13
Units: percent change				
least squares mean (confidence interval 95%)	0.5 (-11.0 to 11.9)	-44.1 (-59.5 to -28.7)	-49.6 (-60.1 to -39.0)	-64.5 (-77.4 to -51.7)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v AGT-LRX 40 mg

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean of Difference
Point estimate	-44.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.5
upper limit	-25.6

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.4
upper limit	-47.6

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-50
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.6
upper limit	-34.5

Secondary: Absolute Level of Plasma AGT

End point title	Absolute Level of Plasma AGT

End point description:

FAS consisted of all randomised subjects who received at least 1 injection of study drug and had at least 1 post-baseline efficacy or exploratory measurement. ‘n’ indicates the number of subjects available for analysis at the given timepoints. '99999' indicates standard deviation was not evaluable for 1 subject.

End point type	Secondary

End point timeframe:

Baseline to Day 169

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	12	26	13
Units: nanomoles per litre (nmol/L)				
arithmetic mean (standard deviation)				
Baseline (n= 20, 12, 25, 13)	858.1 (± 356.0)	805.5 (± 265.9)	727.9 (± 205.6)	704.2 (± 347.3)
Day 15 (n= 19, 12, 25, 13)	847.9 (± 295.7)	623.5 (± 273.8)	565.7 (± 184.3)	448.8 (± 212.7)
Day 29 (n= 18, 11, 22, 13)	769.4 (± 263.1)	592.5 (± 316.3)	456.2 (± 186.7)	291.5 (± 123.3)
Day 43 (n= 19, 10, 23, 13)	815.3 (± 302.7)	484.4 (± 177.5)	444.9 (± 184.5)	264.5 (± 100.1)
Day 57 (n= 16, 10, 21, 13)	773.9 (± 219.1)	415.4 (± 163.9)	404.4 (± 140.0)	245.8 (± 87.5)
Day 71 (n= 19, 10, 21, 13)	798.5 (± 292.1)	380.9 (± 148.6)	384.3 (± 156.4)	292.3 (± 148.8)
Day 85 (n= 19, 10, 20, 13)	802.7 (± 260.1)	400.0 (± 163.8)	370.8 (± 154.5)	260.6 (± 91.2)
Day 92 (n= 19, 11, 22, 12)	743.3 (± 260.1)	471.3 (± 185.9)	399.2 (± 181.2)	298.4 (± 109.7)
Day 99 (n= 18, 10, 22, 13)	784.1 (± 232.3)	488.0 (± 151.7)	429.9 (± 174.2)	390.3 (± 131.2)
Day 120 (n= 19, 11, 23, 13)	749.5 (± 225.7)	689.1 (± 262.4)	533.9 (± 176.9)	509.2 (± 204.6)
Day 148 (n= 19, 11, 23, 13)	797.9 (± 302.4)	718.0 (± 244.3)	667.4 (± 294.5)	539.0 (± 171.9)
Day 169 (n= 0, 1, 0, 0)	0 (± 0)	844.8 (± 99999)	0 (± 0)	0 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Plasma AGT From Baseline to Each Scheduled, Post-Baseline Visit

End point title	Change in Plasma AGT From Baseline to Each Scheduled, Post-Baseline Visit

End point description:

FAS consisted of all randomised subjects who received at least 1 injection of study drug and had at least 1 post-baseline efficacy or exploratory measurement. ‘n’ indicates the number of subjects available for analysis at the given timepoints. '-99999' indicates upper limit and '99999' indicates lower limit for 95% CI were not evaluable for 1 subject.

End point type	Secondary
End point timeframe: Baseline to Day 169	

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	12	26	13
Units: nmol/L				
least squares mean (confidence interval 95%)				
Day 15 (n= 19, 12, 24, 13)	14.647 (-73.963 to 103.258)	-174.057 (-283.242 to -64.872)	-199.879 (-276.467 to -123.291)	-292.249 (-396.937 to -187.562)
Day 29 (n= 18, 11, 21, 13)	-43.475 (-141.481 to 54.531)	-198.044 (-322.549 to -73.538)	-322.420 (-411.196 to -233.645)	-464.425 (-577.798 to -351.051)
Day 43 (n= 19, 10, 22, 13)	-0.306 (-88.721 to 88.110)	-298.227 (-417.308 to -179.146)	-313.819 (-393.296 to -234.341)	-485.127 (-588.976 to -381.277)
Day 57 (n= 16, 10, 20, 13)	-49.605 (-122.719 to 23.509)	-365.535 (-454.553 to -276.517)	-362.547 (-425.168 to -299.925)	-514.430 (-592.170 to -436.691)
Day 71 (n= 19, 10, 20, 13)	-25.450 (-107.300 to 56.400)	-409.873 (-520.456 to -299.290)	-392.864 (-470.220 to -315.507)	-462.624 (-559.180 to -366.069)
Day 85 (n= 19, 10, 20, 13)	-8.006 (-86.504 to 70.491)	-384.270 (-490.323 to -278.217)	-404.984 (-479.172 to -330.796)	-500.238 (-592.838 to -407.638)
Day 92 (n= 19, 11, 21, 12)	-80.433 (-163.080 to 2.214)	-335.227 (-442.479 to -227.975)	-368.335 (-444.870 to -291.800)	-470.447 (-571.923 to -368.970)
Day 99 (n= 18, 10, 21, 13)	-46.275 (-121.120 to 28.570)	-305.358 (-403.534 to -207.182)	-334.772 (-401.978 to -267.567)	-368.138 (-453.838 to -282.438)
Day 120 (n= 19, 11, 22, 13)	-62.844 (-136.107 to 10.419)	-101.913 (-198.134 to -5.692)	-217.345 (-284.478 to -150.211)	-230.610 (-318.021 to -143.199)
Day 148 (n= 19, 11, 22, 13)	-34.360 (-141.639 to 72.919)	-80.289 (-219.068 to 58.490)	-78.438 (-175.381 to 18.504)	-203.100 (-329.313 to -76.888)
Day 169 (n= 0, 1, 0, 0)	0 (0 to 0)	-210.600 (-99999 to 99999)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Plasma AGT From Baseline to Each Scheduled, Post-Baseline Visit

End point title	Percent Change in Plasma AGT From Baseline to Each Scheduled, Post-Baseline Visit

End point description:

FAS consisted of all randomised subjects who received at least 1 injection of study drug and had at least 1 post-baseline efficacy or exploratory measurement. ‘n’ indicates the number of subjects available for analysis at the given timepoints. '-99999' indicates upper limit and '99999' indicates lower limit for 95% CI were not evaluable for 1 subject.

End point type	Secondary

End point timeframe:

Baseline through Day 169

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	12	26	13
Units: Percent Change				
least squares mean (confidence interval 95%)				
Day 15 (n= 19, 12, 24, 13)	5.5 (-6.2 to 17.2)	-22.0 (-36.5 to -7.6)	-23.9 (-34.0 to -13.8)	-35.9 (-49.7 to -22.0)
Day 29 (n= 18, 11, 21, 13)	-1.5 (-13.2 to 10.2)	-24.8 (-39.7 to -10.0)	-39.6 (-50.1 to -29.0)	-58.7 (-72.2 to -45.2)
Day 43 (n= 19, 10, 22, 13)	2.4 (-8.6 to 13.3)	-33.3 (-48.1 to -18.5)	-39.4 (-49.2 to -29.5)	-62.6 (-75.5 to -49.7)
Day 57 (n= 16, 10, 20, 13)	-5.5 (-14.8 to 3.8)	-41.7 (-53.0 to -30.4)	-44.9 (-52.9 to -37.0)	-65.6 (-75.5 to -55.8)
Day 71 (n= 19, 10, 20, 13)	0.5 (-9.5 to 10.5)	-49.4 (-62.9 to -35.9)	-48.1 (-57.5 to -38.6)	-60.8 (-72.6 to -49.0)
Day 85 (n= 19, 10, 20, 13)	5.8 (-5.6 to 17.2)	-45.8 (-61.2 to -30.4)	-50.1 (-60.9 to -39.3)	-64.6 (-78.1 to -51.1)
Day 92 (n= 18, 10, 21, 13)	-4.4 (-14.5 to 5.6)	-40.0 (-53.1 to -27.0)	-45.2 (-54.5 to -35.9)	-58.7 (-71.0 to -46.4)
Day 99 (n= 18, 10, 21, 13)	-0.4 (-9.6 to 8.8)	-35.5 (-47.5 to -23.4)	-41.1 (-49.3 to -32.8)	-44.5 (-55.0 to -33.9)
Day 120 (n= 19, 11, 22, 13)	-0.8 (-11.8 to 10.2)	-14.5 (-28.9 to 0.0)	-25.5 (-35.6 to -15.4)	-28.4 (-41.6 to -15.3)
Day 148 (n= 19, 11, 22, 13)	3.0 (-11.8 to 17.7)	-10.1 (-29.2 to 9.0)	-7.1 (-20.4 to 6.3)	-19.9 (-37.2 to -2.5)
Day 169 (n= 0, 1, 0, 0)	0 (0 to 0)	-20.0 (-99999 to 99999)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Level of NT-proBNP

End point title	Absolute Level of NT-proBNP

End point description:

FAS consisted of all randomised subjects who received at least 1 injection of study drug and had at least 1 post-baseline efficacy or exploratory measurement. ‘n’ indicates the number of subjects available for analysis at the given timepoints.

End point type	Secondary

End point timeframe:

Baseline through Day 169

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	12	26	13
Units: picogram per millilitre (pg/mL)				
arithmetic mean (standard deviation)				
Baseline (n = 20, 12, 26, 13)	1432 (± 969)	2632 (± 3581)	2158 (± 3308)	1748 (± 1455)
Day 43 (n= 19, 10, 23, 13)	1480 (± 954)	1442 (± 1245)	1758 (± 1729)	1539 (± 1346)
Day 85 (n= 18, 10, 21, 13)	1386 (± 771)	1664 (± 1566)	1757 (± 1716)	1670 (± 1329)
Day 99 (n= 18, 10, 22, 13)	1525 (± 1044)	1550 (± 1800)	2018 (± 2552)	1702 (± 1220)
Day 169 (n = 20, 10, 23, 13)	1266 (± 809)	2190 (± 2569)	1852 (± 3184)	1651 (± 1169)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NT-proBNP From Baseline to Each Scheduled, Post-Baseline Visit

End point title	Change in NT-proBNP From Baseline to Each Scheduled, Post-Baseline Visit

End point description:

FAS consisted of all randomised subjects who received at least 1 injection of study drug and had at least 1 post-baseline efficacy or exploratory measurement. 'n' indicates the number of subjects available for analysis at the given timepoints. ANCOVA was used for the analyses.

End point type	Secondary

End point timeframe:

Baseline to Day 169

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	12	26	13
Units: pg/mL				
arithmetic mean (standard deviation)				
Day 43 (n= 19, 10, 23, 13)	117 (± 484)	-228 (± 522)	-530 (± 2550)	-210 (± 468)
Day 85 (n= 18, 10, 21, 13)	-11 (± 693)	-6 (± 887)	-537 (± 2095)	-78 (± 559)
Day 99 (n= 18, 10, 22, 13)	128 (± 640)	-120 (± 1077)	-262 (± 1289)	-47 (± 713)
Day 169 (n= 20, 10, 23, 13)	-166 (± 560)	520 (± 1226)	-381 (± 920)	-97 (± 868)

Statistical analyses

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 43
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.284
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-897
upper limit	546

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 43
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-136
Confidence interval	
level	95 %
sides	2-sided
lower limit	-716
upper limit	443

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 43
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-779
upper limit	552

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 85
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	140
Confidence interval	
level	95 %
sides	2-sided
lower limit	-404
upper limit	683

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 85
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.665
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-532
upper limit	363

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 85
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	106

Confidence interval	
level	95 %
sides	2-sided
lower limit	-396
upper limit	607

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 99
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-171
Confidence interval	
level	95 %
sides	2-sided
lower limit	-758
upper limit	417

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 99
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-620
upper limit	338

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 99
Comparison groups	Placebo v AGT-LRX 120 mg

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.709
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-618
upper limit	467

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 169
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	711
Confidence interval	
level	95 %
sides	2-sided
lower limit	56
upper limit	1365

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 169
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.793
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-132
Confidence interval	
level	95 %
sides	2-sided
lower limit	-653
upper limit	390

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 169

Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.503
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-501
upper limit	704

Secondary: Percent Change from Baseline in NT-proBNP to Each Scheduled, Post-Baseline Visit

End point title	Percent Change from Baseline in NT-proBNP to Each Scheduled, Post-Baseline Visit

End point description:

FAS consisted of all randomised subjects who received at least 1 injection of study drug and had at least 1 post-baseline efficacy or exploratory measurement. 'n' indicates the number of subjects available for analysis at the given timepoints. ANCOVA was used for the analyses.

End point type	Secondary

End point timeframe:

Baseline through Day 169

End point values	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg	AGT-LRX 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	12	26	13
Units: Percent Change				
arithmetic mean (standard deviation)				
Day 43 (n= 19, 10, 23, 13)	16.8 (± 46.1)	3.2 (± 40.0)	-3.5 (± 42.8)	-4.5 (± 32.6)
Day 85 (n= 18, 10, 21, 13)	20.7 (± 76.9)	22.2 (± 87.2)	9.4 (± 84.7)	9.5 (± 45.1)
Day 99 (n= 18, 10, 22, 13)	26.9 (± 73.8)	0.6 (± 39.0)	14.9 (± 86.4)	13.1 (± 47.0)
Day 169 (n = 20, 10, 23, 13)	1.9 (± 56.1)	42.6 (± 89.1)	-11.2 (± 34.2)	15.8 (± 69.0)

Statistical analyses

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 43
Comparison groups	Placebo v AGT-LRX 40 mg

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.456
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	19.4

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 85
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.8
upper limit	44.6

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 169
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	41.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	87

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 43

Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-15.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.9
upper limit	9.6

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 43
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-19.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.4
upper limit	9.6

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 85
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.7
upper limit	62.4

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 85
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.642
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.2
upper limit	45.9

Statistical analysis title	Placebo and ISIS 757456 40 mg at Day 99
Comparison groups	Placebo v AGT-LRX 40 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-24.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78.7
upper limit	29.9

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 99
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.526
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-5.9
Confidence interval	
level	Other: 94 %
sides	2-sided
lower limit	-50.2
upper limit	38.3

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 99
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.5
upper limit	38.8

Statistical analysis title	Placebo and ISIS 757456 80 mg at Day 169
Comparison groups	Placebo v AGT-LRX 80 mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.9
upper limit	26.4

Statistical analysis title	Placebo and ISIS 757456 120 mg at Day 169
Comparison groups	Placebo v AGT-LRX 120 mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	26.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.5
upper limit	56.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From signing of informed consent form up to end of study (up to Day 169)	
Adverse event reporting additional description:	
Safety set consisted of all subjects who were randomised and received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received AGT-LRX-matching placebo, subcutaneous (SC) injection once every week up to Day 78.	
Reporting group title	AGT-LRX 40 mg
Reporting group description:	
Subjects received AGT-LRX 40 mg, SC injection once every week up to Day 78.	
Reporting group title	AGT-LRX 80 mg
Reporting group description:	
Subjects received AGT-LRX 80 mg, SC injection once every week up to Day 78.	
Reporting group title	AGT-LRX 120 mg
Reporting group description:	
Subjects received AGT-LRX 120 mg, SC injection once every week up to Day 78.	

Serious adverse events	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	2 / 12 (16.67%)	5 / 26 (19.23%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal Adenocarcinoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression Fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur Fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypovolaemic Shock			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Failure Chronic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Arrhythmia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiorenal Syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac Failure congestive			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic Stroke			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Pneumococcal			

subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AGT-LRX 120 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal Adenocarcinoma			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Compression Fracture			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur Fracture			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypovolaemic Shock			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac Failure Chronic			

subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular Arrhythmia				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular Tachycardia				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiorenal Syndrome				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure congestive				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ischaemic Stroke				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient Ischaemic Attack				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				

Acute Respiratory Failure			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	AGT-LRX 40 mg	AGT-LRX 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	7 / 12 (58.33%)	10 / 26 (38.46%)
Vascular disorders			
Blood Pressure Fluctuation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection Site Haemorrhage			

subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Chest Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Injection Site Haematoma			
subjects affected / exposed	2 / 20 (10.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Pulmonary Fibrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood Glucose Increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Blood Potassium Increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Platelet Count Decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Occult Blood Positive			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Limb Injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Atrial Fibrillation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Cardiorenal Syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Ventricular Extrasystoles			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	2	2	0
Headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Sciatica			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Normocytic Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Dental Caries			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Peptic Ulcer			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Acute Kidney Injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Infections and infestations			
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 12 (8.33%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
COVID-19			

subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Urinary Tract Infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	4
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 12 (8.33%)	2 / 26 (7.69%)
occurrences (all)	0	1	4

Non-serious adverse events	AGT-LRX 120 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)		
Vascular disorders			
Blood Pressure Fluctuation			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection Site Haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Chest Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Injection Site Haematoma			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal			

disorders			
Pulmonary Fibrosis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Blood Potassium Increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Platelet Count Decreased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Occult Blood Positive			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Atrial Fibrillation			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cardiorenal Syndrome			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Ventricular Extrasystoles			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Normocytic Anaemia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dental Caries			

subjects affected / exposed occurrences (all) Peptic Ulcer subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Acute Kidney Injury subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0 1 / 13 (7.69%) 1		
Infections and infestations Pharyngitis Streptococcal subjects affected / exposed occurrences (all) Gastroenteritis Viral subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0		
Metabolism and nutrition disorders			

Dehydration subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2021	The main purpose of amendment 1 was to incorporate changes from the Protocol Clarification Memorandum dated 18 March 2021.
15 October 2021	The purpose of amendment 2 was to: 1. update the eGFR exclusion criterion to < 30 mL/min/1.73 m2 2. clarify the types of cardiomyopathies that are excluded from the trial 3. clarify the testing needed for HBV at screening 4. update the K+ exclusion criterion to the upper limit of normal of the standard reference range of the study's central lab (5.1 mmol/L) and update, accordingly, the potassium safety monitoring rule to allow for physiological variability from the upper limit of normal.
15 March 2022	The purpose of amendment 3 was to: 1. extend the screening period from four to ten weeks 2. include an additional dose cohort (cohort C, 120 mg) or placebo). Based on AGT levels observed at the interim analysis, a decision was made to close enrollment for Cohort A and enroll the remainder of the subjects into Cohort B (approximately n=36) and Cohort C (approximately n=18).

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.

None reported

Notes: