



## Clinical trial results:

### A Phase 2b, Randomized, Double-blind, Placebo-controlled Study of NEOD001 in Previously Treated Subjects with Light Chain (AL) Amyloidosis who have Persistent Cardiac Dysfunction

#### Summary

EudraCT number	2015-004318-14
Trial protocol	DE GB GR ES AT
Global end of trial date	05 March 2018

#### Results information

Result version number	v2 (current)
This version publication date	06 December 2018
First version publication date	03 September 2018
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> The numbers relating to the non-serious adverse events have been updated.

#### Trial information

##### Trial identification

Sponsor protocol code	NEOD001-201
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02632786
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Prothena Therapeutics Limited
Sponsor organisation address	Adelphi Plaza, Upper George's Street, Co. Dublin, Dun Laoghaire, Ireland, A96 T927
Public contact	Communications Office, Prothena Biosciences Inc, info@prothena.com
Scientific contact	Clinical Trials Office, Prothena Biosciences Inc, info@prothena.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 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2018
Global end of trial reached?	Yes
Global end of trial date	05 March 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study is to determine the efficacy and safety of NEOD001 versus placebo in subjects with AL amyloidosis who have persistent cardiac dysfunction.

Protection of trial subjects:

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, and with the laws of the countries in which the study was conducted.

The Investigator had the ability to break the blind for a specific subject in the event of an immediate medical emergency, wherein knowledge of the subject's treatment (NEOD001 or placebo) needed to be known in order to provide adequate medical treatment. In these situations, the breaking of the blind was to be reported to the Sponsor or its designee within 24 hours.

An independent Safety Monitoring Committee (SMC) was used during the study, it consisted of at least 2 clinicians and a biostatistician not directly involved with the conduct of the trial. The SMC met at defined timepoints to review specified blinded subject data during the conduct of the study. The purpose of these independent data reviews was to assess the totality of the safety data and provide a recommendation to the Sponsor for continuation of dosing or protocol modifications. A non-scheduled meeting could be called at the discretion of the Chairperson or the request of the Sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	United States: 57

Worldwide total number of subjects	129
EEA total number of subjects	55

Notes:

<b>Subjects enrolled per age group</b>	
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)	70
From 65 to 84 years	59
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 129 subjects were enrolled in the study, 66 randomly assigned to receive NEOD001 and 63 randomly assigned to receive placebo. A total of 111 (86.0%) subjects completed the study and 18 (14.0%) subjects discontinued the study. In the EEA there were a total of 55 subjects randomized.

### Pre-assignment

Screening details:

Screening evaluations and procedures were performed within 28 days prior to the first study drug administration on Month 1-Day 1. Individual test results that did not meet eligibility requirements could be repeated, with the exception of 6MWT; full rescreening was only allowed once per subject.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	NEOD001 24 mg/kg

Arm description:

NEOD001, 24 mg/kg IV every 4 weeks for 12 months

Arm type	Experimental
Investigational medicinal product name	NEOD001 24 mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug administered intravenously every 4 weeks for 12 months, starting at the Month 1-Day 1 Visit. Subjects received up to 12 infusions of study drug.

<b>Arm title</b>	Placebo
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Arm description:

Placebo, 0.9% Saline IV every 4 weeks for 12 months

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

Dosage and administration details:

Intravenous drip use (Noncurrent)

<b>Number of subjects in period 1</b>	NEOD001 24 mg/kg	Placebo
Started	66	63
Completed	55	56
Not completed	11	7
Consent withdrawn by subject	1	-
Physician decision	5	4
Adverse event, non-fatal	2	1
Death	3	2

## Baseline characteristics

### Reporting groups

Reporting group title	NEOD001 24 mg/kg
Reporting group description: NEOD001, 24 mg/kg IV every 4 weeks for 12 months	
Reporting group title	Placebo
Reporting group description: Placebo, 0.9% Saline IV every 4 weeks for 12 months	

Reporting group values	NEOD001 24 mg/kg	Placebo	Total
Number of subjects	66	63	129
Age categorical Units: Subjects			
From 65-84 years	25	34	59
From 18-64 Years	41	29	70
Age continuous Units: years			
arithmetic mean	62.09	63.90	
standard deviation	± 9.188	± 8.332	-
Gender categorical Units: Subjects			
Female	27	24	51
Male	39	39	78
Race Units: Subjects			
White	61	56	117
Black or African American	3	2	5
Not Reported	0	2	2
Arab	1	0	1
Asian	1	0	1
Indian	0	1	1
North African, Bereber	0	1	1
Persian	0	1	1
Ethnicity Units: Subjects			
Not Reported	2	2	4
Not Hispanic or Latino	64	61	125

### Subject analysis sets

Subject analysis set title	NEOD001 24 mg/kg (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population includes all subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT Population includes all randomized subjects who received any amount of study drug	

Subject analysis set title	NEOD001 24 mg/kg (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	NEOD001 24 mg/kg (Peripheral Neuropathy Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Peripheral Neuropathy Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score $\geq 2$ and at least one postbaseline NIS-LL total score assessment	
Subject analysis set title	NEOD001 24 mg/kg (Hepatic Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Hepatic Evaluable Population includes all ITT subjects who had a baseline alkaline phosphatase $>1.5 \times$ ULN and at least one postbaseline assessment of alkaline phosphatase	
Subject analysis set title	Placebo (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Population includes all subjects who received any amount of study drug	
Subject analysis set title	Placebo (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	Placebo (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	Placebo (Peripheral Neuropathy Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Peripheral Neuropathy Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score $\geq 2$ and at least one postbaseline NIS-LL total score assessment	
Subject analysis set title	Placebo (Hepatic Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Hepatic Evaluable Population includes all ITT subjects who had a baseline alkaline phosphatase $>1.5 \times$ ULN and at least one postbaseline assessment of alkaline phosphatase	

Reporting group values	NEOD001 24 mg/kg (Safety Population)	NEOD001 24 mg/kg (ITT Population)	NEOD001 24 mg/kg (Renal Evaluable Population)
Number of subjects	66	66	13
Age categorical Units: Subjects			
From 65-84 years	25	25	5
From 18-64 Years	41	41	8
Age continuous Units: years			
arithmetic mean	62.09	62.09	64.21
standard deviation	$\pm 9.188$	$\pm 9.188$	$\pm 8.372$

Gender categorical Units: Subjects			
Female	27	27	3
Male	39	39	10
Race Units: Subjects			
White	61	61	13
Black or African American	3	3	0
Not Reported	0	0	0
Arab	1	1	0
Asian	1	1	0
Indian	0	0	0
North African, Bereber	0	0	0
Persian	0	0	0
Ethnicity Units: Subjects			
Not Reported	2	2	1
Not Hispanic or Latino	64	64	12

Reporting group values	NEOD001 24 mg/kg (Peripheral Neuropathy Evaluable Population)	NEOD001 24 mg/kg (Hepatic Evaluable Population)	Placebo (Safety Population)
Number of subjects	12	5	63
Age categorical Units: Subjects			
From 65-84 years	6	1	34
From 18-64 Years	6	4	29
Age continuous Units: years			
arithmetic mean	62.70	58.29	63.90
standard deviation	± 9.962	± 9.811	± 8.332
Gender categorical Units: Subjects			
Female	4	3	24
Male	8	2	39
Race Units: Subjects			
White	12	5	56
Black or African American	0	0	2
Not Reported	0	0	2
Arab	0	0	0
Asian	0	0	0
Indian	0	0	1
North African, Bereber	0	0	1
Persian	0	0	1
Ethnicity Units: Subjects			
Not Reported	0	1	2
Not Hispanic or Latino	12	4	61

Reporting group values	Placebo (ITT)	Placebo (Renal)	Placebo (Peripheral)
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	Population)	Evaluable Population)	Neuropathy Evaluable Population)
Number of subjects	63	18	14
Age categorical Units: Subjects			
From 65-84 years	34	9	8
From 18-64 Years	29	9	6
Age continuous Units: years			
arithmetic mean	63.90	63.28	64.85
standard deviation	± 8.332	± 9.157	± 6.481
Gender categorical Units: Subjects			
Female	24	6	4
Male	39	12	10
Race Units: Subjects			
White	56	16	14
Black or African American	2	1	0
Not Reported	2	0	0
Arab	0	0	0
Asian	0	0	0
Indian	1	0	0
North African, Bereber	1	1	0
Persian	1	0	0
Ethnicity Units: Subjects			
Not Reported	2	0	1
Not Hispanic or Latino	61	18	13

<b>Reporting group values</b>	Placebo (Hepatic Evaluable Population)		
Number of subjects	4		
Age categorical Units: Subjects			
From 65-84 years	0		
From 18-64 Years	4		
Age continuous Units: years			
arithmetic mean	60.12		
standard deviation	± 3.419		
Gender categorical Units: Subjects			
Female	0		
Male	4		
Race Units: Subjects			
White	4		
Black or African American	0		
Not Reported	0		
Arab	0		

Asian	0		
Indian	0		
North African, Bereber	0		
Persian	0		
Ethnicity			
Units: Subjects			
Not Reported	0		
Not Hispanic or Latino	4		

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## End points

### End points reporting groups

Reporting group title	NEOD001 24 mg/kg
Reporting group description: NEOD001, 24 mg/kg IV every 4 weeks for 12 months	
Reporting group title	Placebo
Reporting group description: Placebo, 0.9% Saline IV every 4 weeks for 12 months	
Subject analysis set title	NEOD001 24 mg/kg (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population includes all subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	NEOD001 24 mg/kg (Peripheral Neuropathy Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Peripheral Neuropathy Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score $\geq 2$ and at least one postbaseline NIS-LL total score assessment	
Subject analysis set title	NEOD001 24 mg/kg (Hepatic Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Hepatic Evaluable Population includes all ITT subjects who had a baseline alkaline phosphatase $>1.5 \times$ ULN and at least one postbaseline assessment of alkaline phosphatase	
Subject analysis set title	Placebo (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population includes all subjects who received any amount of study drug	
Subject analysis set title	Placebo (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	Placebo (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	Placebo (Peripheral Neuropathy Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Peripheral Neuropathy Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score $\geq 2$ and at least one postbaseline NIS-LL total score assessment	

Subject analysis set title	Placebo (Hepatic Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Hepatic Evaluable Population includes all ITT subjects who had a baseline alkaline phosphatase >1.5 × ULN and at least one postbaseline assessment of alkaline phosphatase	
<b>Primary: Cardiac Best Response</b>	
End point title	Cardiac Best Response
End point description:	
N-terminal pro-brain natriuretic peptide (NT-proBNP) best response (Response or Non-Response [Stable, Progression]) from baseline through 12 months of treatment	
End point type	Primary
End point timeframe:	
Baseline through 12 months of treatment	

End point values	NEOD001 24 mg/kg (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	63		
Units: Subjects				
Response	26	30		
Non-Response	40	33		

### Statistical analyses

<b>Statistical analysis title</b>	Primary Eff Endpt: Cardiac Best Resp thru 12m Tx
Statistical analysis description:	
Test to determine if the percentage of NT-proBNP best responders through 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (ITT Population) v Placebo (ITT Population)
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.319
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.21

### Secondary: SF-36v2 PCS Score

End point title	SF-36v2 PCS Score
End point description: Change in Short Form-36 (SF-36v2) Questionnaire Physical Component Summary (PCS) Score; the lower the score the more disability	
End point type	Secondary
End point timeframe: Baseline to 12 months of treatment	

End point values	NEOD001 24 mg/kg (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	63		
Units: SF-36v2 PCS Score				
least squares mean (confidence interval 95%)				
SF-36v2 PCS Score	0.19 (-1.83 to 2.22)	0.97 (-0.99 to 2.93)		

### Statistical analyses

Statistical analysis title	Change from Baseline SF-36v2 PCS Score to 12m Tx
Statistical analysis description: Test to determine if the mean change from baseline in the SF-36v2 PCS score after 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (ITT Population) v Placebo (ITT Population)
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5563
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.37
upper limit	1.81

### Secondary: 6MWT Distance

End point title	6MWT Distance
End point description: Change in 6 Minute Walk Test (6MWT) Distance (meters)	
End point type	Secondary

End point timeframe:

Baseline to 12 months of treatment

End point values	NEOD001 24 mg/kg (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	63		
Units: meters				
median (inter-quartile range (Q1-Q3))				
6MWT Distance (meters)	19.25 (-21.75 to 59.37)	8.00 (-24.99 to 47.24)		

## Statistical analyses

Statistical analysis title	Change from Baseline in 6MWT Distance to 12m Tx
Statistical analysis description: Test to determine if mean ranked change from baseline in 6MWT distance (meters) after 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (ITT Population) v Placebo (ITT Population)
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8992
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	23

## Secondary: NT-proBNP Slope

End point title	NT-proBNP Slope
End point description: Rate of change in NT-proBNP (ng/L per infusion)	
End point type	Secondary
End point timeframe: Baseline through 12 Months of Treatment	

End point values	NEOD001 24 mg/kg (ITT Population)	Placebo (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	63		
Units: ng/L per infusion				
least squares mean (confidence interval 95%)				
NT-proBNP (ng/L per infusion)	9.45 (-45.66 to 64.55)	81.41 (25.15 to 137.68)		

## Statistical analyses

Statistical analysis title	NT-proBNP (ng/L) Rate of Change thru 12m Tx
Statistical analysis description: Test to determine if the rate of change (i.e., slope) of NT-proBNP over 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (ITT Population) v Placebo (ITT Population)
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0729
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-71.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-150.72
upper limit	6.79

## Secondary: Renal Best Response

End point title	Renal Best Response
End point description: Proteinuria and estimated Glomerular Filtration Rate (eGFR) response (Response or Non-Response [Stable, Progression]) from baseline through 12 months of treatment in subjects with renal involvement	
End point type	Secondary
End point timeframe: Baseline through 12 months of treatment	

End point values	NEOD001 24 mg/kg (Renal Evaluable Population)	Placebo (Renal Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	18		
Units: Count of Participants				
Response	7	6		
Non-Response	6	12		

## Statistical analyses

Statistical analysis title	Renal Best Response thru 12m of Tx
Statistical analysis description:	
Test to determine if the percentage of renal best responders through 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (Renal Evaluable Population) v Placebo (Renal Evaluable Population)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3529
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.94

## Secondary: NIS-LL Total Score

End point title	NIS-LL Total Score
End point description:	
Change in Neuropathy Impairment Score-Lower Limb (NIS-LL) Total Score in subjects with peripheral nerve involvement	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	



<b>End point values</b>	NEOD001 24 mg/kg (Peripheral Neuropathy Evaluable Population)	Placebo (Peripheral Neuropathy Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: NIS-LL Total Score				
least squares mean (confidence interval 95%)				
NIS-LL Total Score	-1.2 (-3.9 to 1.6)	-0.6 (-3.0 to 1.8)		

## Statistical analyses

<b>Statistical analysis title</b>	Change from Baseline in NIS-LL Total Score to 12m
Statistical analysis description:	
Test to determine if the mean change from baseline in NIS-LL total score after 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (Peripheral Neuropathy Evaluable Population) v Placebo (Peripheral Neuropathy Evaluable Population)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.757
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	3

## Secondary: Hepatic Best Response

End point title	Hepatic Best Response
End point description:	
Alkaline Phosphatase response (Response or Non-Response [Stable, Progression]) from baseline through 12 months of treatment in subjects with hepatic involvement	
End point type	Secondary
End point timeframe:	
Baseline through 12 months of treatment	

<b>End point values</b>	NEOD001 24 mg/kg (Hepatic Evaluable Population)	Placebo (Hepatic Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	4		
Units: Count of Participants				
Response	1	0		
Non-Response	4	4		

## Statistical analyses

<b>Statistical analysis title</b>	Hepatic Best Response thru 12m of Tx
Statistical analysis description:	
Test to determine if the percentage of hepatic best responders through 12 months of treatment is the same or different between placebo and NEOD001.	
Comparison groups	NEOD001 24 mg/kg (Hepatic Evaluable Population) v Placebo (Hepatic Evaluable Population)
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4142
Method	Cochran-Mantel-Haenszel

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Initiation of study drug through the last study visit or up to 30 days after date of last dose

Adverse event reporting additional description:

AE that newly appears, increases in frequency, or worsens in severity following initiation of study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	NEOD001 24 mg/kg
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Reporting group description:

NEOD001, 24 mg/kg IV every 4 weeks for 12 months

Reporting group title	Placebo
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Reporting group description:

Placebo, 0.9% Saline IV every 4 weeks for 12 months

Reporting group title	Total
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Reporting group description:

NEOD001 + Placebo

Serious adverse events	NEOD001 24 mg/kg	Placebo	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 66 (21.21%)	15 / 63 (23.81%)	29 / 129 (22.48%)
number of deaths (all causes)	2	2	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant urinary tract neoplasm			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 66 (0.00%)	2 / 63 (3.17%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sudden death			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 66 (3.03%)	1 / 63 (1.59%)	3 / 129 (2.33%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 66 (3.03%)	1 / 63 (1.59%)	3 / 129 (2.33%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 66 (3.03%)	0 / 63 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 63 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 66 (0.00%)	3 / 63 (4.76%)	3 / 129 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	2 / 66 (3.03%)	0 / 63 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 66 (1.52%)	3 / 63 (4.76%)	4 / 129 (3.10%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Ureteric obstruction			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 66 (3.03%)	1 / 63 (1.59%)	3 / 129 (2.33%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 66 (0.00%)	4 / 63 (6.35%)	4 / 129 (3.10%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Respiratory tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 63 (1.59%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 66 (1.52%)	1 / 63 (1.59%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 63 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	NEOD001 24 mg/kg	Placebo	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 66 (87.88%)	52 / 63 (82.54%)	110 / 129 (85.27%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 66 (3.03%)	4 / 63 (6.35%)	6 / 129 (4.65%)
occurrences (all)	2	5	7
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 66 (3.03%)	4 / 63 (6.35%)	6 / 129 (4.65%)
occurrences (all)	3	4	7

Hypertension subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	5 / 63 (7.94%) 6	8 / 129 (6.20%) 9
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6	8 / 63 (12.70%) 11	13 / 129 (10.08%) 17
Headache subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 11	6 / 63 (9.52%) 7	15 / 129 (11.63%) 18
Hypoaesthesia subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6	2 / 63 (3.17%) 2	7 / 129 (5.43%) 8
Paraesthesia subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	3 / 63 (4.76%) 3	7 / 129 (5.43%) 7
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	11 / 63 (17.46%) 14	17 / 129 (13.18%) 20
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	14 / 66 (21.21%) 15	14 / 63 (22.22%) 26	28 / 129 (21.71%) 41
Oedema peripheral subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 7	8 / 63 (12.70%) 12	15 / 129 (11.63%) 19
Pyrexia subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	4 / 63 (6.35%) 4	8 / 129 (6.20%) 8
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	4 / 63 (6.35%) 5	7 / 129 (5.43%) 8
Constipation			

subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 9	6 / 63 (9.52%) 8	13 / 129 (10.08%) 17
Diarrhoea subjects affected / exposed occurrences (all)	13 / 66 (19.70%) 15	11 / 63 (17.46%) 12	24 / 129 (18.60%) 27
Nausea subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	14 / 63 (22.22%) 15	20 / 129 (15.50%) 21
Vomiting subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7	4 / 63 (6.35%) 4	10 / 129 (7.75%) 11
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	8 / 66 (12.12%) 9	6 / 63 (9.52%) 8	14 / 129 (10.85%) 17
Dyspnoea subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 7	7 / 63 (11.11%) 9	14 / 129 (10.85%) 16
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 3	5 / 63 (7.94%) 6	7 / 129 (5.43%) 9
Rash macular subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 63 (1.59%) 11	1 / 129 (0.78%) 11
Urticaria subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 63 (1.59%) 8	1 / 129 (0.78%) 8
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 5	2 / 63 (3.17%) 2	7 / 129 (5.43%) 7
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6	4 / 63 (6.35%) 5	9 / 129 (6.98%) 11

Muscle spasms subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7	3 / 63 (4.76%) 3	9 / 129 (6.98%) 10
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 5	4 / 63 (6.35%) 4	9 / 129 (6.98%) 9
Respiratory tract infection subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 5	2 / 63 (3.17%) 3	7 / 129 (5.43%) 8
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	8 / 63 (12.70%) 10	14 / 129 (10.85%) 16
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	3 / 63 (4.76%) 5	9 / 129 (6.98%) 11
Metabolism and nutrition disorders			
Hypocalcaemia subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	4 / 63 (6.35%) 4	7 / 129 (5.43%) 7
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 4	3 / 63 (4.76%) 6	6 / 129 (4.65%) 10

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2016	Amendment 1 was dated 28 June 2016 and included the following key changes: <ul style="list-style-type: none"><li>- Modified inclusion and exclusion criteria to clarify definition of the subject population</li><li>- Prohibited use of doxycycline for 6 weeks before study entry and during the study (unless required for treatment of infection)</li><li>- Clarified timing of 6-minute walk tests (6MWTs) and emphasized that two 6MWTs were required at Screening</li><li>- Clarified management of suspected systemic infusion-related/hypersensitivity AEs</li><li>- Extended the AE/serious adverse event (SAE) reporting period</li><li>- Expanded description of safety analyses</li></ul>
25 April 2017	Amendment 2 was dated 25 April 2017 and included the following key changes: <ul style="list-style-type: none"><li>- Added new endpoints and modified existing endpoints; secondary and exploratory endpoints were modified following receipt of scientific advice on the statistical analysis plan (SAP)</li><li>- Increased the number of subjects (from at least 100 to up to 130)</li><li>- Removed a requirement for monthly collection of additional coagulation indices</li><li>- Corrected Inclusion Criterion #7 to align with existing stratification factor</li><li>- Updated analysis populations and statistical analyses to align with the SAP</li></ul>
22 October 2017	Amendment 3 was dated 22 October 2017 and included the following key changes: <ul style="list-style-type: none"><li>- Modified existing secondary and exploratory endpoints</li><li>- Added NT-proBNP slope over 12 months of treatment as a secondary endpoint</li><li>- Modified statistical section to align with updated secondary and exploratory endpoints</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported