# 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 | • Correction of full data set<br>The numbers relating to the non-serious adverse events have been updated. |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | NEOD001-201 |

### 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:

| **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) | 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 |
| **Arm title** | 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.

| | |
|---|---|
| **Arm title** | Placebo |

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)

| **Number of subjects in period 1** | 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<br>Units: Subjects | | | |
| From 65-84 years | 25 | 34 | 59 |
| From 18-64 Years | 41 | 29 | 70 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.09 | 63.90 | |
| standard deviation | ± 9.188 | ± 8.332 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 27 | 24 | 51 |
| Male | 39 | 39 | 78 |
| Race<br>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<br>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 >= 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 × 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 >= 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

| **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<br>Units: Subjects | | | |
| From 65-84 years | 25 | 25 | 5 |
| From 18-64 Years | 41 | 41 | 8 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.09 | 62.09 | 64.21 |
| standard deviation | ± 9.188 | ± 9.188 | ± 8.372 |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 27 | 27 | 3 |
| Male | 39 | 39 | 10 |
| Race<br>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<br>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<br>Units: Subjects | | | |
| From 65-84 years | 6 | 1 | 34 |
| From 18-64 Years | 6 | 4 | 29 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.70 | 58.29 | 63.90 |
| standard deviation | ± 9.962 | ± 9.811 | ± 8.332 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | 3 | 24 |
| Male | 8 | 2 | 39 |
| Race<br>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<br>Units: Subjects | | | |
| Not Reported | 0 | 1 | 2 |
| Not Hispanic or Latino | 12 | 4 | 61 |

| **Reporting group values** | Placebo (ITT | Placebo (Renal | Placebo (Peripheral |
|---|---|---|---|

| | Population) | Evaluable Population) | Neuropathy Evaluable Population) |
|---|---|---|---|
| Number of subjects | 63 | 18 | 14 |
| Age categorical<br>Units: Subjects | | | |
| From 65-84 years | 34 | 9 | 8 |
| From 18-64 Years | 29 | 9 | 6 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 63.90 | 63.28 | 64.85 |
| standard deviation | ± 8.332 | ± 9.157 | ± 6.481 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 6 | 4 |
| Male | 39 | 12 | 10 |
| Race<br>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<br>Units: Subjects | | | |
| Not Reported | 2 | 0 | 1 |
| Not Hispanic or Latino | 61 | 18 | 13 |

| **Reporting group values** | Placebo (Hepatic Evaluable Population) | | |
|---|---|---|---|
| Number of subjects | 4 | | |
| Age categorical<br>Units: Subjects | | | |
| From 65-84 years | 0 | | |
| From 18-64 Years | 4 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 60.12 | | |
| standard deviation | ± 3.419 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | | |
| Male | 4 | | |
| Race<br>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<br>Units: Subjects | | | |
| Not Reported | 0 | | |
| Not Hispanic or Latino | 4 | | |

## 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 >= 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 × 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 >= 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

## Primary: Cardiac Best Response

| | |
|---|---|
| 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

| Statistical analysis title | 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

| End point values | 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**

| Statistical analysis title | 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 | |

| End point values | 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

| Statistical analysis title | 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 |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

| 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 title | Total |
| 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 %

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

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

| | | | |
|---|---|---|---|
| Muscle spasms | | | |
| subjects affected / exposed | 6 / 66 (9.09%) | 3 / 63 (4.76%) | 9 / 129 (6.98%) |
| occurrences (all) | 7 | 3 | 10 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 4 / 63 (6.35%) | 9 / 129 (6.98%) |
| occurrences (all) | 5 | 4 | 9 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 2 / 63 (3.17%) | 7 / 129 (5.43%) |
| occurrences (all) | 5 | 3 | 8 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 66 (9.09%) | 8 / 63 (12.70%) | 14 / 129 (10.85%) |
| occurrences (all) | 6 | 10 | 16 |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 66 (9.09%) | 3 / 63 (4.76%) | 9 / 129 (6.98%) |
| occurrences (all) | 6 | 5 | 11 |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 4 / 63 (6.35%) | 7 / 129 (5.43%) |
| occurrences (all) | 3 | 4 | 7 |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 3 / 63 (4.76%) | 6 / 129 (4.65%) |
| occurrences (all) | 4 | 6 | 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:<br>- Modified inclusion and exclusion criteria to clarify definition of the subject population<br>- Prohibited use of doxycycline for 6 weeks before study entry and during the study (unless required for treatment of infection)<br>- Clarified timing of 6-minute walk tests (6MWTs) and emphasized that two 6MWTs were required at Screening<br>- Clarified management of suspected systemic infusion-related/hypersensitivity AEs<br>- Extended the AE/serious adverse event (SAE) reporting period<br>- Expanded description of safety analyses |
| 25 April 2017 | Amendment 2 was dated 25 April 2017 and included the following key changes:<br>- Added new endpoints and modified existing endpoints; secondary and exploratory endpoints were modified following receipt of scientific advice on the statistical analysis plan (SAP)<br>- Increased the number of subjects (from at least 100 to up to 130)<br>- Removed a requirement for monthly collection of additional coagulation indices<br>- Corrected Inclusion Criterion #7 to align with existing stratification factor<br>- Updated analysis populations and statistical analyses to align with the SAP |
| 22 October 2017 | Amendment 3 was dated 22 October 2017 and included the following key changes:<br>- Modified existing secondary and exploratory endpoints<br>- Added NT-proBNP slope over 12 months of treatment as a secondary endpoint<br>- Modified statistical section to align with updated secondary and exploratory endpoints |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported