Clinical trial results:
A randomised, double-blind study evaluating the safety, tolerability, and clinical outcome of Neoven compared to Vaminolact® in premature extreme low birth weight (ELBW) infants.

Summary

EudraCT number	2009-012603-26
Trial protocol	BE DE FR
Global end of trial date	16 April 2011

Results information

Result version number	v1 (current)
This version publication date	09 March 2019
First version publication date	09 March 2019

Trial information

Trial identification

Sponsor protocol code	005-NEOV-003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi Deutschland GmbH
Sponsor organisation address	Borkenberg 14, Oberursel, Germany, 61440
Public contact	Divisional Medical & Clinical Affairs Clinical Nutrition & Ketosteril, Fresenius Kabi Deutschland GmbH , trial-disclosure@fresenius-kabi.com
Scientific contact	Divisional Medical & Clinical Affairs Clinical Nutrition & Ketosteril, Fresenius Kabi Deutschland GmbH , trial-disclosure@fresenius-kabi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000042-PIP01-07
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	24 February 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to evaluate the safety, tolerability, protein accretion, amino acid plasma levels and clinical outcome of Neoven compared to Vaminolact in hospitalized premature extreme low birth weight infants.

The hypothesis of this study is that Neoven is non-inferior compared to Vaminolact. Non-inferiority for the primary endpoints in this study was defined as the lack of a pre-defined difference in specific primary safety endpoints (azotemia, metabolic acidosis, hyperammonemia, hyperaminoacidemia and hyperglycemia) between the two treatment groups.

The study presented here, 05-NEOV-003 and another similar study, 05-NEOV-002 (EudraCT number: 2009-012602-39), were prematurely terminated due to a very low recruitment rate. The data of both studies were analyzed together and described in one report. Due to the premature termination of the studies, it was decided to produce an abridged statistical evaluation only. All planned inference statistics were dropped.

Protection of trial subjects:

Subject protection was ensured by high medical and ethical standards in accordance with Declaration of Helsinki, Good Clinical Practice and applicable national and local laws and regulations. The signed informed consent was obtained from the legal representative of the patient prior to inclusion in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2010
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	Belgium: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Netherlands: 12
Worldwide total number of subjects	17
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	17
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

12 patients were enrolled in study 05-NEOV-002 and 5 patients were enrolled in study 05-NEOV-003. Overall, 17 patients were enrolled in both studies in 3 centers, thereof 9 (52.9 %) patients in the Neoven group and 8 (47.1 %) patients in the Vaminolact group. The data of patients enrolled in both prematurely ended studies were analyzed together.

Pre-assignment

Screening details:

Following patients were enrolled:
Study 05-NEOV-002: male and female very low birth weight (bw) infants with a bw of 800 g to 1500 g, gestational age of 25 to 31 weeks, and < 48 hours after birth
Study 05-NEOV-003: male and female premature extreme low bw infants with a bw ≤ 1000 g, gestational age of ≤ 29 weeks, and < 48 hours after birth

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

Blinding implementation details:

Study medication was provided as bulk products to the hospital pharmacy and/or to laboratory for masking due to the different strengths of products: Neoven has strength of 10 % and Vaminolact of 6.5 %. Neoven was diluted to a strength of 6.5 %. The responsible contractor provided a blinded final PN product which did not reveal any treatment allocation. Additional independent unblinded study monitors checked adherence to pre-defined working procedures.

Arms

Are arms mutually exclusive?	Yes
Arm title	Neoven

Arm description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 3 patients in study 05-NEOV-003.
Participants received Neoven to provide amino acids (AA) in the frame of a complete parenteral nutrition

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

Dosage and administration details:

Neoven was infused over at least 20 hours per treatment day for a minimum of 5 days in Study 05-NEOV-002 or for a minimum of 6 days in Study 05-NEOV-003.
If clinically needed, the treatment period lasted until patient’s discharge; the maximum duration of the treatment period was limited to 28 days.
In study 05-NEOV-002, the dose was increased stepwise up to 2.0 to 3.0 g AA/kg body weight/day on Day 3 of treatment, and in study 05-NEOV-003 up to 2.5 to 4.0 g AA/kg body weight/day on Day 4 of treatment.

Arm title	Vaminolact

Arm description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 2 patients in study 05-NEOV-003.
Participants received Vaminolact to provide AA in the frame of a complete parenteral nutrition

Arm type	Active comparator

Investigational medicinal product name	Vaminolact
Investigational medicinal product code	
Other name	Vaminolac, Vamin Infant
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vaminolact was infused over at least 20 hours per treatment day for a minimum of 5 days in the study 05-NEOV-002 or for a minimum of 6 days in study 05-NEOV-003.
If clinically needed, the treatment period lasted until patient's discharge; the maximum duration of the treatment period was limited to 28 days.
In Study 05-NEOV-002, the dose was increased stepwise up to 2.0 to 3.0 g AA/kg body weight/day on Day 3 of treatment, and in study 05-NEOV-003 up to 2.5 to 4.0 g AA/kg body weight/day on Day 4 of treatment.

Number of subjects in period 1	Neoven	Vaminolact
Started	9	8
Completed	7	8
Not completed	2	0
Adverse event, serious fatal	1	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Neoven

Reporting group description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 3 patients in study 05-NEOV-003.
Participants received Neoven to provide amino acids (AA) in the frame of a complete parenteral nutrition

Reporting group title	Vaminolact

Reporting group description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 2 patients in study 05-NEOV-003.
Participants received Vaminolact to provide AA in the frame of a complete parenteral nutrition

Reporting group values	Neoven	Vaminolact	Total
Number of subjects	9	8	17
Age categorical			
Patients from two studies: 05-NEOV-002 and 05-NEOV-003			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	9	8	17
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Patients from two studies: 05-NEOV-002 and 05-NEOV-003			
Units: hours			
arithmetic mean	38.89	37.25	
standard deviation	± 8.038	± 13.709	-
Gender categorical			
Patients from two studies: 05-NEOV-002 and 05-NEOV-003			
Units: Subjects			
Female	2	5	7
Male	7	3	10

Subject analysis sets

Subject analysis set title	Safety Set Based on Joint Study Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Where possible, the tables and listings were based on the joined populations of two studies: 05-NEOV-002 and 05-NEOV-003 (joint study population).
The only analysis population was the Safety Set, which was defined as all patients who were treated with study medication, regardless how much and when they received study treatment. The patient description and the analysis of safety and efficacy was performed for this population.

Reporting group values	Safety Set Based on Joint Study Population		
Number of subjects	17		
Age categorical			
Patients from two studies: 05-NEOV-002 and 05-NEOV-003			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	17		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Patients from two studies: 05-NEOV-002 and 05-NEOV-003			
Units: hours			
arithmetic mean	38.12		
standard deviation	± 10.735		
Gender categorical			
Patients from two studies: 05-NEOV-002 and 05-NEOV-003			
Units: Subjects			
Female	7		
Male	10		

End points

End points reporting groups

Reporting group title	Neoven

Reporting group description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 3 patients in study 05-NEOV-003.
Participants received Neoven to provide amino acids (AA) in the frame of a complete parenteral nutrition

Reporting group title	Vaminolact

Reporting group description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 2 patients in study 05-NEOV-003.
Participants received Vaminolact to provide AA in the frame of a complete parenteral nutrition

Subject analysis set title	Safety Set Based on Joint Study Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Where possible, the tables and listings were based on the joined populations of two studies: 05-NEOV-002 and 05-NEOV-003 (joint study population).
The only analysis population was the Safety Set, which was defined as all patients who were treated with study medication, regardless how much and when they received study treatment. The patient description and the analysis of safety and efficacy was performed for this population.

Primary: Occurrence of hyperammonaemia

End point title	Occurrence of hyperammonaemia[1]

End point description:

The primary variables were seen as safety parameters. The assessment of hyperammonaemia was based on the ammonia measurements.

End point type	Primary

End point timeframe:

The assessment of hyperammonaemia was based on the ammonia measurements, which were planned on Study Day 3 in Study 05-NEOV-002 and on Study Day 4 or Study Day 5 in Study 05-NEOV-003.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature termination of the study, it was decided to produce an abridged statistical evaluation only.
All planned inference statistics were dropped.

End point values	Neoven	Vaminolact	Safety Set Based on Joint Study Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9[2]	8[3]	17[4]	
Units: Number of Subjects with at Least 1 Event	1	0	1	

Notes:

[2] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events
[3] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events
[4] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of metabolic acidosis

End point title	Occurrence of metabolic acidosis[5]

End point description:

The primary variables were seen as safety parameters. Metabolic acidosis was assessed from pH

End point type	Primary

End point timeframe:

05-NEOV-002: On Study Day (D) 3, D5 & on D of last infusion.
05-NEOV-003: once between D6 & 8 and on D of last infusion.
Also on D8, 11 or 12, 15 & 22 in 05-NEOV-002 and once between D13 & 15 in 05-NEOV-003 if patient continued to receive study drugs

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature termination of the study, it was decided to produce an abridged statistical evaluation only.
All planned inference statistics were dropped.

End point values	Neoven	Vaminolact	Safety Set Based on Joint Study Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9[6]	8[7]	17[8]	
Units: Number of Subjects with at Least 1 Event	4	1	5	

Notes:

[6] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events
[7] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events
[8] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of azotaemia

End point title	Occurrence of azotaemia[9]

End point description:

The primary variables were seen as safety parameters. Azotaemia was assessed from blood urea nitrogen

End point type	Primary

End point timeframe:

05-NEOV-002: On Study Day (D) 3, D5 & on D of last infusion.
05-NEOV-003: once between D6 & 8 and on D of last infusion.
Also on D8, 11 or 12, 15 & 22 in 05-NEOV-002 and once between D13 & 15 in 05-NEOV-003 if patient continued to receive study drugs

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature termination of the study, it was decided to produce an abridged statistical evaluation only.
All planned inference statistics were dropped.

End point values	Neoven	Vaminolact	Safety Set Based on Joint Study Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9[10]	8[11]	17[12]	
Units: Number of Subjects with at Least 1 Event	1	0	1	

Notes:

[10] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

[11] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

[12] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of hyperaminoacidaemia

End point title	Occurrence of hyperaminoacidaemia[13]

End point description:

The primary variables were seen as safety parameters. Hyperaminoacidaemia was assessed based on measurements of AAs

End point type	Primary

End point timeframe:

The measurements of amino acids, by means of which hyperaminoacidaemia was assessed, were performed on Day 5 and on the day last study infusion stopped in 05-NEOV-002, and on Day 5 or Day 6 and on the day last study infusion stopped in 05-NEOV-003

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature termination of the study, it was decided to produce an abridged statistical evaluation only.
All planned inference statistics were dropped.

End point values	Neoven	Vaminolact	Safety Set Based on Joint Study Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6[14]	7[15]	13[16]	
Units: Number of Subjects with at Least 1 Event	0	0	0	

Notes:

[14] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

[15] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

[16] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of hyperglycaemia

End point title	Occurrence of hyperglycaemia[17]

End point description:

The primary variables were seen as safety parameters. Hyperglycaemia was assessed based on measurements of blood glucose.

End point type	Primary

End point timeframe:

05-NEOV-002: On Study Day (D) 3, D5 & on D of last infusion.
05-NEOV-003: once between D6 & 8 and on D of last infusion.
Also on D8, 11 or 12, 15 & 22 in 05-NEOV-002 and once between D13 & 15 in 05-NEOV-003 if patient continued to receive study drugs

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature termination of the study, it was decided to produce an abridged statistical evaluation only.
All planned inference statistics were dropped.

End point values	Neoven	Vaminolact	Safety Set Based on Joint Study Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9[18]	8[19]	17[20]	
Units: Number of Subjects with at Least 1 Event	1	0	1	

Notes:

[18] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

[19] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

[20] - Safety Set Based on Joint Study Population (05-NEOV-002 and 05-NEOV-003). Post-baseline events

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From receipt of informed consent until the end of 1st period of investigations (28 days after last treatment with study drugs) in 05-NEOV-002 and until the end of follow-up (4- 6 weeks after last treatment with study drugs) in 05-NEOV-003

Adverse event reporting additional description:

05-NEOV-002: Reporting period for serious AEs (SAEs) started from receipt of informed consent until the end of 2nd period of investigations (up to the age of 2 years life-corrected age)

All SAEs and all treatment-emergent AEs (treatment period + follow-up period), occurred in the studies, are listed below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Neoven

Reporting group description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 3 patients in study 05-NEOV-003.
Participants received Neoven to provide AA in the frame of a complete parenteral nutrition

Reporting group title	Vaminolact

Reporting group description:

This arm includes patients from both studies: 05-NEOV-002 and 05-NEOV-003.
Of these, 6 patients were enrolled in Study 05-NEOV-002 and 2 patients in study 05-NEOV-003.
Participants received Vaminolact to provide AA in the frame of a complete parenteral nutrition

Serious adverse events	Neoven	Vaminolact	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	4 / 8 (50.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intraventricular haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Gastrointestinal disorders			
Necrotising colitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Neoven	Vaminolact	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	8 / 8 (100.00%)	
Vascular disorders			
Hypertension	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	3 / 8 (37.50%)	
occurrences (all)	2	3	
Hypotension	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Discomfort	Additional description: Treatment-emergent AE		

subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Oedema peripheral	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Investigations			
Blood calcium increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	5 / 8 (62.50%)	
occurrences (all)	2	5	
Blood urea increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	4 / 9 (44.44%)	3 / 8 (37.50%)	
occurrences (all)	4	3	
Alanine aminotransferase decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	4 / 8 (50.00%)	
occurrences (all)	1	4	
Aspartate aminotransferase decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	3 / 8 (37.50%)	
occurrences (all)	2	4	
Base excess increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	3 / 8 (37.50%)	
occurrences (all)	1	3	
Blood albumin increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Blood phosphorus decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	2 / 8 (25.00%)	
occurrences (all)	1	3	
Mean arterial pressure increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Platelet count increased	Additional description: Treatment-emergent AE		

subjects affected / exposed	0 / 9 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	3	
Blood bicarbonate increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Blood triglycerides increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Gamma-glutamyltransferase increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Haemoglobin decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Ammonia increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Bilirubin conjugated increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Blood chloride increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Body temperature decreased	Additional description: Treatment-emergent AE		

subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Body temperature increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Haematocrit decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Protein total decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Congenital choroid plexus cyst	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Patent ductus arteriosus	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tachycardia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	4 / 9 (44.44%)	1 / 8 (12.50%)	
occurrences (all)	5	1	
Anaemia neonatal	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Thrombocytopenia	Additional description: Treatment-emergent AE		

subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation	Additional description: Treatment-emergent AE		
subjects affected / exposed	3 / 9 (33.33%)	1 / 8 (12.50%)	
occurrences (all)	3	2	
Impaired gastric emptying	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vomiting	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hyperbilirubinaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	5 / 8 (62.50%)	
occurrences (all)	1	5	
Cholestasis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Erythema	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Azotaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Staphylococcal infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Device related infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Staphylococcal sepsis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Conjunctivitis bacterial	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Neonatal infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Staphylococcal skin infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Metabolic acidosis	Additional description: Treatment-emergent AE		
subjects affected / exposed	4 / 9 (44.44%)	1 / 8 (12.50%)	
occurrences (all)	5	1	
Feeding disorder	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Hyponatraemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Hypercalcaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hyperglycaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypocalcaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypoproteinaemia	Additional description: Treatment-emergent AE		

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2010	Relevant reasons for amendment: - Correction of some errors in exclusion criteria, more detailed description of some exclusion criteria - Correction of reference ranges for haematocrit and haemoglobin - Correction of blood sampling procedure - Removal of interim analysis statement - Clarified description of random and patient number allocation included - Corrected description of medical monitoring process - Clarification of laboratory data documentation to prevent unblinding - Clarification of withdrawal procedure - The optional N-balance will be done at Day 6 instead of day of enrolment - Correction of study drug label description - Clarification that unused study drug and material has to be returned to sponsor - Clarification that adverse event reporting period starts after first study-related procedure - Addition of a physical examination at Day Last Study Infusion Stops - Clarification of AE reporting procedure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Premature termination of studies 05-NEOV-002 and 05-NEOV-003 due to a very low recruitment rate. Data of both studies were analyzed together and described in one clinical study report. Abridged statistical evaluation only.

Notes: