



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) | EMA-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 | | |

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 18 October 2010 | <p>Relevant reasons for amendment:</p> <ul style="list-style-type: none">- 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: