Clinical trial results:
A randomised, double-blind study evaluating the safety, tolerability, and amino acid plasma levels of Neoven compared to Vaminolact® in infants after surgical interventions

Summary

EudraCT number	2008-000429-20
Trial protocol	NL BE DE
Global end of trial date	18 December 2009

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	05-NEOV-001

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 September 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate non-inferiority of Neoven when comparing all individual plasma amino acids (AA) concentrations.

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:

Routine post-operative therapy

Evidence for comparator:

Vaminolact is a well-established paediatric AA solution in many countries. As Neoven has compositional similarities to Vaminolact (e.g. mostly identical composition of essential AA), the proof-of-consept of new compositional design elements can be evaluated better.

Actual start date of recruitment	30 December 2008
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	Germany: 6
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Netherlands: 14
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	10
Newborns (0-27 days)	11
Infants and toddlers (28 days-23 months)	2
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:

Overall, 23 patients were enrolled in the study in 4 centres in total: in The Netherlands (2 centres), Belgium (1 centre) and Germany (1 centre)

Pre-assignment

Screening details:

Screened were male and female preterm and term newborns, infants and toddlers with surgical interventions of the gastrointestinal tract due to congenital malformations.
There were no screening failures - all patients screened for this study (n=23) were randomized.

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 hospital pharmacists for masking due to different strengths of study products: Neoven had a strength of 10% AAs and Vaminolact a strength of 6.5%. Neoven was diluted to a strength of 6.5 %. The unblinded pharmacists provided a blinded PN product whereas the labelling of the final product did not reveal the 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:

Participants received Neoven to provide 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 a minimum of 5 days -7 days and a maximum of 10 days. Dosage was increased over the first 3 study days from 1.0 g/kg/day +/- 0.5 g/kg/day at study day 1 to 2.0 g/kg/day +/- 0.5 g/kg/day at study day 2 and 2.5 g/kg/day +/- 0.25 g/kg/day at study day 3. From Day 3 onwards the dosage was maintained until the end of study. Study treatment was to be ceased on study day 10 or in the event that enteral/oral intake exceeded 35 % of energy (calories) of PN; in which case the amount of PN intake was to be lowered correspondingly.

Arm title	Vaminolact

Arm description:

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 a minimum of 5 days-7 days and a maximum of 10 days. Dosage was

increased over the first 3 study days from 1.0 g/kg/day +/- 0.5 g/kg/day at study day 1 to 2.0 g/kg/day +/- 0.5 g/kg/day at study day and 2.5 g/kg/day +/- 0.25 g/kg/day at study day 3. From Day 3 onwards the dosage was maintained until the end of study. Study treatment was to be ceased on study day 10 or in the event that enteral/oral intake exceeded 35 % of energy (calories) of PN; in which case the amount of PN intake was to be lowered correspondingly.

Number of subjects in period 1	Neoven	Vaminolact
Started	17	6
Completed	12	6
Not completed	5	0
Adverse event, serious fatal	1	-
Adverse event, non-fatal	1	-
Protocol deviation	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Neoven
Reporting group description:	
Participants received Neoven to provide AA in the frame of a complete parenteral nutrition	
Reporting group title	Vaminolact
Reporting group description:	
Participants received Vaminolact to provide AA in the frame of a complete parenteral nutrition	

Reporting group values	Neoven	Vaminolact	Total
Number of subjects	17	6	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	10	0	10
Newborns (0-27 days)	5	6	11
Infants and toddlers (28 days-23 months)	2	0	2
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 Units: days			
arithmetic mean	19.7	1.8	
standard deviation	± 51.82	± 0.98	-
Gender categorical Units: Subjects			
Female	13	3	16
Male	4	3	7

End points

End points reporting groups

Reporting group title	Neoven

Reporting group description:

Participants received Neoven to provide AA in the frame of a complete parenteral nutrition

Reporting group title	Vaminolact

Reporting group description:

Participants received Vaminolact to provide AA in the frame of a complete parenteral nutrition

Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Population for the intent-to-treat (ITT) analysis was defined as all patients in the safety population, for whom one AA profile was available after having reached full-dose for at least one day.

Subject analysis set title	Amino Acid (AA) Pattern Analysis Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The AA Pattern Analysis Population was defined as all patients in the Full Analysis Population, for whom one AA profile was available after at least 5 treatment days were performed and who completed as described in the protocol. The AA Pattern Analysis Population was the target population for the 12:6 patients allocation. It was used only for the analysis of AA Levels.

Subject analysis set title	Per-Protocol (PP) Population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP Population was defined as all patients in the AA pattern analysis population, for whom one AA profile was available after at least 5 treatment days were performed and who completed as described in the protocol without major protocol violations. Efficacy parameters and AAs were evaluated for the PP Population.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population was defined as all patients who were treated with study medication, regardless how much and how they received study treatment. The patient description and the analysis of safety were performed for this population

Primary: Sum of individual relative changes of the 23 pre-specified AA in plasma

End point title	Sum of individual relative changes of the 23 pre-specified AA in plasma

End point description:

For each of the 23 pre-specified AAs (20 standard AAs + taurine, citrulline, and ornithine), the relative difference to the midpoint of the normal range was computed and the absolute change (relative difference at baseline compared to relative difference after last treatment) was generated. Then the sum of all 23 changes was computed.

End point type	Primary

End point timeframe:

AA plasma concentrations at baseline and after last treatment (maximum 10 days) were used to calculate the primary endpoint.

End point values	Neoven	Vaminolact		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[1]	6[2]		
Units: percent change				
arithmetic mean (standard deviation)	-35.1 (± 330.5)	202.4 (± 150)		

Notes:

[1] - AA Pattern Analysis Population
Based on normal ranges of Medizinisches Labor Bremen
[2] - AA Pattern Analysis Population
Based on normal ranges of Medizinisches Labor Bremen

Statistical analyses

Statistical analysis title	Non-inferiority

Statistical analysis description:

The study hypothesis was that the plasma AA profile of Neoven was not inferior to that of Vaminolact. Non-inferiority meant that, when the relative differences of all AAs from the midpoint of the normal range were considered, the sum would not be relevantly higher (inferior) to that sum observed in the Vaminolact group. For this comparison, the baseline concentrations were taken into account.

Comparison groups	Neoven v Vaminolact
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Absolute change of relative differences
Point estimate	237.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.8
upper limit	538.7
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for adverse events (AEs) started from the time of informed consent and ended 28 (+ 7) days after last treatment

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Neoven

Reporting group description: -

Reporting group title	Vaminolact

Reporting group description: -

Serious adverse events	Neoven	Vaminolact	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	0 / 6 (0.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Persistent foetal circulation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Shock			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	14 / 17 (82.35%)	6 / 6 (100.00%)	
Investigations			
White blood cell count increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Platelet count increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased	Additional description: Treatment-emergent AE		
subjects affected / exposed	5 / 17 (29.41%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Gamma-glutamyltransferase increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 17 (11.76%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Blood bilirubin increased	Additional description: Treatment-emergent AE		

subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Postoperative wound infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Atrial septal defect	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Congenital hydronephrosis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Congenital megaureter	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia	Additional description: Treatment-emergent AE		
subjects affected / exposed	3 / 17 (17.65%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Tachycardia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Convulsion	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Infusion site swelling	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 17 (11.76%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Constipation	Additional description: Treatment-emergent AE		
subjects affected / exposed	2 / 17 (11.76%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Gastrointestinal hypomotility	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal motility disorder	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Intestinal perforation	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Umbilical hernia	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis neonatal	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pleural effusion	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholestasis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Kidney enlargement	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Polyuria	Additional description: Treatment-emergent AE		

subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Omphalitis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Bacterial sepsis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Catheter related infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Catheter sepsis	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nasopharyngitis	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oral fungal infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	0 / 17 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Staphylococcal infection	Additional description: Treatment-emergent AE		
subjects affected / exposed	1 / 17 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2008	Reason for amendment: - both sites in UK cancelled their study participation and will be replaced by a new site in Germany - modification of the reasons for a premature termination of the trial - detailed definitions in expedited safety reporting - correction of sample size calculation model - more precise description of IMP handling - modification of follow-up investigation - involvement of a new third party for amino acid sample shipments
21 April 2009	Relevant reason for amendment: - Inclusion of the new site into the study - Adaptation of the planned study start and end - Allowance of additional surgery - Vaminolact continuation solution will be provided by Fresenius Kabi also for Belgium and the Netherlands - Introduction of updated laboratory information - Introduction of new safety reporting procedures - New Study Drug Labels in Appendix 3 for Neoven and Vaminolact continuation solution

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported