Clinical Protocol: 7032-001

TITLE PAGE/PASS INFORMATION

Protocol Title:	A Multicenter, Non-interventional, Uncontrolled, Open-label, Observational Study in Children (up to Age 24 Months) to Evaluate Serum Mg Levels Associated with the Intake of Numeta G 16% E
Protocol ID#:	7032-001
Protocol Date Original	2013 DEC 02
Protocol Amendment No. 1	2014 JUL 25
Protocol Amendment No. 2	2016 AUG 24
EU PASS Register #:	ENCEPP/SDPP/7113
MEDICINAL PRODUCT	
Active Substance:	Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil
Medicinal Product:	Numeta G 16% E
Product Reference #:	SE/H/0918/02/DC
Procedure #:	SE/H/918
Marketing Authorization Holder (MAH)	Baxter Healthcare Corporation initiated, managed, and financed this study.
Joint PASS	No
RESEARCH QUESTIONS & OBJECTIVES	
Research Question & Objectives	
Primary Objective:	The primary objective of this study is to generate descriptive data for serum magnesium (Mg) levels in full-term, new born infants and children up to 24 months of age following dosing with Numeta G 16% E.
Secondary Objectives:	The secondary objectives of this study are to observe the following parameters in subjects who receive parenteral nutrition (PN) with Numeta G 16% E: Actual infused Numeta G 16% E intake (mL/kg/day) Actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta) Adverse events (AEs) and serious adverse events (SAEs), including clinically significant (CS) abnormal laboratory results and CS abnormal vital signs
Countries of Study:	Belgium, France, Sweden

Author:	Drew S. Jones, MD, MPH, MBA Clinical Development Lead Baxter Healthcare Corporation Round Lake, IL 60076-9610, USA Tel: 1+224-270-2659
MAH:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015 United States Tel: 1+224-948-2601
MAH Contact Person:	Eloïse Roussat Project Manager Clinical Operations BE-ALLIANCE-PARK, Braine, Belgium Tel: +32(0)2 386 9697

SUMMARY AND JUSTIFICATION OF AMENDMENT CHANGES

According to the agreed Milestones the Study Progress Report 1 was provided in February 2016 to the RMS of the medicinal product after 12 months of enrolment. As described in the report, there is a very slow recruitment in the age group of 1-2 years old children. Through the draft assessment report, RMS accepted that Final Study Report be submitted Q1 2018 and recommended to submit an update of the Study Progress Report 2 to Pharmacovigilance Risk Assessment Committee (PRAC) Q4 2016.

Substantive changes to the original protocol include:

- Increase study duration
- Update of milestones
- Corrections of minor inconsistencies

INDIVIDUAL CHANGES

Section 4.0 (ABSTRACT), paragraph Study size:

- The target sample size of 100 infants/children (ages 0 to 24 months) is based on the feasibility of timely enrollment of subjects for generating reference data and summary descriptive statistics in an 18-month period, rather than based on a formal power calculation.

Will be changed to read:

- The target sample size of 100 infants/children (ages 0 to 24 months) is based on the feasibility of timely enrollment of subjects for generating reference data and summary descriptive statistics in an 33-month period, rather than based on a formal power calculation.

Section 4.0 (ABSTRACT), paragraph Data Analysis

- Vital signs and laboratory tests will be summarized on a daily basis. Laboratory results and vital signs will also be summarized in shift tables comparing results at end of treatment with those at baseline (based on CS categories).

Will be changed to read:

- Vital signs and laboratory tests will be summarized on a daily basis. Laboratory results and vital signs will also be summarized in shift tables comparing results during treatment with those at baseline.

Section 5.0 (Amendments and Updates):

Will be added

- Amendment 2 dated 2016 AUG 24

Section 6.0 (Milestones):

Milestone	Planned Date
Start of data collection (first subject in)	Q1 2015
End of data collection (last subject out)	Q1 2017
Study Progress Report 1	Q1 2016 After 12 months of enrollment, the number of subjects enrolled in the study to date, as well as the enrollment rate, will be provided to PRAC.
Study Progress Report 2	NA
Registration in EU PASS Register	prior to start of data collection
Final Report of Study Results	Q3 2017

Will be changed to read:

Milestone	Planned Date
Q4 Start of data collection (first subject in)	Dec 2014
End of data collection (last subject out)	Q3 2017
Study Progress Report 1	Q1 2016 After 12 months of enrollment, the number of subjects enrolled in the study to date, as well as the enrollment rate, will be provided to PRAC.
Study Progress Report 2	Q4 2016
Registration in EU PASS Register	prior to start of data collection
Final Report of Study Results	Q1 2018

Section 9.2 paragraph 3 (Setting):

- Enrollment for this study is anticipated to continue for approximately 18 months after initiation of the study.

Will be changed to read:

- Enrollment for this study is anticipated to continue for approximately 33 months after initiation of the study.

Section 9.2.2 paragraph 1 (Duration of Study Period(s) and Subject Participation):

- The expected overall duration of the study is approximately 18.5 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject procedure).

  Enrollment for this study is anticipated to continue for approximately 18 months after initiation of the study. Screening is limited to a maximum of 2 days. Subjects will participate in this study for a maximum of 15 days after initiation of treatment with Numeta G 16% E.

Will be changed to read:

- The expected overall duration of the study is approximately 33.5 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject procedure).

  Enrollment for this study is anticipated to continue for approximately 33 months after initiation of the study. Screening is limited to a maximum of 2 days. Subjects will participate in this study for a maximum of 15 days after initiation of treatment with Numeta G 16% E.

Section 9.3.2.3 (Vital Signs):

- Vital signs will be measured as determined by the Standard of Care for the study site and recorded in the CRF on a daily basis (refer to Table 1). Vital signs may

include body temperature (°C or °F), respiratory rate (breaths/minute), pulse rate (beats/minute), and supine systolic and diastolic blood pressure (mmHg).

Will be changed to read:

- Vital signs will be measured as determined by the Standard of Care for the study site and recorded in the CRF on a daily basis (refer to Table 1). Vital signs may include body temperature (°C), respiratory rate (breaths/minute), pulse rate (beats/minute), and supine systolic and diastolic blood pressure (mmHg).

Section 9.5 (Study Size):

- The total sample size of 100 infants/children (ages 0 to 24 months) is based on the feasibility of enrollment (within 18 months at the selected sites where collecting Mg levels is standard of care) of subjects for generating reference data and summary descriptive statistics, rather than based on a formal power calculation. A formal power calculation is not planned as no formal hypothesis is being tested in this study. Efforts will be made to enroll an adequate distribution of infants in the age groups of 0 to 1 month and >1 month to 12 months, as well as at least 20 subjects age >12 months to 2 years, in order to ensure adequate sample size to produce summary statistics for the primary endpoint for the above subgroups and to reflect overall clinical practice in the target population.

Will be changed to read:

- The total sample size of 100 infants/children (ages 0 to 24 months) is based on the feasibility of enrollment (within 33 months at the selected sites where collecting Mg levels is standard of care) of subjects for generating reference data and summary descriptive statistics, rather than based on a formal power calculation. A formal power calculation is not planned as no formal hypothesis is being tested in this study. Efforts will be made to enroll an adequate distribution of infants in the age groups of 0 to 1 month and >1 month to 12 months, as well as at least 20 subjects age >12 months to 2 years, in order to ensure adequate sample size to produce summary statistics for the primary endpoint for the above subgroups and to reflect overall clinical practice in the target population.

Section 9.7.3.2 paragraph 2 (Primary Endpoint):

- Analyses pooling together all 100 subjects will be done, followed by a subgroup analysis of subjects age 0 to 1 month, >1 month to 12 months, and >12 months to 2 years. A listing of serum Mg levels for each subject by day will be generated to facilitate monitoring both high and low levels of Mg. Additionally, a listing of subjects with impaired renal function and of patients who have received Mg will be generated. Summaries of Mg level results for these subgroups may be provided, contingent on the sample size in the subgroups.

Will be changed to read:

- Analyses pooling together all 100 subjects will be done, followed by a subgroup analysis of subjects age 0 to 1 month, >1 month to 12 months, and >12 months to 2 years. A listing of serum Mg levels for each subject will be generated to facilitate monitoring both high and low levels of Mg. Additionally, a listing of subjects with impaired renal function and of patients who have received Mg will be generated. Summaries of Mg level results for these subgroups may be provided, contingent on the sample size in the subgroups.

Section 9.7.3.3 (Secondary Endpoints):

- Vital signs and laboratory tests will be summarized on a daily basis. Laboratory results and vital signs will also be summarized in shift tables comparing results at end of treatment with those at baseline (based on CS categories).

Will be changed to read:

- Vital signs and laboratory tests will be summarized on a daily basis. Laboratory results and vital signs will also be summarized in shift tables comparing results during treatment with those at baseline.

Section 14.5 (Investigator Signature) and 14.6 (Sponsor Signatures):

Will be added:

- AMENDMENT No. 2: 2016 AUG 24

ADMINISTRATIVE CHANGES TO THE ORIGINAL PROTOCOL

Administrative changes to the original protocol include:

- Update Sponsor signatures

SERIOUS ADVERSE EVENT REPORTING

The Investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs), to the ethics committee(s) (ECs).

ALL SAEs ARE TO BE REPORTED ON THE
SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND
TRANSMITTED TO THE RESPONSIBLE PARTY
WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

See SAER form for contact information.
Further details are also available in the study team roster.

For information on the assessment and definitions of these events refer to: assessment of AEs in Section 11.1, and definitions of AE in Section 11.2.1, SAE in Section 11.2.2.

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
CRF	case report form
CS	clinically significant
FAS	full analysis set
IC	informed consent
ICF	informed consent form
ICH	International Conference on Harmonizations
IEC	Independent Ethics Committee
IRB	Institutional Review Board
Mg	magnesium
PAS	primary analysis set
PN	parenteral nutrition
PRAC	Pharmacovigilance Risk Assessment Committee
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code

3. RESPONSIBLE PARTIES

The complete list of Investigators and contact information for them will be maintained by the study Sponsor in a separate document (see Section 14.1).

3.1 Investigator(s)

Protocol Author and Sponsor Medical Monitor	Drew S. Jones, MD, MPH, MBA Senior Medical Director Baxter Healthcare Corporation Deerfield, IL 60015, USA Tel: +1 224-948-4274
Qualified Person in Pharmacovigilance	TBD
Principal Investigator	TBD
Coordinating Investigator	TBD
Coordinating Investigator	TBD

4. ABSTRACT

Title: A Multicenter, Non-interventional, Uncontrolled, Open-label, Observational Study in Children (up to Age 24 Months) to Evaluate Serum Magnesium (Mg) Levels Associated with the Intake of Numeta G 16% E

Origin Protocol Dated: 2013 DEC 02
Protocol Amendment 1 Dated: 2014 JUL 25

Protocol Amendment 2 Dated: 2016 AUG 24

Author: Drew S. Jones, MD, MPH, MBA
Senior Medical Director
Baxter Healthcare Corporation
Round Lake, IL 60015-, USA
Tel: +1 224-948-4274

Rationale and background: This non-interventional, observational study is being undertaken to generate data to assess the impact of Numeta G 16% E on serum magnesium (Mg) levels in full-term, new born infants and children up to 24 months of age who require >70% parenteral nutrition (PN) at study entry and who are expected to require at least 50% PN for 5 days.

Research question and objectives: The objective of this study is to generate descriptive data for serum Mg levels in full-term, new born infants and children up to 24 months of age following dosing with Numeta G 16% E.

Study design: This is a multicenter, non-interventional, uncontrolled, open-label, observational, safety study to be conducted in a minimum of 5 study centers in at least 3 European countries (Belgium, France, and Sweden). Baseline serum Mg will be obtained, as Standard of Care, prior to initiating Numeta G 16% E infusions. Subsequent Mg levels will be obtained during routine/Standard of Care for serum electrolyte blood draws. In the event a serum Mg level is found to be outside the reference range for the study site, the Mg level may be repeated at the discretion of the Investigator.

Population: Target enrollment for this study is 100 children (full-term, new born infants and children up to age 24 months) who require >70% PN at study entry and who are expected to require at least 50% PN for 5 days. Efforts will be made to enroll an adequate distribution of infants in the age groups of 0 to 1 month and >1 month to 12 months as well as at least 20 subjects age >12 months to 2 years.

Variables: The key safety variables to be collected for analysis include:

- Serum Mg levels during the study
- Numeta dosing information (actual)
- Nutritional intake (actual)
- AE assessment
- Reason for end of study participation

Data sources: Data will be collected from the medical records of the enrolled subjects and from observation of the subjects during the study.

Study size: The target sample size of 100 infants/children (ages 0 to 24 months) is based on the feasibility of timely enrollment of subjects for generating reference data and summary descriptive statistics in an 33-month period, rather than based on a formal power calculation. Efforts will be made to enroll an adequate distribution of infants in the age groups of 0 to 1 month and >1 month to 12 months, as well as 20 subjects age >12 months to 2 years.

Data analysis: The full analysis set (FAS) will include all subjects who received at least 1 dose of Numeta G 16% E. All subjects who received 5 days of treatment with Numeta

and who have a baseline and a postdose serum Mg level will be included in the primary analysis set (PAS). The FAS and PAS populations will be used to generate summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and graphical displays for the primary endpoint. The secondary endpoints as well as all the listings of individual subjects on each day will be generated using the FAS population. Analysis pooling together all 100 subjects will be done, followed by subgroup analysis of subjects age 0 to 1 month, >1 month to 12 months, and >12 months to 2 years.

Serum Mg levels at baseline and after infusion with Numeta G 16% E will be presented using descriptive summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) at baseline and during treatment for each time point.

Secondary endpoints will be addressed as follows:

- Actual Numeta G 16% E intake (mL/kg/day) will be summarized on a daily basis.
- Actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta) will be summarized on a daily basis.
- All AEs and SAEs will be tabulated by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) coded terms and by seriousness, severity, and relationship.
- Frequency and percentage will be presented for AEs and SAEs as well as CS abnormal laboratory results and CS abnormal vital signs.
- Vital signs and laboratory tests will be summarized on a daily basis. Laboratory results and vital signs will also be summarized in shift tables comparing results during treatment with those at baseline.

5. AMENDMENTS AND UPDATES

Amendment 1 dated2014 JUL 25

Amendment 2 dated 2016 AUG 24

6. MILESTONES

Milestone	Planned Date
Start of data collection (first subject in)	Dec 2014
End of data collection (last subject out)	Q3 2017
Study Progress Report 1	Q1 2016 After 12 months of enrollment, the number of subjects enrolled in the study to date, as well as the enrollment rate, will be provided to PRAC.
Study Progress Report 2	Q4 2016
Registration in EU PASS Register	prior to start of data collection
Final Report of Study Results	Q1 2018

7. RATIONALE AND BACKGROUND

7.1 Medicinal Product Safety Profile

Parenteral nutrition (PN) is the delivery of glucose, amino acids, lipids, electrolytes, vitamins, trace elements, and fluids to provide nutritional support intravenously to patients who cannot be fed by oral or enteral nutrition. It is estimated that PN is used in approximately 12% to 71% of hospitalized patients.[1,2] PN can be prescribed for patients using 1 of 2 methods: the solutions can be either individually tailored or given as a standardized formula. Tailored solutions are based on the principle that no single parenteral regimen can be ideal for all patients because of wide variations of pathological processes, varying ages of patients, and changing nutritional requirements of patients throughout their disease process.[3,4] A standardized PN formulation on the other hand is intended to meet the daily maintenance requirements of a specific patient population (eg, age-, stress- or disease state-specific).

Pediatric patients are especially vulnerable to the energy and protein restriction seen during periods of serious illness, including chronic intestinal failure, respiratory disease, oncological and hematological diseases. The reported prevalence of acute malnutrition in infants and children admitted to hospitals from different countries ranges from 6.1% to 40.9%.[5] In children with an underlying disease, higher prevalence of chronic malnutrition (44-64%) was reported in several studies,[6-11] including a recent study demonstrating a prevalence of 90% in children with congenital heart defects.[9] Poor nutritional status in critically ill children is associated with higher mortality and can result in long-term effects on growth. Therefore, for children who cannot receive adequate enteral nutrition, PN can be lifesaving.[12,13] Given that pediatric patients have different metabolic requirements from adults, a formulation specific to pediatric patients would be optimal.

Numeta is a standardized commercial PN designed to deliver PN to pediatric patients and is presented in the form of a 3-chamber bag. Numeta is offered in 3 different formulations, Numeta G 13% E, Numeta G 16% E, and Numeta G 19% E. Numeta G 13% E is specifically designed to meet the nutritional requirement for preterm newborn infants for whom oral or enteral nutrition is not possible, insufficient or contraindicated. Similarly Numeta G 16% E is formulated for term newborn infants and children up to 2 years, and Numeta G 19% E is indicated for children older than 2 years and adolescents 16 to 18 years old.

The 3 chambers contain a glucose solution, a pediatric amino acids solution with electrolytes, and a lipid emulsion. The amino acids solution of Numeta consists of Primene 5.9%. Primene is currently and has been for several years registered in 5% and 10% concentrations in 14 European countries and is indicated for all pediatric age groups. The lipid emulsion in Numeta contains 12.5% ClinOleic, a dilution of 20% ClinOleic, which is currently approved throughout Europe. Activation of the lipid chamber is optional, resulting in a solution containing amino acids with electrolytes and glucose, with or without lipid.[12] Reconstitution of the components within NUMETA achieves macronutrient/electrolyte/fluid volume ratios meeting the nutritional requirements outlined in the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Guidelines. Numeta is for single use only and it is recommended that after opening the bag, the contents should be used immediately.

7.2 Critical Review of Available Data

Numeta has been registered through the decentralized procedure in Europe in 18 countries. The first implementation of the national license within this decentralized procedure was 20 Jan 2011 in the United Kingdom, which is the international birth date for this product. In March 2013, the marketing authorization holder (MAH) for Numeta (Baxter Healthcare Ltd) became aware of case reports of hypermagnesemia in 3 preterm neonates from Italy receiving Numeta G 13% E. No associated AEs were reported in conjunction with the hypermagnesemia episodes in these patients. In May 2013, Baxter was informed that there were 8 additional case reports of hypermagnesemia from a clinical study (investigator initiated study) in preterm infants (Study Title: Organization and surveillance of PN in premature newborn infants weighing less than 1500 g using Numeta G 13% from first day of life. A prospective, single center, non-interventional, non-comparative, open-labeled, data collection on intakes and nutritional markers as available). No AEs were reported with these 8 cases of hypermagnesemia. A review of the Global Pharmacovigilance database on 04 JUN 2013 identified 13 case reports

(3 from Italy, 8 from the investigator-initiated study, and 2 from Finland had just been received).

Clinically, moderate elevation of Mg concentration in plasma is accompanied by only a few signs such as nausea and vomiting but marked hypermagnesemia is followed by severe neurological and cardiovascular impairment. Hypotension, electrocardiographic changes and evidence of sedation appear at serum Mg concentrations of 3 to 8 mEq/L (1.5 to 4 mmol/L). Disappearance of deep tendon reflexes, respiratory depression, weakness and coma are reported at Mg levels of 2.5 to 7.5 mmol/L; cardiac arrest is reported at serum Mg levels of >7.5 mmol/L. Clinical signs of neuromuscular depression with floppiness, lethargy, and respiratory depression are frequent manifestations of severe neonatal hypermagnesemia.

Following these case reports of hypermagnesemia in preterm neonates, on 10 June 2013, the MAH informed the European national competent authorities that Numeta G 13% E batches had been put on hold at warehouse level. Furthermore, the MAH also outlined a decision to enact a recall of the product from the market to prevent any potential harm to preterm neonates.

On 13 June 2013, considering uncertainties regarding the appropriateness of the levels of Mg in Numeta G 13% E and the clinical consequences of this along with uncertainties regarding the availability of adequate alternatives across the EU member states, the Swedish competent authority (Medical Products Agency) notified the European Medicines Agency, in accordance with Article 107i of Directive 2001/83/EC, of the urgency to undertake a review and agree whether the benefit/risk balance of Numeta G 13 E% remains positive, and to consider whether there is need for additional risk minimization measures.

Although no reports were received for Numeta G 16% E, the Pharmacovigilance Risk Assessment Committee (PRAC) decided at its June 2013 meeting that this product would also be included in the European Medicines Agency review because of its Mg content and of its use in neonates and infants/toddlers up to the age of 2 years who may also be at risk of developing hypermagnesemia.

As such, Baxter is conducting a non-interventional study of Numeta G 16% E to evaluate the impact of Numeta G 16% E on serum Mg levels in children 0 to 24 months of age as a result of its overview of the risk/benefit of the product.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Primary Objective

The primary objective of this study is to generate descriptive data for serum Mg levels in full-term, new born infants and children up to 24 months of age following dosing with Numeta G 16% E.

8.2 Secondary Objectives

The secondary objectives of this study are to observe the following parameters in subjects who receive PN with Numeta G 16% E:

- Actual infused Numeta G 16% E intake (mL/kg/day)
- Actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta)
- AEs and SAEs, including clinically significant (CS) abnormal laboratory results and CS abnormal vital signs

9. RESEARCH METHODS

This is strictly an observational safety study. The measurements performed in this study are as per the Standard of Care for the indication or subject population being studied.

9.1 Study Design

This is a multicenter, non-interventional, uncontrolled, open-label, observational study to evaluate the safety of Numeta G 16% E in approximately 100 pediatric subjects who require >70% PN at study entry and who are expected to require at least 50% PN for 5 days. Treatment with Numeta will be followed for a maximum of 15 days. The study will be conducted in a minimum of 5 study centers in at least 3 European countries (Belgium, France, and Sweden) where the subjects will receive Standard of Care treatment that includes the monitoring of Mg blood levels.

The study consists of a Screening Period to confirm the subject's eligibility for the study, after the informed consent form (ICF) is signed and a Treatment Period where Day 1 is defined as the first day the subject receives Numeta G 16% E. Subjects will participate in this study for a maximum of 15 days after initiation of treatment with Numeta G 16% E.

The overall study design is illustrated in Figure 1.

Figure 1. Study Design

Screening Period (Day -2 to Day 1)	→	Study Treatment Period (Day 1 to Day 15)

9.2 Setting

Target enrollment for this study is 100 hospitalized children (full-term, new born infants, and children up to 24 months of age) who require >70% PN at study entry and who are expected to require at least 50% PN for 5 days. Study participation is limited to 15 days of treatment.

The study will be conducted in a minimum of 5 study centers in at least 3 European countries (Belgium, France, and Sweden). Only study centers that routinely collect Mg blood levels as Standard of Care will participate in this study.

Enrollment for this study is anticipated to continue for approximately 33 months after initiation of the study.

9.2.1 Medicinal Product(s)

All subjects in this study will be treated with Numeta G 16% E. Intravenous dosing is as per the product label and the Investigator's prescription which is based on the individual subject's nutritional needs, body weight (BW), clinical status, and other relevant factors (eg, enteral or oral nutrition intake). Administration, packaging, labeling, and storage for the medicinal product are also described in the product labeling. As this is an open-label study; no blinding will be implemented.

Numeta G 16% E product batch (lot) number(s) will be recorded in the case report form (CRF).

9.2.2 Duration of Study Period(s) and Subject Participation

The expected overall duration of the study is approximately 33.5 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject procedure).

Enrollment for this study is anticipated to continue for approximately 33 months after initiation of the study. Screening is limited to a maximum of 2 days. Subjects will participate in this study for a maximum of 15 days after initiation of treatment with Numeta G 16% E.

9.2.3 Subject Selection Criteria

9.2.3.1 Inclusion Criteria

Subjects who meet ALL of the following criteria are eligible for this study:

1. Hospitalized full term, new born infants and children up to the age of 24 months who require >70% PN at study entry and who are expected to require at least 50% PN for 5 days. Subjects who, while born prematurely, present with a postmenstrual age of ≥ 37 weeks also may be included.
2. Subjects with legal representatives who are able to understand and have voluntarily signed the ICF
3. Subjects who are able to provide both a baseline and at least 1 post-baseline serum Mg level

9.2.3.2 Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. Subjects with a life expectancy <6 days or with a severe illness with foreseeable intercurrent events that could jeopardize the subject's participation
2. Subjects with pathologically elevated concentrations of sodium, potassium, magnesium, calcium and/or phosphorus
3. Subjects with severe hyperglycemia (glucose ≥300 mg/dL)
4. Subjects with uncorrected metabolic disorders, severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (triglycerides >400 mg/dL)
5. Subjects with a congenital abnormality of the amino acid metabolism
6. Subjects with a known hypersensitivity to egg, soy or peanut proteins, or to any of the active substances, excipients, or components of the container
7. Subjects receiving concomitant treatment with ceftriaxone in newborns (≤28 days of age), even if separate infusion lines are used
8. Subjects with specific nutritional requirements that cannot be met by Numeta G 16% E
9. Subjects who are currently using any investigational drug or who are currently enrolled in another clinical study

10. Subjects who are family members or employees of the Investigator.

9.2.4 Informed Consent and Enrollment

Any subject whose legal representative provides informed consent (IC) (ie, signs and dates the ICF and assent form, if applicable) is considered enrolled in the study.

9.2.5 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier (eg, 7032001) to be provided by the responsible party, 2- or 3-digit number study site number (eg, 02) to be provided by the responsible party, and 3- or 4-digit subject number (eg, 0003) reflecting the order of enrollment (ie, signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 7032001-020003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

9.2.6 Screening and Treatment Periods

9.2.6.1 Screening Period (Days -2 to 1)

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome.

After providing written IC, subjects will be screened. Signing of the ICF and Screening may occur on the same day. The Screening Period is defined as the period after the ICF is signed until initiation of treatment on Day 1. The maximum duration of this period is 2 days. The aim of Screening is to assess the eligibility of subjects for participation in the study.

Details on the procedures to be performed at Screening can be found in Table 1.

9.2.6.2 Treatment Period (Days 1 to 16)

During the Treatment Period, subject data will be collected for the following assessments: concomitant medications (nursing mother and infant/child as per the

protocol), serum Mg levels, Numeta G 16% E actual intake, nutritional information (total calorie intake); and AEs.

The aforementioned data may be collected retrospectively for those subjects who were screened within 48 hours after having already received Numeta as per the Standard of Care at the investigative site provided there is a baseline Mg level.

The Study Treatment Period is limited to a maximum of 15 days of dosing with Numeta.

Further details are provided in Table 1.

Table 1. Schedule of Study Procedures and Assessments

Evaluation/Assessment	Screening/ Baseline (Days -2 to 1)	Study Treatment Period (Days 1 to 15)	
		Testing Frequency	Maximum Recording Frequency for SOC Assessments
Informed Consent[a]	X		
Inclusion/Exclusion Criteria (eligibility assessment)	X		
Demographics (including age in months and gender)	X		
Medical history (including diagnosis requiring PN)	X		
Prior Medications/Therapy[b]	X		
Physical Examination	X	EOT	
Height (cm)	X	weekly	
Weight (kg)	X	daily	
BMI (kg/m^2)	X	daily	
Head circumference	X	SOC	once per week
Vital Signs (HR, BP, RR)	X	SOC	once a day in AM
Laboratory Evaluations (NOTE: Blood samples should be collected during SOC blood draws, ideally during a window of time when lipid emulsions are not being infused)			
Hematology			
CBC	X		
Chemistry			
Basic metabolic panel including glucose, calcium, sodium, potassium, bicarbonate, chloride, BUN, creatinine, and phosphorous	X	SOC	once a day

Magnesium level[c]	X	SOC	once a day
Nutrition			
Numeta G 16% E infusion (study therapy; mL/kg/day)[d]		daily	
Breast milk (mL)[e]	X	daily	
Enteral formula (mL)[e, f]	X	daily	
Oral food intake (calories)[e]	X	daily	
Concomittent Medication Assessment[g]	X	daily	
AE Assessment	X[h]	daily	

BMI=body mass index; BP=blood pressure; BUN=blood urea nitrogen; CBC=complete blood count; EOT=end of treatment; HR=heart rate; PN=parenteral nutrition; RR=respiratory rate; SOC=standard of care

[a] Only subjects whose legal representatives provide written IC will undergo Screening assessment.

[b] Collect prior (48 hours) medications/therapy for the subject and mother as applicable.

[c] Blood collection and analysis for serum Mg levels will be performed as per the Standard of Care at the study sites, if possible at 2 to 4 hours post Numeta infusion. In the event a serum Mg level is found to be outside of the reference range for the study site, the Mg level may be repeated at the discretion of the Investigator.

[d] Actual Numeta G 16% E intake (mL/kg/day) plus potential additions to Numeta G 16% E will be recorded as well as start and stop times for Numeta infusions.

[e] Actual nutritional intake (total intake from oral, enteral, and PN sources other than Numeta) will be recorded in mL and converted to calories.

[f] Record the brand name of the formula.

[g] Both subjects' and nursing mothers' concomitant medications will be recorded.

[h] Adverse event collection will commence once the IC has been sign.

9.2.7 Subject Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Treatment CRF. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the Investigator and responsible party have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

9.2.8 Study Stopping Rules

The Sponsor, in conjunction with the approval of the competent authorities and PRAC recommendations, may prematurely terminate this study at any time for any reason. A single study center may also be terminated from participation in the study with the same aforementioned approvals at any time for various reasons such as:

- Inadequate rate of subject enrollment into the study
- Noncompliance with protocol requirements or data collection methods
- Noncompliance with Good Pharmacovigilance Practices guidelines; applicable national and local laws; and/or applicable guidelines or regulations for protecting the rights, safety, and welfare of subjects
- Knowingly submitting false information to the Sponsor or designee.

If the study is prematurely terminated, all collected study data must be provided to the Sponsor.

9.3 Variables

Data will be collected during the Screening Period and throughout the Treatment Period.

9.3.1 Demographics

Demographic data including age and gender will be collected at Screening.

9.3.2 Medical History, Medications, and Non-Drug Therapies

Medical history information will be collected at Screening and recorded in the CRF. APGAR scores for neonates <30 days old will also be collected at Screening.

Medications and therapies received within 48 hours prior to treatment will be recorded at Screening. In addition, mother's antepartum medications within 48 hours of delivery for infants <1 month old will also be recorded at Screening. Prior medication need not be collected for nursing mothers who stopped breast feeding more than 48 hours prior to initiating treatment with Numeta.

There are no restrictions for prior therapy.

Ongoing therapy will be considered as concomitant therapy once Screening has been initiated. During Treatment both subjects' and nursing mothers' concomitant medications will be recorded.

9.3.2.1 Physical Examinations

Physical examinations will be conducted at Screening and End of Treatment as per the Standard of Care for the study site. Any CS new abnormal condition or worsening of a preexisting condition from baseline will be recorded on the AE CRF page.

Weight, height, body mass index (BMI), and head circumference (for infants only) will be collected/calculated at Screening and as per the Schedule of Study Procedures and Assessments (Table 1).

9.3.2.2 Clinical Laboratory Parameters

Blood collection for laboratory tests and serum Mg levels will be performed as per the Standard of Care at the study sites following local laboratory requirements and procedures. Laboratory tests and serum Mg levels are required at Screening. The frequency of blood collection during the Treatment Period will be determined by the Investigator in conjunction with the Standard of Care at the study site (refer to Table 1).

Screening/Baseline Mg levels will be obtained from serum samples already drawn for routine clinical care prior to initiating Numeta G 16% E infusions. Subsequent Mg levels will be obtained during routine/Standard of Care for serum electrolyte blood draws. When possible, samples will be collect 2 to 4 hours post Numeta infusion, and the actual time will be recorded in the CRF. In the event a serum Mg level is found to be outside the reference range for the study sites, the Mg level may be repeated at the discretion of the Investigator (refer to Appendix 14.3).

For each laboratory value outside the reference range of the study site, the Investigator will determine whether the value is CS or not. For CS values, the Investigator will also indicate if the value constitutes a new AE and record the sign(s), symptom(s), or medical diagnosis on the AE CRF. Any abnormal value that persists should be followed at the discretion of the Investigator.

9.3.2.3 Vital Signs

Vital signs will be measured as determined by the Standard of Care for the study site and recorded in the CRF on a daily basis (refer to Table 1). Vital signs may include body temperature (°C), respiratory rate (breaths/minute), pulse rate (beats/minute), and supine systolic and diastolic blood pressure (mmHg).

For each abnormal vital signs value (as per the study site's reference range), the Investigator will determine whether the value is CS or not. For CS values, the Investigator will also indicate if the value constitutes a new AE and record the sign(s),

symptom(s), or medical diagnosis on the AE CRF. Any abnormal value that persists should be followed at the discretion of the Investigator.

9.3.3 Numeta Administration

Intravenous dosing of Numeta G 16% E is as per the product label and the Investigator's prescription which is based on the individual subject's nutritional needs, BW, and other relevant factors (eg, enteral or oral nutrition intake).

The actual intake for Numeta G 16% E (plus any potential additions to Numeta G 16% E) will be recorded in the CRF. Start and stop times for Numeta infusions also will be recorded in the CRF.

9.3.4 Nutrition

Nutritional information, as well as any indication of malabsorption, will be collected and recorded in the CRF during the course of the study. Actual nutritional intake (total intake from oral, enteral, and PN sources other than Numeta) will be recorded in mL and converted to calories.

9.3.5 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, progressive disease, non-compliance with medicinal product/protocol violations, recovery), study terminated by responsible party, or other (reason to be specified by the Investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

The reason for discontinuation will be recorded in the CRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations performed as part of the evaluation of the event will take place under the direction of the Investigator and will be reported to the responsible party. Details of the

outcome may be reported to the appropriate regulatory authorities by the responsible party.

9.4 Data Sources

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study may comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

9.5 Study Size

The total sample size of 100 infants/children (ages 0 to 24 months) is based on the feasibility of enrollment (within 33 months at the selected sites where collecting Mg levels is standard of care) of subjects for generating reference data and summary descriptive statistics, rather than based on a formal power calculation. A formal power calculation is not planned as no formal hypothesis is being tested in this study. Efforts will be made to enroll an adequate distribution of infants in the age groups of 0 to 1 month and >1 month to 12 months, as well as at least 20 subjects age >12 months to 2 years, in order to ensure adequate sample size to produce summary statistics for the primary endpoint for the above subgroups and to reflect overall clinical practice in the target population.

9.6 Data Management

9.6.1 Data Collection Methods

The Investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed ICFs, drug disposition records, correspondence with the EC and the study monitor/responsible party, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), subject diaries (if used), and data clarifications requested by the responsible party.

The Investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The Investigator is responsible for the procurement of data and for the quality of data recorded in the CRFs. CRFs will be provided in paper or electronic form.

If paper format CRFs are provided by the responsible party, all required study data, including corrections, will be clearly and accurately recorded by authorized study site personnel in the CRFs. The CRFs will remain at the site until they are reviewed by the study monitor or responsible party's representative. All original CRFs will be collected by the study monitor, and an identical copy of the complete set of CRFs for each subject will remain in the investigator file at the study site.

If electronic format CRFs are provided by the responsible party, only authorized study site personnel will record or change data in the CRFs. All data should preferably be entered in the CRFs. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site.

The handling of data by the responsible party, including data quality assurance, will comply with regulatory guidelines and the standard operating procedures of the responsible party. Data management and control processes specific to the study will be described in the data management plan (see Annex 14.1).

9.6.2 Software

The software for data management and statistical analysis will be addressed in the Statistical Analysis Plan.

9.7 Data Analysis

9.7.1 Datasets and Analysis Cohorts

The full analysis set (FAS) will include all subjects who received at least 1 dose of Numeta. All subjects who received 5 days of treatment with Numeta G 16% E and who have a baseline and a postdose serum Mg level will be included in the primary analysis set (PAS).

Both the FAS and PAS populations will be used to generate summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and graphical displays for the primary endpoint. The secondary endpoints, as well as all the listings of individual subjects on each day, will be generated using the FAS population.

9.7.2 Handling of Missing, Unused, and Spurious Data

Any procedures used to account for missing, unused, and spurious data will be presented in the Statistical Analysis Plan.

9.7.3 Methods of Analysis

9.7.3.1 Demographics and Baseline Characteristics

Continuous demographics and baseline variables will be summarized using the number of subjects, mean, standard deviation, median, minimum, and maximum. Some variables will be categorized, such as age (infants/children ages 0 to 1 month, >1 month to 2 months, and >12 months to 2 years). These and other categorical variables such as sex will be summarized by reporting the number and percentage of subjects in each category.

9.7.3.2 Primary Endpoint

Serum Mg levels at baseline and after first infusion with Numeta G 16% E as well as the change from baseline will be presented using descriptive summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) at baseline and during treatment on a daily basis for the overall population and by infusion dose. The change from baseline will be plotted by infusion day and infusion dose categories. Additional details will be provided in the Statistical Analysis Plan.

Analyses pooling together all 100 subjects will be done, followed by a subgroup analysis of subjects age 0 to 1 month, >1 month to 12 months, and >12 months to 2 years. A listing of serum Mg levels for each subject will be generated to facilitate monitoring both high and low levels of Mg. Additionally, a listing of subjects with impaired renal function and of patients who have received Mg will be generated. Summaries of Mg level results for these subgroups may be provided, contingent on the sample size in the subgroups.

9.7.3.3 Secondary Endpoints

Secondary endpoints will be addressed as follows:

- Actual Numeta G 16% E intake (mL/kg/day) will be summarized on a daily basis.
- Actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta) will be summarized on a daily basis.

- All AEs and SAEs will be tabulated by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) coded terms and by seriousness, severity, and relationship.
- Frequency and percentage will be presented for AEs and SAEs as well as CS abnormal laboratory results and CS abnormal vital signs.
- Vital signs and laboratory tests will be summarized on a daily basis. Laboratory results and vital signs will also be summarized in shift tables comparing results during treatment with those at baseline.

9.7.4 Planned Interim Analysis of the Study

Not applicable, no interim analyses are planned for this study.

9.8 Quality Control

9.8.1 Investigator's Responsibility

The Investigator will comply with the protocol (which has been approved/given favorable opinion by the competent/health authority and/or EC, as applicable), ICH Good Pharmacovigilance Practices, and applicable regulatory requirements as described in the Noninterventional Trial Agreement. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the responsible party. The term "Investigator" as used in this protocol as well as in other study documents, refers to the Investigator or authorized study personnel that the Investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

9.8.2 Direct Access to Source Data/Documents

The Investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the responsible party or its representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Noninterventional Trial Agreement. If contacted by an applicable regulatory authority, the Investigator will notify the responsible party of contact, cooperate with the authority, provide the responsible party with copies of all documents received from the authority, and allow the responsible party to comment on any responses, as described in the Noninterventional Trial Agreement.

9.8.3 Training

The study monitor will ensure that the Investigator and study site personnel understand all requirements of the protocol and his/her regulatory responsibilities as an Investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the Investigator and will serve as the liaison between the study site and the responsible party.

9.8.4 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The Investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Noninterventional Trial Agreement. Monitoring processes specific to the study will be described in the Clinical Operations Plan (see Annex 14.1).

9.8.5 Auditing

The responsible party and/or responsible party's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH Good Pharmacovigilance Practices, and applicable regulatory guidelines/requirements. The Investigator will permit auditors to visit the study site, as described in the Noninterventional Trial Agreement. Auditing processes specific to the study will be described in the Auditing Plan (see Annex 14.1).

9.8.6 Non-Compliance with the Protocol

The Investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the Investigator will notify the responsible party immediately by phone and confirm notification to the responsible party in writing as soon as possible, but within 1 calendar day after the change is implemented. The responsible party (Baxter) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the responsible party may terminate the Investigator's participation. The responsible party will notify the EC and applicable regulatory authorities of any Investigator termination.

9.9 Limitations of the Research Methods

The non-controlled, observational study design is considered suitable to achieve the study purpose. Possible limitations may include limited study size and lack of a comparator.

9.10 Other Aspects

Not applicable; all aspects of the study are described in the other sections of this protocol.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Compliance Statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for Good Pharmacovigilance Practices.

10.2 Subject Privacy

The Investigator will comply with applicable subject privacy regulations/guidance as described in the Noninterventional Trial Agreement.

10.3 Ethics Committee(s) and Regulatory Authorities

Before enrollment of subjects into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the responsible party's receipt of approval/favorable opinion from the EC and, if required, upon the responsible party's notification of applicable regulatory authority(ies) approval, as described in the Noninterventional Trial Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and relevant regulatory authorities, where applicable. The protocol amendment will only be implemented upon the responsible party's receipt of approval and, if required, upon the responsible party's notification of applicable regulatory authority(ies) approval. Substantive protocol amendments will also be presented to PRAC for approval.

10.4 Informed Consent

Investigators will choose subjects for enrollment considering the study eligibility criteria. The Investigator will exercise no selectivity so that no bias is introduced from this source.

All subjects and/or their legally authorized representative must sign an ICF before entering into the study according to applicable regulatory requirements. Before use, the ICF will be reviewed by the responsible party and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The ICF will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by applicable regulatory requirements. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, subjects or their legally authorized representative(s) agree to participate in the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The responsible party will provide to the Investigator in written form any new information that significantly bears on the subjects' risks associated with medicinal product exposure. The IC will be updated, if necessary. This new information and/or revised ICF that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the Investigator to the subjects who consent to participate in the study.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Assessment of Adverse Events

Each AE from the first medicinal product exposure until study completion/discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous or colloquial expressions (see definitions in Section 11.2). Each AE will be evaluated by the Investigator for:

- Seriousness as defined in Section 11.2.2
- Severity as defined in Section 11.2.4
- Causal relationship to medicinal product exposure as defined in Section 11.2.5

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after study completion/termination, whichever comes first. For purposes of data

capture, the highest severity rating during the course of a single AE will be the severity rating entered on the AE CRF.

If an Investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness.

11.2 Definitions

11.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered medicinal product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product. Events that do not necessarily meet the definition of AEs, regardless of causal association with medicinal product, should be treated as AEs because they may be reportable to Regulatory Authorities according to AE reporting regulation; these include the following:

1. Medicinal product overdose, whether accidental or intentional
2. Medicinal product abuse
3. An event occurring from medicinal product withdrawal
4. Any failure of expected pharmacological action
5. Exposure to medicinal product during pregnancy
6. Unexpected therapeutic or clinical benefit from the medicinal product

11.2.2 Serious Adverse Event

A serious adverse event is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the Investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe

- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse.

11.2.3 Non-Serious Adverse Event

A non-serious AE is an AE that does not meet the criteria of an SAE.

11.2.4 Severity

The Investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild

The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.

The AE resolves spontaneously or may require minimal therapeutic intervention.

- Moderate

The AE produces limited impairment of function and may require therapeutic intervention.

The AE produces no sequelae.

- Severe

The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.

The AE produces sequelae, which require (prolonged) therapeutic intervention.

11.2.5 Causality

Causality is a determination of whether there is a reasonable possibility that the medicinal product is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE assessed as not related or unlikely related, the Investigator shall provide an alternative etiology. For each AE, the Investigator will assess the causal relationship between the medicinal product and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)

Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs and is not associated with the medicinal product (ie, does not follow a reasonable temporal relationship to the administration of medicinal product

Has a much more likely alternative etiology)

- Unlikely related (either 1 or both circumstances are met)

Has little or no temporal relationship to the medicinal product

A more likely alternative etiology exists

- Possibly related (both circumstances must be met)

Follows a reasonable temporal relationship to the administration of medicinal product

An alternative etiology is equally or less likely compared to the potential relationship to the medicinal product

- Probably related (both circumstances must be met)

Follows a strong temporal relationship to the administration of medicinal product and/or recurs on rechallenge

Positive results in a drug sensitivity test (skin test, etc.)

Unlikely to be attributed to disease or other drugs

Improves upon withdrawal of medicinal product

11.2.6 Preexisting Diseases

Preexisting diseases that are present before entry in to the study are described in the medical history; those that manifest with the same severity, frequency, or duration after medicinal product exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

11.2.7 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, product labeling). “Unexpected” also refers to the AEs that are mentioned in the product labeling as occurring with a class of medicinal products or as anticipated from the pharmacological properties of the medicinal product, but are not specifically mentioned as occurring with the particular medicinal product under investigation.

For the purposes of this study, each unexpected AE experienced by a subject undergoing any study related procedures will be recorded on the AE CRF.

11.2.8 Untoward Medical Occurrences Not Considered Adverse Events

Each serious untoward medical occurrence experienced before the first medicinal product exposure (eg, from the time of signed IC up to but not including the first medicinal product exposure) will be described on the SAE Report. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing any study-related procedure(s) before the first medicinal product exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

11.2.9 Non-Medical Complaints

A non-medical complaint is any alleged product deficiency that relates to identity, quality, durability, reliability, safety, and performance of the product but **does not result in an AE**. Non-medical complaints include but are not limited to the following:

- Device malfunctions, which are defined as failure of the device to meet its performance specifications or otherwise to perform as intended
- Reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product that causes it to malfunction or to present a hazard or fail to meet label claims

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Investigator will comply with the publication policy as described in the Noninterventional Trial Agreement.

The Investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

13. REFERENCE LIST

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Appendix 1 Study Drug Preparation and Dispensing Instructions

Insert product label.

14. ANNEXES

14.1 List of Stand-Alone Documents

No.	Document Reference No.	Date	Title
1	TBD	not finalized	Study Organization
2	TBD	not finalized	Clinical Operations Plan
3	TBD	not finalized	Data Management Plan
4	TBD	not finalized	Auditing Plan

Study Organization: The name and contact information of the individuals involved with the study (eg, investigator(s), responsible party's medical expert and study monitor, responsible party's representative(s), laboratories, steering committees, and oversight committees [including ECs, as applicable] will be maintained by the responsible party and provided to the investigator.

14.2 ENCePP Checklist for Study Protocols

Refer to the completed ENCePP Checklist.

14.3 CALIPER Database

Magnesium levels are presented in the Caliper Database at www.caliperdatabase.com

14.4 Summary of Changes

None

14.5 Investigator Signature

INVESTIGATOR ACKNOWLEDGEMENT

Numeta G 16% E

A Multicenter, Non-interventional, Uncontrolled, Open-label, Observational Study in Children (up to Age 24 Months) to Evaluate Serum Mg Levels Associated with the Intake of Numeta G 16% E

PROTOCOL IDENTIFIER: 7032-001

ORIGINAL: 2013 DEC 02

AMENDMENT No. 1: 2014 JUL 25

AMENDMENT No. 2: 2016 AUG 24

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing ethics committee(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Noninterventional Trial Agreement, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

14.6 Sponsor Signatures

Study Title:	A Multicenter, Non-interventional, Uncontrolled, Open-label, Observational Study in Children (up to Age 24 Months) to Evaluate Serum Mg Levels Associated with the Intake of Numeta G 16% E
Study Number:	7032-001
Final Date:	2013 DEC 02
Amendment No. 1 Date	2014 JUL 25
Amendment No. 2 Date	2016 AUG 24

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

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Project Manager
Life Sciences & Operations

Signed:_____ Date:_____
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