Statistical Analysis Plan: 6344-001

Study Title:	A Randomized, Double-Blind, Controlled, Clinical Trial to Evaluate the Risk of Developing Essential Fatty Acid Deficiency in Pediatric Patients, Including Neonates, Receiving Either Clinolipid (lipid injectable emulsion, USP) 20% or Standard-of-Care Soybean Oil-Based Lipid Emulsion
Study Number:	6344-001
Study Phase:	IV
Study Design	This is a multi-center, randomized, double-blind, controlled, 2-arm, prospective study to evaluate occurrence of essential fatty acid deficiency (EFAD) (diagnosed by Holman Index >0.4) in 100 randomized pediatric patients including neonates, to either Clinolipid or standard-of-care soybean oil-based Intralipid. The study will be conducted at approximately 10 sites in the US.
Product Name:	Clinolipid (lipid injectable emulsion, USP) 20%
Indication:	Clinolipid 20% is a lipid emulsion currently indicated for parenteral nutrition in adults providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated
Statistician:	[redacted]
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, Illinois 60015, USA
Responsible Medical Officer:	[redacted], MD, FACP
Final Date:	30JAN2023

[redacted]

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Study Number:	6344-001
Statistician:	[redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the planned analyses of the study.

Prepa[redacted] Date: 30 January 2023 | 14:03:13 CST

[redacted]
Worldwide Medical
Baxter Healthcare Corporation

Approved [redacted] Date: 30 January 2023 | 14:02:34 CST

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Approved b[redacted] Date: 30 January 2023 | 14:08:02 CST

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Baxter Healthcare Corporation

REVISION HISTORY

Version	Revision Summary	Reason(s) for Revision
1.0	Initial release	N/A
2.0	Amendment 1	Fixed incorrect formulas (gain in weight from baseline, gain in head circumference from baseline, treatment exposure) Updated units and formula for PN carbohydrate intake Added additional parameters to treatment exposure Added new fortifier conversions to conversion table 3 Additional minor clarifications added to nutrition section

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADaM	Analysis Data Models
AE	Adverse Event
AESI	AE of Special Interest
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
ARA	Arachidonic Acid
AST	Aspartate Aminotransferase
AT	Aminotransferase
ATC	Anatomical Therapeutic Chemical
BPD	Bronchopulmonary Dysplasia
BUN	Blood Urea Nitrogen
BW	Body Weight
CA	Corrected Age
Ca	Calcium
CDC	Center for Disease Control
Cl	Chloride
CO2	Bicarbonate
CRA	Clinical Research Associate
CRO	Contract Research Organization
DHA	Docosahexaenoic Acid
DILI	Drug Induced Liver Injury
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
EFAD	Essential Fatty Acid Deficiency
EPA	Eicosapentaenoic Acid
FA	Fatty Acid
FADS1	Fatty Acid Desaturase 1 Gene
FADS2	Fatty Acid Desaturase 2 Gene
FAS	Full Analysis Set
GA	Gestational Age
GGT	Gamma-Glutamyl Transferase
hCG	Human Chorionic Gonadotropin
Hct	Hematocrit
Hgb	Hemoglobin
ICF	Informed Consent Form
ILE	Intravenous Lipid Emulsion
IVH	Intraventricular Hemorrhage
IWRS	Interactive Web Response System
K	Potassium
LA	Linoleic acid

MCH	Mean Corpuscular Hemoglobin
MCHC	MCH Concentration
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
MPV	Mean Platelet Volume
Na	Sodium
NEC	Necrotizing Enterocolitis
P	Phosphorus
PN	Parenteral Nutrition
PNALD	Parenteral Nutrition-Associated Liver Disease
PPS	Per Protocol Set
PT	Preferred Term
PVL	Periventricular Leukomalacia
Q1	First Quartile
Q3	Third Quartile
RBC	Red Blood Cells
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDS	Standard Deviation Score
SDTM	Study Data Tabulation Models
SNPs	Single Nucleotide Polymorphisms
SOC	System Organ Class
SS	Safety Set
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, and Figures
ULN	Upper Limit of Normal
USPI	United States Prescribing Information
WBC	White Blood Cells
WHO	World Health Organization

1. STUDY DETAILS

This statistical analysis plan (SAP) is provided to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on clinical trial protocol 6344-001 amendment version 5.6, dated 22 Feb 2022.

1.1 Study Objectives and Endpoints

1.2 Primary Objective

The primary objective of this study is to evaluate the risk of developing essential fatty acid deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid or standard-of-care 100% soybean oil-based intravenous lipid emulsion (ILE: Intralipid) as a component of parenteral nutrition (PN) within the hospital setting from 7 up to 90 days.

Complete fatty acid (FA) profile will be regularly assessed and EFAD will be defined using a Holman Index (plasma triene:tetraene ratio, specifically 5,8,11-eicosatrienoic acid [mead acid] to 5,8,11,14 eicosatetraenoic acid [arachidonic acid, ARA] ratio) value of >0.4 in the context of low linoleic acid (LA), low ARA, and high eicosatrienoic acid.

Genetic polymorphisms in the fatty acid desaturase 1 gene (FADS1) and fatty acid desaturase 2 gene (FADS2) will also be assessed in a subset of patients (approximately 20%) through Familial Mutation Targeted Testing and the distribution of the polymorphisms will be assessed in the context of the FA profile as the synthesis of gamma-LA and ARA from LA (n-6 pathway) and the synthesis of stearidonic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA (n-3 pathway) require both the delta-5 and delta-6 desaturase enzymes (coded for by FADS1 and FADS2 genes). Genetic material will be obtained from buccal smears in all patients with consent to analysis of FADS1 and FADS2 polymorphisms. From the subset of patients consenting to genetic analysis, the 10 patients (5 Intralipid and 5 Clinolipid) with the lowest levels of ARA at any point during the study and the 10 patients (5 Intralipid and 5 Clinolipid) with the highest levels of ARA at any point during the study will be selected for analysis of single nucleotide polymorphisms (SNPs) within FADS1 and FADS2 genes.

1.3 Secondary Objective(s)

The secondary objectives in patients receiving either Clinolipid or Intralipid are to evaluate:

- The risk of developing liver disease including parenteral nutrition-associated liver disease (PNALD):
  - PNALD will be defined by direct bilirubin ≥2 mg/dL when no other etiology for liver dysfunction is present;
  - Hepatic integrity will be assessed by measuring plasma liver function tests: alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total and direct bilirubin;
  - Plasma main phytosterols (stigmasterol, campesterol, sitosterol), cholesterol and squalene levels will be assessed. Phytosterols levels will be correlated with the risk of developing PNALD.
- The adequacy of nutritional interventions:
  - Prescribed and actual nutritional intakes (energy, protein, carbohydrates, and lipid) from both PN and enteral/oral nutrition will be collected and recorded on a daily basis and summarized on a daily basis during the first 2 weeks of treatment and on an approximately 15-day basis afterwards up to the end of study treatment in each of the treatment groups.
  - Growth will be assessed and evaluated from baseline to end of study treatment on an approximately every 15-day basis using descriptive summary statistics for weight, and height/length (and head circumference in infant <1 year) in each of the treatment groups as follows:
    - Gain in weight (g/kg/day in infants <1 year of age, g/day in children and adolescents) and gain in length/height (mm/week in all) and head circumference (mm/week in infants <1 year);
    - Changes in the standard deviation score (SDS or z-score) from reference growth curves (Fenton growth curve for premature infants, World Health Organization (WHO) growth standards for infants and children ages 0 to 2 years, or Center for Disease Control (CDC) growth charts for children age ≥2 years).
- The safety profiles of Clinolipid and Intralipid, as assessed by adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)
  - AESIs are known AEs related to PN with Intravenous Lipid Emulsions (ILEs), per Intralipid and Clinolipid United States Prescribing Information

(USPI) and include the following: catheter related infection, thrombophlebitis; EFAD as well as ILE-related Immediate or Early adverse reactions including: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, irritation at the site of infusion, and ILE-related delayed adverse reactions including: hepatomegaly, jaundice, splenomegaly, thrombocytopenia, leukopenia, transient increases in liver function tests, and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly and shock).

1.4 Study Design

1.4.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, controlled, safety and efficacy study to evaluate the occurrence of EFAD (diagnosed by Holman Index >0.4) in pediatric patients receiving either Clinolipid or standard-of-care soybean oil-based ILE (Intralipid) in the hospital setting from 7 up to 90 days as part of PN. The risk of developing liver disease, including PNALD (defined by direct bilirubin ≥2 mg/dL) when no other etiology for liver dysfunction is present, also will be assessed.

Approximately 100 pediatric patients, including neonates, will participate in the study. Patients will be randomized in a 1:1 ratio to the treatment groups (Clinolipid or Intralipid) according to a central dynamic randomization scheme stratified by site and age group (premature infants born <37 weeks of gestation, full-term neonates born ≥37 weeks of gestation to <1 month of age, infants 1 to <12 months of age, children 1 to <10 years of age, adolescent 10 to <18 years of age). In the case of multiple birth pregnancies, the infants will be assigned to the same treatment group.

Holman Index and FA profile will be evaluated. Select polymorphisms in the FA desaturase genes FADS1 and FADS2, will be determined in a subset of patients. The major plasma phytosterols found in the ILEs (stigmasterol, campesterol, sitosterol), cholesterol, and squalene will also be assessed.

The study consists of a Screening Period to confirm the patient's eligibility for the study after the informed consent form (ICF) and assent (if applicable) is signed and a Treatment Period, where study Day 1 is defined as the first day the patient receives study treatment.

End of study treatment is defined as the last day of PN with Intralipid or Clinolipid; maximum 90 days of study treatment is allowed.

1.4.2 Determination of Sample Size

The sample size of 100 patients (50 in each of the 2 treatment groups: Clinolipid vs Intralipid), including neonates, is based on the feasibility of timely enrollment of patients for generating reference data and summary descriptive statistics, rather than on a formal power calculation. No formal hypothesis testing is planned.

1.4.3 Randomization Procedure

Approximately 100 pediatric patients, including neonates, will participate in the study. Patients will be randomized in a 1:1 ratio to the treatment groups (Clinolipid or Intralipid) according to a central dynamic randomization scheme stratified by site and age group (premature infants born <37 weeks of gestation, full-term neonates born ≥37 weeks of gestation to <1 month of age, infants 1 to <12 months of age, children 1 to <10 years of age, adolescent 10 to <18 years of age). In the case of multiple birth pregnancies, the infants will be assigned to the same treatment group.

For this study, a patient should be randomized within 24 hours of signing informed consent, when possible, but must be randomized within 3 days of signing informed consent. See randomization plan for more details.

1.4.4 Blinding

This is a double blinded study and most study roles will be blinded except the unblinded statistician, unblinded clinical project manager, clinical supplies manager and unblinded CRA. The pharmacist(s) involved in the study medication preparation will also be unblinded.

The dynamic randomization will be built using Prancer software and no end user will have direct access to the patient level randomization codes. The statistician that reviews the randomization scheme via simulations will not have any access to the patient level randomization codes and therefore will remain blinded.

Planned unblinding of the study will take place for the Data Safety and Monitoring Board (DSMB) meetings and all unblinding activities are outsourced to a secondary team at the Contract Research Organization (CRO). See DSMB Charter for more details.

Dry runs of SDTM/ADaM data and tables, listings, and figures (TLFs) will be conducted in a blinded manner.

Final study unblinding after the final database lock will be requested by Baxter and unblinding codes will be provided by the IWRS manager.

Data points or parameters that are potentially unblinding are not foreseen for this study. All protocol deviations related to drug preparation by the unblinded pharmacist will not be shared with the study team prior to study unblinding.

1.4.5 Schedule of Visits and Procedures

Evaluation	Screening	Baseline [a]	Daily	Study Treatment Day (every 15 days ±2 days)					End of Study Treatment[o] or Day 90 (± 2 days)
				15	30	45	60	75	
Informed consent / assent (as applicable)	X								
Confirm eligibility	X								
Randomization[b]	X								
Demographics[c]	X								
Medical history including diagnosis for requiring PN	X	X							
Physical examination including length or height and head circumference	X	X		X	X	X	X	X	X
Body weight[d]	X	X	X	X	X	X	X	X	X
Vital signs[e]	X	X	X	X	X	X	X	X	X
Diagnosis of neonatal morbidities[f]									X
Laboratory Evaluations									
Hematology and serum chemistry	X	X	Standard-of-Care and every 15 days ±2 days						
Triglyceride levels	X	X	Standard-of-Care and every 15 days ±2 days						
Hepatic function tests	X	X	Standard-of-Care and every 15 days ±2 days						

Evaluation	Screening	Baseline [a]	Daily	Study Treatment Day (every 15 days ±2 days)					End of Study Treatment[o] or Day 90 (± 2 days)
				15	30	45	60	75	
Fatty acid profile and Holman Index[g]		X		X	X	X	X	X	X
Genetic polymorphism sample (buccal swab)[h]		X							
Phytosterol, cholesterol, and squalene levels[i]		X		X	X	X	X	X	X
Human chorionic gonadotropin (hCG)[j]	X								
Nutritional Intake									
PN lipid intake[k]		X	X	X	X	X	X	X	X
Other macronutrient PN intake		X	X	X	X	X	X	X	X
Breast milk intake[l]	X	X	X	X	X	X	X	X	X
Enteral formula intake	X	X	X	X	X	X	X	X	X
Oral food intake	X	X	X	X	X	X	X	X	X
Concomitant medications / nutritional supplements[m]	X	X	X	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X	X	X	X
Adverse events[n]	X	X	X	X	X	X	X	X	X

PN=parenteral nutrition

[a] Baseline evaluations should be done ≤24 hours before first study treatment administration, however, baseline laboratory assessments may be done within ±24 hours of first study treatment administration. Baseline tests need not be repeated if within 24 hours of screening sampling. Buccal swabs can be collected at any time before the end of study treatment.

[b] Randomization is recommended within 24 hours of signing consent but must occur within 3 days of signing consent (protocol section 7.1)

[c] For all neonates (premature infants born <37 weeks of gestation up to 1 month CA and full-term neonates <1 month of age), gestational age (GA) will be recorded at Screening and categorized as full-term (born ≥37 weeks of gestation), preterm (32-36 weeks of gestation), very preterm (28-31 weeks of gestation), or extremely preterm (<28 weeks of gestation).

[d] Including weight and length or height (and head circumference for infants <1 year of age). For all neonates (premature infants born <37 weeks of gestation up to 1 month CA and full-term neonates <1

Evaluation	Screening	Baseline [a]	Daily	Study Treatment Day (every 15 days ±2 days)					End of Study Treatment[o] or Day 90 (± 2 days)
				15	30	45	60	75	

month of age), BW will be recorded at Screening and categorized as normal BW (≥2500 g), low BW (1500-2499 g), very low BW (1000-1499 g), or extremely low BW (<1000 g).

[e] Vital signs will be collected once daily at approximately the same time each day (e.g. 8 AM), with a window of approximately 2-3 hours. Vital signs include heart rate (beats/min), respiratory rate (breaths/min), systolic and diastolic blood pressure (mmHg), and body temperature (°C).

[f] Diagnosis of neonatal morbidities diagnoses including BPD, ROP, IVH, PVL, NEC, and late-onset sepsis in enrolled premature and low birth weight neonates. Diagnostic criteria and severity grading will be per standard-of-care.

[g] Samples are to be collected ≥4 hours after completing last lipid infusion. Samples are to be collected at the same time every day.

[h] Buccal swab samples for the determination of genetic polymorphisms for FADS1 (rs174553) and FADS2 (rs174575, rs99780, rs174583) will be collected after enrollment in all patients for whom consent is obtained. Buccal swabs can be collected at any time before the end of study treatment. Buccal swabs will be destroyed once all analyses have been completed.

[i] Clarification on laboratory measurements will be provided in a separate laboratory manual.

[j] All female patients ≥12 years of age must have a negative urine human chorionic gonadotropin (hCG) pregnancy test at screening. For female patients <12 years of age, a urine hCG test at screening will be performed at the discretion of the investigator based on childbearing potential.

[k] Parenteral nutrition therapy may be interrupted and restarted (based on the initial randomization) within a 1 to 2-day window, subject to adjudication from the medical monitor who conducts clinical review of current patient status, assessment of any potential AE/SAEs, discussion/clarification with investigator to resume or abort study treatment. If there is a likelihood that the patient will require restart of PN within 1 to 2 days of the initial stoppage, then it is recommended to delay performing the End of Study Treatment procedures. However, the End of Study Treatment procedures should be completed within 2 days of the initial stoppage if the patient has not restarted PN.

[l] When breastfeeding intakes cannot be measured, the best estimation (volume) of the investigator will be recorded.

[m] Medications and nutrition supplements received within 30 days prior to randomization by the patient and the nursing mother (if applicable) also will be recorded at Screening. The nursing mother's medication history will be collected from the patient's chart (if available).

[n] Adverse events occurring prior to the initiation of the first study procedure will be recorded as signs and symptoms in the patient's medical history. During the course of the study, and for 30 days after the last dose of study drug, the Investigator or designee will routinely monitor and solicit each patient for the occurrence of any AEs. All SAEs or any pregnancy reports with or without an associated SAE must be reported to Baxter Global Pharmacovigilance within 24 hours of site's knowledge of the event.

[o] End of study treatment is defined as the last day of PN with Intralipid or Clinolipid; maximum 90 days of study treatment is allowed. After 90 days, the patient will receive nutritional intervention as prescribed by their healthcare provider if still required.

1.5 Analysis Populations

Three main analysis sets are defined for this study.

1.5.1 Definition of Analysis Populations

Full analysis set (FAS): all patients who are randomized to receive either Clinolipid or standard of care soybean oil-based lipid emulsion (Intralipid) and have received at least one randomized study treatment. This dataset will follow the intent-to-treat principle and will analyze patients by planned randomized arm.

Per protocol set (PPS): all patients in the FAS who have Holman Index measurements taken at baseline and at least 1 other timepoint post-baseline, who have received a minimum of 7 days of ILE treatment, and are without a major protocol violation (i.e. violation that potentially impacts the primary endpoint).

Deviations that could be considered for exclusion in a PP analysis

- Randomization or treatment errors
- Investigational product not handled properly
- Key exclusion criteria such as:
  - Patients with liver disease including cholestasis
  - Patients with severe hyperlipidemia or severe disorders of lipid metabolism
  - Patients who are unable to tolerate necessary laboratory monitoring
  - Patient requires or is expected to require propofol for sedation

Deviations that should **not** lead to exclusion of data in a PP analysis

- Patients who violate inclusion/exclusion criteria relating to patient safety
- Missed informed consent signature/date
- Any deviation that does not directly impact the primary endpoint

Safety analysis set (SS): the set of all patients who have been administered study treatment (Clinolipid or Intralipid). Patients will be analyzed according to treatment received.

1.5.2 Protocol Deviations

Protocol deviations will be summarized for all patients in the FAS pooled together. Patient counts will be presented for minor protocol deviations, major protocol deviations, and for each category of major protocol deviation.

Protocol deviations will also be listed for the FAS. The listing will include patient id, age, randomized treatment, verbatim description of the protocol deviation, the assigned category of protocol deviation, major/minor status and whether the protocol deviation was determined to be exclusionary for PPS.

1.6 Endpoints

1.6.1 Primary Endpoint

- Risk of EFAD. EFAD will be defined using the Holman Index value of >0.4.

Supportive of the primary endpoint

- Time to developing EFAD
- The Holman Index
- Fatty acid (FA) profiles
- Genetic polymorphisms in FADS1 and FADS2 genes

1.6.2 Secondary Endpoints

The secondary objectives in patients receiving either Clinolipid or Intralipid are to evaluate:

- The risk of developing liver disease including PNALD:
  - PNALD will be defined by direct bilirubin ≥2 mg/dL when no other etiology for liver dysfunction is present;
  - Hepatic integrity will be assessed by measuring plasma liver function tests: alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total and direct bilirubin;
  - Plasma main phytosterols (stigmasterol, campesterol, sitosterol), cholesterol and squalene levels will be assessed. Phytosterols levels will be correlated with the risk of developing PNALD.
- The adequacy of nutritional interventions:

- Prescribed and actual nutritional intakes (energy, protein, carbohydrates, and lipid) from both PN and enteral/oral nutrition will be collected and recorded on a daily basis and summarized on a daily basis during the first 2 weeks of treatment and on an approximately 15-day basis afterwards up to the end of study treatment in each of the treatment groups.
- Growth will be assessed and evaluated from baseline to end of study treatment on an approximately every 15-day basis using descriptive summary statistics for weight, and height/length (and head circumference in infant <1 year) in each of the treatment groups as follows:
  - Gain in weight (g/kg/day in infants <1 year of age, g/day in children and adolescents) and gain in length/height (mm/week in all) and head circumference (mm/week in infants <1 year);
  - Changes in the standard deviation score (SDS or z-score) from reference growth curves (Fenton growth curve for premature infants, World Health Organization (WHO) growth standards for infants and children ages 0 to 2 years, or Center for Disease Control (CDC) growth charts for children age ≥2 years).

- The safety profiles as evaluated by:
  - Adverse events (AEs)
  - Serious adverse events (SAEs)
  - Adverse events of special interest (AESIs)
    - AESIs are known AEs related to PN with ILEs, per Intralipid and Clinolipid United States Prescribing Information (USPI) and include the following: catheter related infection, thrombophlebitis; EFAD as well as ILE-related Immediate or Early adverse reactions including: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, irritation at the site of infusion, and ILE-related delayed adverse reactions including: hepatomegaly, jaundice, splenomegaly, thrombocytopenia, leukopenia, transient increases in liver function tests, and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly and shock).

- Vital signs
- Laboratory tests (see Table 1 below)
- Additional neonatal morbidities including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), and late-onset sepsis in enrolled premature infants born <37 weeks of gestation up to 1 month corrected age (CA)

Table 1. List of Local Laboratory Tests

Hematology: • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Mean Platelet Volume (MPV) • Red blood cell (RBC) count • White blood cell (WBC) count with differential • Urine human chorionic gonadotropin (hCG)[a]	Liver function tests: • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Gamma-glutamyl transferase (GGT) • Total bilirubin • Direct bilirubin Serum Chemistry: • Glucose • Triglycerides • Serum Albumin • Creatinine • Blood urea nitrogen (BUN) • Bicarbonate (CO2) • Sodium (Na) • Potassium (K) • Chloride (Cl) • Calcium (Ca) • Phosphorus (P) • Magnesium (Mg)

[a] All female patients ≥12 years of age must have a negative urine human chorionic gonadotropin (hCG) pregnancy test at screening. For female patients <12 years of age, a urine hCG test at screening will be performed at the discretion of the investigator based on childbearing potential.

1.7 Interim Analysis

An interim analysis has not been planned for this study.

2. ANALYSIS METHODS

2.1 General Principles

Unless otherwise specified, summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values) will be presented for continuous variables. Counts and, if relevant, percentages will be presented for categorical variables.

Unless otherwise specified, data listings will include patient ID, treatment group, sex, age at screening (given in months) and baseline weight.

Unless otherwise noted, all analyses will be performed using SAS/Graph® 9.4 software, SAS/STAT® 15.1 software, and Base SAS® 9.4. Copyright © 2016, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All Rights Reserved

Except for height, weight, head circumference, or otherwise specified, the estimated mean, Q1, median, and Q3 for a set of values will be displayed to 1 more significant digit than the original values, standard deviations will be displayed to 2 more significant digits, and minimum and maximum values will be displayed with the same number of significant digits as the original values. If an original value has more than 2 decimal places, the significant digits will be counted as if there are 2 decimal places. All percentages will be displayed with 1 decimal place unless more decimal places are needed to show 1 significant digit (i.e. a percentage of 0.01 will be shown as 0.01 as opposed to 0.0). For height, weight, and head circumference, up to 4 reported decimals are shown.

Unless otherwise specified, age group will be defined and stratified as follows: Pre-Term Neonate (24 weeks to <37 weeks), Full Term Neonate (≥37 weeks to <1 month), Infant (≥1 month to <12 months), Child (≥1 year to <10 years), and Adolescent (≥10 years to <18 years)

Unless otherwise specified, weight at birth will be grouped as follows: Normal (≥2500 g), Low (1500-2499 g), Very Low (1000-1499 g), and Extremely Low (<1000 g).

2.1.1 Definition of baseline

Unless otherwise specified, baseline is defined as the values collected at the baseline visit. The value closest to the start of treatment will be used for baseline if multiple values (e.g. laboratory re-tests) are available. If the value at baseline is missing, then the value at the screening visit will be used as baseline.

Any medical condition that is present at the time that a participant is screened will be considered baseline medical history and will not be reported as an adverse event.

Change from baseline variables will be calculated as the post-treatment value minus the value at baseline.

2.1.2 Visit Windows

The study visits can be obtained from the eCRF and need not be derived programmatically. The visits will be displayed as: Screening, Day 1 (Baseline), Day 2, … Day 14, Day 15, Day 30, Day 45, Day 60, Day 75, Day 90/End of treatment (EOT).

Results from unscheduled visits will not be included in table summaries. These values will only be presented in the listings.

2.1.3 Completion and Discontinuation

A patient is considered to have completed the study when he/she ceases active participation in the study because the patient has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations). Any other cases are classified as discontinuation.

Reasons for early termination will be reported on the Completion/Discontinuation electronic case report form (eCRF), including:

- Adverse Event
- Clinically significant change in laboratory parameter
- Protocol violation
- Pregnancy
- Patient or any legal representative requests to withdraw from the study
- Sponsor or Investigator terminates study
- Other

Regardless of the reason, all data available for the patient up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

2.2 Patient Disposition

Patient disposition will be summarized by treatment group and will include:

- Number of patients who signed informed consent (enrolled)

- Number of patients who screen fail. These patients will also be summarized by primary reason for screen failure from the study. The percentage associated with each reason will have the total number of patients who screen fail as the denominator.
- Number of patients eligible for randomization. This will be calculated by taking the number enrolled minus the number of screen failures.
- Number of patients randomized
- Number of patients treated with study treatment (SS)
- Number of patients in the FAS
- Number of patients in the PPS. Patients included in the FAS but excluded from the PPS will be summarized by reason for removal (missing Holman Index measurement at baseline and/or one other timepoint, did not receive a minimum of 7 days of ILE treatment, or protocol deviation). The denominator for the percentage will be based off of the total number of patients excluded.
- Number of patients who completed the study in the FAS
- Number of patients who discontinued (withdrew early) from the study in the FAS. These patients will also be summarized by primary reason for withdrawal from the study. The percentages associated with each reason for early withdrawal will have the total number of patients who withdrew early as the denominator.

A listing of all patients enrolled in the study will be created including patient ID, age (in months), sex, treatment group, whether the patient is in each of the analyses sets, completion status, reason for discontinuation (if applicable), and the number of days that the patient remained in the study. The number of days the patient was in the study will be calculated using the following:

$$(Date\ of\ Study\ Completion/Discontinuation - Date\ of\ Informed\ Consent) + 1$$

2.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized descriptively by treatment group for the FAS population. Listings will also be provided for this population.

2.3.1 Demographics

Demographics including sex, race, and ethnicity will be summarized descriptively by treatment group. Age will be summarized by age group and treatment as follows: Pre-

Term Neonate (GA in weeks, age at consent in days), Full Term Neonate (GA in weeks and days, age at consent in days), Infant (age at consent in months), Child (age at consent in years), Adolescent (age at consent in years). Diagnosis for PN will also be included in this summary.

To calculate gestational age, gestational age (weeks) will be added to gestational age (days)/7 to get the gestational age in weeks.

2.3.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Medical history will also be listed.

2.3.3 Prior and Concomitant Medications (Mother and Child)

Prior and concomitant medications for both mother and child will be summarized using WHODrug Anatomical Therapeutic Chemical (ATC) class level 4 and PT by treatment group. A listing will also be prepared.

2.3.4 Concomitant Procedures

Concomitant procedures will be listed only.

2.3.5 Other Baseline Characteristics

Baseline characteristics will be summarized descriptively by treatment group and stratified by age groups: a. Pre-Term Neonate, b. Full Term Neonate, c. Infant, d. Child, e. Adolescent as follows:

- length (a and b) height (c, d, e)
- head circumference (a, b, c)
- weight (a, b, c, d, e)
- body mass index (d and e)
- birth weight (a and b)

2.4 Endpoint Analyses

2.4.1 Primary Endpoint

The primary efficacy analysis will be carried out on the FAS with a supportive analysis performed on the PPS.

2.4.1.1 Derivation of Primary Endpoint

The primary endpoint is the incidence of EFAD which is defined in the protocol and will be derived based on the Holman Index (Triene/Tetraene Ratio) provided by the central laboratory.

- Holman Index <0.2: normal EFA
- Holman Index 0.2 – 0.4: at risk for EFAD
- Holman Index >0.4: EFAD

A patient will be considered 'at risk for developing EFAD' if they have a Holman Index of 0.2 – 0.4 at any timepoint during the study treatment.

A patient will be considered as an incident of EFAD (the 'event') if they have a Holman Index >0.4 at any timepoint during the study treatment.

For time to EFAD Kaplan Meier analyses, the index time will be the start of treatment. The first incident of EFAD will be considered the event and will use the date of EFAD (date first lab with Holman Index >0.4 reported). Patients will be censored if they do not develop EFAD during their follow-up or if they die before developing EFAD at the time of their last Holman Index laboratory measurement. Time to EFAD will be calculated for each patient who develops EFAD as follows and standardized to days:

$$Date\ of\ EFAD - Date\ of\ Start\ of\ Treatment + 1$$

The incidence rate of EFAD (events per 100 patient days) will be calculated as the following per treatment group:

$$\frac{Number\ of\ patients\ developing\ EFAD * 100}{Total\ patient\ days}$$

The total number of patient days will be calculated per treatment group as follows:

$$\sum_{i=1}^{n}(Date\ of\ First\ EFAD\ Occurrence\ or\ End\ Date\ of\ Treatment - Start\ Date\ of\ Treatment)_i + 1$$

Where n is the total number of patients per treatment group. If a patient develops EFAD, then the date of first EFAD occurrence will be used, and if they do not, then end date of treatment will be used. If more than one instance of EFAD occurs, the patient will be counted once and the date of first occurrence will be used. This will then be standardized to days.

2.4.1.2 Analysis of Primary Endpoint

Holman index scores will be summarized descriptively by timepoint per treatment group using n, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

The frequency and percentage of patients at risk of developing EFAD (Holman Index 0.2-0.4) as well as those who developed EFAD (Holman Index >0.4) will be summarized by timepoint and at the maximum by treatment group. The denominator for the percentage of patients will be the number of patients in the population who had at least one post-baseline Holman Index measurement available. The incidence rate (per 100 patient days) of EFAD will also be calculated per treatment group.

If there are more than 5 cases of EFAD per arm, then time to develop EFAD will be analyzed using survival analysis approach (cumulative incidence), and the mean, standard error, Q1, median, Q3, minimum, and maximum for each treatment group will be displayed, where calculable. A cumulative incidence plot will also be produced. If there are less than 5 cases of EFAD in each treatment arm, then time to developing EFAD will be summarized descriptively by treatment group using n, mean, standard deviation, minimum, Q1, median, Q3, and maximum. If no events occur, then time to EFAD will not be calculated.

A spaghetti plot consisting of Holman index values over time will be produced with one line representing each patient, and different types of lines or symbols (e.g. solid and dashed) representing each treatment group. Two bolded lines will be added at y=0.2 and y=0.4 to represent the bounds for being at risk of EFAD and developing EFAD.

As a supportive analysis to the primary endpoint, the following will be analyzed:

- FA profiles will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) in each of the 2 treatment groups (Clinolipid vs Intralipid), as well as descriptive statistics of genetic polymorphisms in the FADS1 and FADS2 genes for the patients with buccal swabs with the 5 highest and 5 lowest arachidonic acid values in each treatment group.

2.4.1.3 Sensitivity Analysis of Primary Endpoint

A sensitivity analysis of the primary endpoint may be done looking at patients who received SMOF vs Intralipid as pre-randomization lipids. If less than ten patients received SMOF pre-randomization, then this sensitivity analysis will not be done.

2.4.2 Secondary Endpoints

All secondary endpoints will be performed on the FAS.

2.4.2.1 Liver Disease, Including Parenteral-Associated Liver Disease

2.4.2.2 Parenteral Nutrition-Associated Liver Disease (PNALD)

2.4.2.2.1 Derivation of PNALD

PNALD will be determined by a direct bilirubin measurement ≥ 2 mg/dL at any timepoint in the study.

Time to PNALD will be derived using the start of treatment as the index date and the date of developing PNALD as the event date. It will be calculated for each patient as follows (standardized to the number of days):

$$Date\ of\ PNALD - Start\ Date\ of\ Treatment + 1$$

Patients will be censored at the time of their last lab value if they do not develop PNALD.

Each patient will have their person time (or total exposure to potentially develop PNALD) calculated in "patient days" as:

$$Date\ of\ first\ occurrence\ of\ PNALD\ or\ End\ Date\ of\ Treatment - Start\ Date\ of\ Treatment + 1$$

If a patient develops PNALD, then date of first occurrence of PNALD will be used. If a patient does not develop PNALD, then end date of treatment will be used. If a patient has more than 1 lab indicating PNALD, they will only be counted once at the date of their first instance. For incidence rate calculations, the total person time per group will be the sum of all individual patient's person time in that group standardized to 100 patient days:

$$Incidence\ Rate\ of\ PNALD = \frac{Total\ \#\ with\ PNALD * 100}{\sum_{i=1}^{n} Person\ Time}$$

2.4.2.2.2 Analysis of PNALD

PNALD will be summarized at each visit as well as at the post-baseline maximal value (maximal being 'yes' to developing PNALD at any timepoint) by treatment group using frequencies and percentages.

If there are more than 5 cases of PNALD per arm, then time to develop PNALD will be analyzed using survival analysis approach (cumulative incidence), and the mean, standard error, Q1, median, Q3, minimum, and maximum for each treatment group will be

displayed, where calculable. A cumulative incidence plot will also be produced. If there are less than 5 cases of PNALD in each treatment arm, then time to developing PNALD will be summarized descriptively by treatment group for all patients developing PNALD using n, mean, standard deviation, minimum, Q1, median, Q3, and maximum. If no events occur, then time to PNALD will not be calculated.

The incidence rate of PNALD will be computed and displayed per treatment group. The proportion of PNALD will be summarized per treatment group as the number of patients who develop PNALD divided by the corresponding total number of patients in each group.

A spaghetti plot consisting of direct bilirubin values over time will be produced with one line representing each patient, and different types of lines or symbols (e.g. solid and dashed) representing each treatment group. A bolded line will be added at y=2 to represent the bound for PNALD.

2.4.2.3 Hepatic Integrity

Hepatic integrity (ALP, AST, ALT, GGT, total and direct bilirubin) will be evaluated by presenting descriptive summary statistics (number of patients, mean, standard deviation, Q1, median, Q3, minimum, and maximum) at different measurement time points from baseline to end of study treatment during the study period in each of the 2 treatment groups (Clinolipid vs Intralipid). Change from baseline will also be summarized.

Each hepatic integrity parameter will also be summarized in shift tables comparing end of study treatment and post-baseline maximal values during the study intervention with those at baseline. Shift categories will include normal and abnormal (>1 to 3 and >3-fold the upper limit of normal range). If a patient is below the normal range, they will be included as 'normal' for this analysis.

The delay (days) between baseline and post-baseline maximal value in each of the 2 treatment groups (Clinolipid vs Intralipid) will also be summarized using n, mean, standard deviation, minimum, Q1, median, Q3, and maximum. Days between baseline and post-baseline maximal value will be calculated by the following:

$$(Date\ of\ Maximal\ Lab\ Value - Date\ of Baseline) + 1$$

If there are two instances of the same maximal value post-baseline, then the first instance of the maximal value will be used as the date of maximal lab value.

In addition, assessment for drug-induced liver injury (DILI) will be conducted according to Hy's Law and eDISH criteria,[1,2]. This will be assessed using two scatterplots in the log log scale between the peak aminotransferase (AT) levels (x upper limit normal (ULN)) and peak total bilirubin (TB) level (xULN) per patient. The two ATs that will be used are AST and ALT. Boundary lines will be put in at x=1 and y=1 signaling the 'box' for the normal range as well as y=3 and x=2 to signify the boundaries for Hy's Law (when peak AT > 3xULN and peak TB >2xULN). To calculate peak AT/TB x ULN,

$$\frac{Maximum\ AT/TB}{Upper\ Limit\ of\ Normal}$$

Different symbols will be used per treatment group.

If any patients appear in the Hy's law range, then the time course of all liver tests (ALT, AST, ALP, and TB) will be shown per patient (one graph per patient who meets Hy's law criteria). The y axis will be the test values x ULN on the log scale, and the x axis will be the time from start of treatment.

2.4.2.4 Plasma Phytosterols, Cholesterol, and Squalene Levels

Plasma phytosterols (stigmasterol, campesterol, and sitosterol), cholesterol, and squalene levels will be summarized using descriptive statistics (mean, standard deviation, Q1, median, Q3, minimum, and maximum) at baseline and the end of study treatment, as well as post-baseline maximal value during the study and the delay (days) between study baseline and post-baseline maximal value in each of the 2 treatment groups (Clinolipid vs Intralipid). In addition, the correlation between plasma phytosterol levels and direct bilirubin values will be assessed by computing a Pearson's correlation coefficient or a Spearman correlation coefficient depending on whether the normality assumption is fulfilled. Normality will be assessed visually with a QQ plot. Values will be paired by patient and visit. A scatterplot of plasma phytosterol and direct bilirubin values will also be produced with different symbols for each of the two different treatment groups.

2.4.3 Adequacy of Nutritional Interventions

Prescribed (ordered) and actual (administered) nutritional intake (fluid, energy, protein, carbohydrates, and lipids) from parenteral, enteral nutrition, and IV fluids will be collected and recorded daily. They will be summarized descriptively on a daily basis during the first 2 weeks of treatment and on a 15-day basis afterwards up to end of study treatment for each of the treatment groups. Summaries of overall nutritional intake will also be done. Box plots will also be produced by day and treatment group.

2.4.3.1 Parenteral Nutritional Intake

Data from parental nutrition will be calculated as follows:

Fluid intake ordered (mL/kg/24 hours):

$$\frac{24 * \frac{Total\ volume\ ordered(mL)}{PN\ dosing\ weight\ (kg)}}{Total\ PN\ Infusion\ Duration\ (hours)}$$

Fluid intake administered (mL/kg/24 hours):

$$\frac{24 * \frac{Total\ volume\ administered(mL)}{PN\ dosing\ weight\ (kg)}}{Total\ PN\ Infusion\ Duration\ (hours)}$$

Energy intake ordered (kCal/kg/24 hours):

Total calories (kCal) should first be calculated as[3]:

$$Protein\ intake\ (\text{g/kg})\ *PN\ dosing\ Weight\ (kg) * 4 + Lipid\ intake\ (\text{g/kg}) * lipid\ dosing\ weight\ (kg) * 10 + \frac{Carbohydrate\ intake\ (\text{g/dL})}{100} * Fluid\ intake\ ordered\ (\text{mL/kg}) * PN\ dosing\ Weight(\text{kg})*3.4$$

Then energy intake can be calculated as:

$$\frac{24 * \frac{Total\ calories\ (kCal)}{PN\ dosing\ Weight\ (kg)}}{Total\ PN\ Infusion\ Duration\ (hours)}$$

Energy intake administered (kCal/kg/24 hours):

$$\frac{Total\ Volume\ Administered}{Total\ Volume\ Ordered} * Energy\ Intake\ Ordered$$

Protein intake ordered (g/kg/24 hours):

$$\frac{24 * Protein\ intake\ (\text{g/kg})}{Total\ PN\ Infusion\ Duration\ (hours)}$$

Protein intake administered (g/kg/24 hours):

$$\frac{Total\ Volume\ Administered}{Total\ Volume\ Ordered} * Protein\ Intake\ Ordered$$

Carbohydrate intake ordered (g/kg/24 hours):

$$\frac{24 * \frac{Dextrose\ intake\ (\mathrm{g/dL}) * Total\ volume\ ordered\ (mL)}{100 * PN\ dosing\ weight\ (kg)}}{Total\ PN\ Infusion\ Duration\ (hours)}$$

Carbohydrate intake administered (g/kg/24 hours):

$$\frac{Total\ Volume\ Administered}{Total\ Volume\ Ordered} * Carbohydrate\ Intake\ Ordered$$

Lipid intake ordered (g/kg/24 hours):

$$\frac{24 * \frac{0.2(\frac{g}{mL}) * Total\ lipid\ volume\ ordered\ (mL)}{Lipid\ dosing\ weight\ (kg)}}{Total\ Lipid\ Infusion\ Duration\ (hours)}$$

Lipid intake administered (g/kg/24 hours):

$$\frac{24 * \frac{0.2\ \left(\frac{g}{mL}\right) *\ Total\ lipid\ volume\ administered\ (mL)}{Lipid\ dosing\ weight\ (kg)}}{Total\ Lipid\ Infusion\ Duration\ (hours)}$$

If lipid dosing weight is missing, PN dosing weight will be used instead. If both are missing, the recorded weight on the closest, prior non-missing day will be used.

2.4.3.2 Enteral Nutritional Intake

Nutrition from formula, breast milk, nutritional shakes, fortifiers, MCT oil, and other enteral intakes are recorded on the CRF. The below data will be calculated and summarized by treatment group. Similarly, all enteral nutrition given on each day will be added together and summarized by treatment group. If weight on that day is missing, then the weight from the prior non-missing day will be used. If the patient had multiple records of the same intake (i.e. 2 different records of breastmilk with no fortifier) on the same day, then the records should be summed together to get the total in a 24 hour period. All units presented below for intake are in mL. If data is given in ounces, multiply the amount of ounces by 29.57 to get mL.

<u>Breastmilk or formula (no additive or fortifier):</u>

Fluid intake ordered (mL/kg/24 hours):

$$\frac{Total\ volume\ ordered\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

If total volume ordered is recorded in ml/3 hours, then the amount should be multiplied by 8 to find the total volume ordered in mL per 24 hours. If total volume ordered is recorded in ml/2 hours, then the amount should be multiplied by 12.

Fluid intake administered (mL/kg/24 hours):

$$\frac{Total\ volume\ received\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

Energy intake ordered (kCal/kg/24 hours):

$$\frac{Original\ kcal\ in\ formulation\ per\ mL * Total\ Volume\ Ordered\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

Energy intake administered (kCal/kg/24 hours):

$$\frac{Original\ kcal\ in\ formulation\ per\ mL * Total\ Volume\ Received\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

Protein intake ordered (g/kg/24 hours):

$$\frac{Total\ Volume\ Ordered\ (mL) * Protein\ Conversion\ from\ Table\ 2}{Weight\ on\ that\ day\ (kg)}$$

Protein intake administered (g/kg/24 hours):

$$\frac{Total\ Volume\ Received\ (mL) * Protein\ Conversion\ from\ Table\ 2}{Weight\ on\ that\ day\ (kg)}$$

Carbohydrate intake ordered (g/kg/24 hours):

$$\frac{Total\ Volume\ Ordered\ (mL) * Carbohydrate\ Conversion\ from\ Table\ 2}{Weight\ on\ that\ day\ (kg)}$$

Carbohydrate intake administered (g/kg/24 hours):

$$\frac{Total\ Volume\ Received\ (mL) * Carbohydrate\ Conversion\ from\ Table\ 2}{Weight\ on\ that\ day\ (kg)}$$

Lipid intake ordered (g/kg/24 hours):

$$\frac{Total\ Volume\ Ordered\ (mL) * Lipid\ Conversion\ from\ Table\ 2}{Weight\ on\ that\ day\ (kg)}$$

Lipid intake administered (g/kg/24 hours):

$$\frac{Total\ Volume\ Received\ (mL) * Lipid\ Conversion\ from\ Table\ 2}{Weight\ on\ that\ day\ (kg)}$$

Table 2. Conversion Factors

Enteral Nutrition Type	Protein	Carbohydrate	Lipid
Breastmilk[4]	0.012 g/mL	0.074 g/mL	0.036 g/mL
Formula: Alfamino[5]	0.019 g/mL	0.074 g/mL	0.034 g/mL
Formula: Alfamino Junior[6]	0.033 g/mL	0.122 g/mL	0.044 g/mL
Formula: Enfamil Neuropro[7]	0.014 g/mL	0.076 g/mL	0.036 g/mL
Formula: Pregestimil[8]	0.019 g/mL	0.069 g/mL	0.038 g/mL
Formula: Similac Special Care[9]	0.024 g/mL	0.083 g/mL	0.044 g/mL
Formula: Similac Neosure[10]	0.021 g/mL	0.075 g/mL	0.041 g/mL
Formula: Kate Farms Pediatric Peptide 1.5[11]	0.052 g/mL	0.16 g/mL	0.068 g/mL
Other: Pedialyte[12]	0 g/mL	0.028 g/mL	0 g/mL

Breastmilk or formula (with additive or fortifier): The amount of additive/fortifier received will need to be calculated and used in the formulas. It can be calculated as:

$$\frac{Total\ Quantity\ Ordered\ (mL)}{Total\ Volume\ Ordered\ In(mL)} * Total\ Volume\ Received\ (mL)$$

Fluid intake ordered (mL/kg/24 hours):

$$\frac{Total\ volume\ ordered\ (mL) + Total\ volume\ ordered\ of\ additive\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

If total volume ordered is recorded in ml/3 hours, then the amount should be multiplied by 8 to find the total volume ordered in mL per 24 hours. If total volume ordered is recorded in ml/2 hours, then the amount should be multiplied by 12.

Fluid intake administered (mL/kg/24 hours):

$$\frac{Total\ volume\ received\ (mL) + Total\ volume\ of\ additive/fortifier\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

Energy intake ordered (kCal/kg/24 hours):

$$\frac{Modified\ kcal\ in\ formulation\ per\ mL * Total\ Volume\ Ordered\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

Energy intake administered (kCal/kg/24 hours):

$$\frac{Modified\ kcal\ in\ formulation\ per\ mL * Total\ Volume\ Received\ (mL)}{Weight\ on\ that\ day\ (kg)}$$

Protein intake ordered (g/kg/24 hours):

$$Protein\ intake\ ordered\ from\ 2.4.3.2 + \frac{Total\ Volume\ Ordered\ of\ Additive(mL, packet, or\ g) * Protein\ Conversion\ from\ Table\ 3}{Weight\ on\ that\ day\ (kg)}$$

Protein intake administered (g/kg/24 hours):

$$Protein\ intake\ administered\ from\ 2.4.3.2 + \frac{Total\ Volume\ Received\ of\ Additive(mL, packet, or\ g) * Protein\ Conversion\ from\ Table\ 3}{Weight\ on\ that\ day\ (kg)}$$

Carbohydrate intake ordered (g/kg/24 hours):

$$Carb\ intake\ ordered\ from\ 2.4.3.2 + \frac{Total\ Volume\ Ordered\ of\ Additive(mL, packet, or\ g) * Carb\ Conversion\ from\ Table\ 3}{Weight\ on\ that\ day\ (kg)}$$

Carbohydrate intake administered (g/kg/24 hours):

$$Carb\ intake\ administered\ from\ 2.4.3.2 + \frac{Total\ Volume\ Received\ of\ Additive(mL, packet, or\ g) * Carb\ Conversion\ from\ Table\ 3}{Weight\ on\ that\ day\ (kg)}$$

Lipid intake ordered (g/kg/24 hours):

$$Lipid\ intake\ ordered\ from\ 2.4.3.2 + \frac{Total\ Volume\ Ordered\ of\ Additive(mL, packet, or\ g) * Lipid\ Conversion\ from\ Table\ 3}{Weight\ on\ that\ day\ (kg)}$$

Lipid intake administered (g/kg/24 hours):

$$Lipid\ intake\ administered\ from\ 2.4.3.2 + \frac{Total\ Volume\ Ordered\ of\ Additive(mL, packet, or\ g) * Lipid\ Conversion\ from\ Table\ 3}{Weight\ on\ that\ day\ (kg)}$$

Table 3. Additive and Human Milk Fortifier (HMF) Conversions

Additive/Fortifier	Protein	Carbohydrate	Lipid
Enfamil liquid HMF[13]	0.084 g/mL	0.056 g/mL	0.116 g/mL
Similac HMF Concentrated Liquid[14]	0.07 g/mL	0.162 g/mL	0.054 g/mL
[A]Similac Hydrolyzed HMF[15]	0.5 g/packet	0.75 g/packet	0.21 g/packet
Similac Neosure Powder[16]	0.021 g/mL	0.075 g/mL	0.041 g/mL
Pregestimil Powder[8]	0.019 g/mL	0.069 g/mL	0.038 g/mL
Prolacta +4[17]	0.06 g/mL	0.095 g/mL	0.095 g/mL
[A]Similac HMF Powder[18]	0.25 g/packet	0.45 g/packet	0.09 g/packet
[A]Neocate Infant Powder[19]	0.135 g/g	0.52 g/g	0.245 g/g

[A]For all additives given as powder (g or packets), the volume of this additive is assumed to be 0 for fluid intake calculations.

2.4.3.3 Intravenous Fluid Nutritional Intake

Only fluid intake administered, energy intake administered, and carbohydrate intake administered will be calculated for intravenous fluid intake as protein and lipid intake are 0 g/mL. These will be calculated as follows:

Fluid intake administered (mL/kg/24 hours):

$$\frac{24 * \frac{Total\ volume\ administered(mL)}{Weight\ on\ that\ day(kg)}}{Total\ Infusion\ Duration\ (hours)}$$

Energy intake administered (kcal/kg/24 hours):

$$\frac{24 * 3.4\ (\frac{kcal}{g}) * \frac{Percentage\ Dextrose * \frac{Total\ volume\ administered\ (mL)}{100}}{Weight\ on\ that\ day\ (kg)}}{Total\ Infusion\ Duration\ (hours)}$$

Carbohydrate intake administered (g/kg/24 hours):

$$\frac{24 * \frac{Percentage\ Dextrose * \frac{Total\ volume\ administered\ (mL)}{100}}{Weight\ on\ that\ day\ (kg)}}{Total\ Infusion\ Duration\ (hours)}$$

2.4.3.4 Overall Nutritional Intake

Overall nutritional intake (ordered and administered) will be calculated per patient per day for fluid intake and energy intake by summing the following:

$$PN\ Intake + EN\ intake + IV\ Fluid\ intake$$

The percentage of PN and EN for fluid and energy intake will be calculated as follows:

Percentage of PN administered:

$$\frac{Total\ PN\ intake\ administered}{Total\ overall\ intake\ administered} x100\%$$

Percentage of EN administered:

$$\frac{Total\ EN\ intake\ administered}{Total\ overall\ intake\ administered} x100\%$$

2.4.3.5 Growth

Weight at baseline and during treatment will be assessed daily and will be summarized on an approximately 15-day basis using descriptive summary statistics in each of the treatment groups.

Length or height (and head circumference for infants <1 year of age) will be assessed and summarized at baseline and approximately every 15 days up to end of study treatment using descriptive summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum in each of the 2 treatment groups (Clinolipid vs Intralipid).

Growth will be assessed and evaluated from baseline to end of study treatment on an approximately every 15-day basis using descriptive summary statistics in each of the treatment group as follows:

- Gain in weight over last 15 days (g/kg/day in infants <1 year of age; i.e. the change between day 15 and baseline, day 30 and day 15, day 45 and day 30, etc):

$$\frac{\frac{Weight\ (g) on\ Day\ (X+15) - Weight(g)\ on\ Day\ X}{Weight\ (kg) on\ Day\ X}}{15}$$

- Gain in weight from baseline (g/kg/day in infants <1 year of age):

$$\frac{\frac{Weight\ (g) on\ Day\ X - Weight(g) at\ baseline}{Weight\ (kg)\ at\ baseline}}{X}$$

- Gain in weight over last 15 days (g/day in children and adolescents):

$$\frac{Weight\ (g) on\ Day\ (X+15) - Weight(g)\ on\ Day\ X}{15}$$

- Gain in weight from baseline (g/day in children and adolescents):

$$\frac{Weight\ (g) on\ Day\ X - Weight(g)\ at\ baseline}{X}$$

- Gain in length/height over last 15 days (mm/week in all):

$$\frac{Length\ (mm) on\ Day\ (X+15) - Length\ (mm) on\ Day\ X}{2.14}$$

- Gain in length/height from baseline (mm/week in all):

$$\frac{Length\ (mm) on\ Day\ X - Length\ (mm)\ at\ baseline}{X/7}$$

- Gain in head circumference over last 15 days (mm/week in infants <1 year);

$$\frac{Head\ circumference\ (mm) on\ Day\ (X+15) - Head\ circumference\ (mm) on\ Day\ X}{2.14}$$

- Gain in head circumference from baseline (mm/week in infants <1 year);

$$\frac{Head\ circumference\ (mm) on\ Day\ (X) - Head\ circumference\ (mm)\ at\ baseline}{X/7}$$

- Changes in the SDS from reference growth curves over last 15 days (Fenton growth curve for premature infants[19], WHO growth standards[20] for infants and children ages 0 to 2 years, or CDC growth charts[21] for children age ≥2 years):

$$SDS\ at\ Day\ (X+15) - SDS\ at\ Day\ X$$

- Changes in the SDS from reference growth curves from baseline (Fenton growth curve for premature infants, WHO growth standards for infants and children ages 0 to 2 years, or CDC growth charts for children age ≥2 years):

$$SDS\ at\ Day\ X - SDS\ at\ baseline$$

Boxplots will also be given for each of the growth parameters by treatment group.

2.5 Safety Analyses

All safety analyses will be performed on the SS.

2.5.1 Adverse Events

2.5.1.1 Derivation of Adverse Events

Adverse events (AEs) will be coded using MedDRA. They will be classified as follows:

Pre-treatment adverse event – An adverse event that starts between the date of signing the informed consent form (ICF) and the study treatment

Treatment-emergent adverse event (TEAE) – An adverse event that starts on or after the start of study treatment

Treatment-emergent adverse events of special interest (AESI) - The following are called out as AESIs in the protocol: catheter related infection, thrombophlebitis, dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, irritation at the site of infusion, hepatomegaly, splenomegaly, thrombocytopenia, leukopenia, and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly and shock). A blinded review of AEs will be conducted at the end of the study before unblinding to flag AESIs.

An adverse event will be considered related to study treatment if they respond 'Probably related' or 'Possibly related' to relationship to study treatment.

In case of incomplete information on study treatment or AE onset, events will be classified as treatment-emergent unless there is sufficient data to rule out the possibility that the event started after the start of study treatment.

If the severity of an adverse event is missing, then that adverse event will be classified as *severe*. If relationship of an adverse event is missing, then that adverse event will be classified as *probably related*.

The number of events per 100 patient days will be calculated as follows:

$$\frac{Number\ of\ Total\ Events}{\frac{\sum_{i=1}^{n}(End\ Date\ of\ Treatment_i - Start\ Date\ of\ Treatment_i + 1)}{100}},$$

where i represents each patient and n represents the total number of patients in the Safety Set for that treatment group.

2.5.1.2 Analysis of Adverse Events

An AE overview summary table will be prepared to include the number of patients, the percentage of patients (%), and the number of events per 100 patient days by treatment group, for the following categories:

1. Any AE
2. Any treatment-emergent adverse event (TEAEs)

3. Treatment emergent non-serious AEs
4. Treatment-emergent serious AEs (SAEs)
5. Treatment-emergent AEs of special interest (AESIs)
6. Treatment-emergent AEs related to study treatment
7. Treatment-emergent SAEs related to study treatment
8. Treatment-emergent AEs leading to death

Additional listings and tables on the above categories (with the exception of #1) will be given by SOC and PT. Pre-treatment adverse events (those occurring between informed consent and treatment) will also be listed. For SAE listings, the seriousness criteria will be included in the listing.

The tables below will display the total number of patients, the percentage of patients (%), the number of events, the number of events per 100 patient days, system organ class (SOC), and preferred term by treatment group. Table summaries will be produced for:

- Treatment-emergent AEs by severity
- Treatment-emergent SAEs by severity
- Treatment-emergent AEs by relationship to study treatment
- Treatment-emergent SAEs by relationship to study treatment
- Treatment-emergent adverse events in ≥5% of patients (in either Clinolipid or Intralipid group)

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order by the percentage of patients.

Adverse event listings will be sorted by patient ID and adverse event start date. They will include primary AE number, SOC, PT, verbatim term, adverse event start and end date and its duration, treatment date, relationship to study treatment, alternate causality, severity, action taken, seriousness, outcome, whether the event is ongoing, and whether AE led to discontinuation from study.

2.5.2 Other Safety Endpoints

2.5.2.1 Neonatal Morbidities

Neonatal morbidities at the end of treatment are defined in the eCRF as bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and late-onset sepsis.

Frequencies and percentages of premature infants born <37 weeks of gestation up to 1 month CA developing neonatal morbidities will be summarized descriptively by treatment group.

2.5.2.2 Derivation of Vital Signs

Vital signs including heart rate (beats/min), respiratory rate (breaths/min), systolic and diastolic blood pressure (mmHg), and body temperature (°C). are collected daily. Change from baseline will be calculated for all visits using the formula below:

$$Value\ post\ baseline - Value\ at\ baseline$$

2.5.2.3 Analysis of Vital Signs

Vital signs will be summarized descriptively using n, mean, standard deviation, minimum, median, and maximum for each visit. Change from baseline will also be summarized descriptively for all post-baseline visits.

2.5.2.4 Derivation of Laboratory Results

Laboratory testing (clinical parameters analyzed at local lab) is collected at baseline and then as per the SOC for each investigational site and on an approximately 15-day basis. Missingness in data is expected since laboratory parameters are collected per SOC and laboratory collection listed are optional.

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline, the descriptive statistics, and shift tables.

2.5.2.5 Analysis of Laboratory Results

Laboratory parameters will be summarized descriptively using n, mean, standard deviation, minimum, median, and maximum at each visit. Change from baseline will also be provided for all cases where baseline assessments are available.

2.5.2.6 Derivation of Treatment Exposure

The following will be calculated to summarize treatment exposure:

Infusion duration (in hours/day):

$$End\ datetime\ of\ administration - Start\ datetime\ of\ administration$$

If multiple infusions were given each day, then the above will be done for each administration and summed together.

Administered Daily Infusion Rate (mL/kg/day):

$$\frac{Total\ Volume\ Administered\ on\ Day\ X\ (mL)}{Lipid\ dosing\ weight\ on\ Day\ X\ (kg)}$$

Administered Daily Dose (g/kg/day):

$$\frac{Total\ Volume\ Administered\ on\ Day\ X\ (mL)}{Lipid\ dosing\ weight\ on\ Day\ X\ (kg)} * 0.2$$

Administered Infusion Rate (g/kg/h):

$$\frac{Administered\ Daily\ Dose\ (g/kg/day)}{Infusion\ Duration\ (hr/day)}$$

Total Study Treatment Days (days):

$$(End\ Date\ of\ Study\ Treatment - Start\ Date\ of\ Study\ Treatment) + 1$$

Total Pre-Study Treatment Days (days): a count of the number of days that pre-randomization lipids were reported. If a patient had more than one infusion per day, then the sum of all infusions over that day should be used in the calculations above. For example, if there are two infusions of 200 mL each over 4 hours a piece, the total volume administered should be 400 mL and the total treatment duration should be 8 hours.

2.5.2.7 Analysis of Treatment Exposure

The above parameters, will be summarized by treatment group using n, mean, standard deviation, minimum, median, and maximum.

2.5.2.8 Physical Examinations

Results of physical examinations will be listed only.

2.5.3 Independent Data Safety Monitoring Board

There is a DSMB for this study that reviews data at four different time points in the study (10%, 50%, and 90% of enrollment). Refer to the DSMB Charter as well as the DSMB SAP for DSMB activities and analyses for the study.

2.6 Other general principles

2.6.1 Adjustment for covariates

There are no adjustments for covariates for any analyses in this study.

2.6.2 Handling of Dropouts or Missing data

All data collected up to the point where the patient drops out will be used for analyses.

Aside from missing weight in the calculation of nutritional intake, no missing data will be imputed for this study.

2.6.3 Multicenter Studies

This study was conducted in approximately 10 sites across the United States. Data from all sites will be pooled together for analyses.

2.6.4 Multiple Comparison/Multiplicity

No formal statistical tests are calculated for this study, so no multiplicity adjustments are needed.

2.6.5 Use of an "efficacy subset" of patients

A sensitivity analysis of the primary endpoint will be completed on the per protocol set. The PPS (as defined in section 1.5.1) is a subset of the full analysis set.

2.6.6 Rounding and Decimal Places

The estimated mean, Q1, median, and Q3 for a set of values will be displayed to 1 more significant digit than the original values, standard deviations will be displayed to 2 more significant digits, and minimum and maximum values will be displayed with the same number of significant digits as the original values. All percentages will be displayed out to 1 decimal place. For height, weight, and head circumference, up to 4 reported decimals are shown.

3. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

There are no planned changes in analyses from the protocol.

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5. APPENDIX

5.1 Appendix 1: List of Tables, Listings, and Figures

Table Number	Analysis Population	Table Name
14.1.1	N/A	Patient Overview
14.1.2	FAS	Patient Disposition
14.1.3	FAS	Protocol Deviations
14.1.4	FAS	Categorical Demographic and Baseline Characteristics
14.1.5	FAS	Continuous Demographic and Baseline Characteristics
14.1.6	FAS	Medical History by Coded Drug Term
14.1.7.1	FAS	Prior and Concomitant Medications by Coded Drug Term for Patient
14.1.7.2	FAS	Prior and Concomitant Medications by Coded Drug Term for Mother
14.2.1	FAS	Growth Parameters
14.3.1.1.1	SS	Summary of Adverse Events
14.3.1.1.2	SS	Treatment Emergent Adverse Events by Treatment, SOC, and Preferred Term
14.3.1.1.3	SS	Treatment Emergent Serious Adverse Events
14.3.1.1.4	SS	Treatment Emergent Adverse Events of Special Interest
14.3.1.1.5	SS	Treatment Emergent Adverse Events related to study treatment
14.3.1.1.6	SS	Treatment Emergent Serious Adverse Events related to study treatment
14.3.1.1.7	SS	Treatment Emergent Adverse Events leading to withdrawal
14.3.1.1.8	SS	Treatment Emergent Adverse Events leading to death
14.3.1.2.1	SS	Treatment Emergent Adverse Events in ≥5% of Patients by Treatment and Preferred Term
14.3.1.3.1	SS	Treatment Emergent Adverse Events by Treatment, SOC, Preferred Term, and Severity
14.3.1.3.2	SS	Serious Treatment Emergent Adverse Events by Treatment, SOC, Preferred Term, and Severity
14.3.1.3.3	SS	Treatment Emergent Adverse Events by Treatment, SOC, Preferred Term, and Relationship to Study Treatment

14.3.1.3.4	SS	Serious Treatment Emergent Adverse Events by Treatment, SOC, Preferred Term, and Relationship to Study Treatment
14.3.4.1	SS	Listing of Abnormal Hematology Values
14.3.4.2	SS	Listing of Abnormal Liver Function Values
14.3.4.3	SS	Listing of Abnormal Serum Chemistry Values
14.3.4.4	SS	Listing of Abnormal Fatty Acid Profile Values
14.3.5.1.1	FAS	Primary Endpoint: Essential Fatty Acid Deficiency
14.3.5.1.2	PPS	Primary Endpoint: Essential Fatty Acid Deficiency
14.3.5.2.1	FAS	Primary Endpoint: Holman Index Values
14.3.5.2.2	PPS	Primary Endpoint: Holman Index Values
14.3.5.3.1	FAS	Primary Endpoint: Time to EFAD
14.3.5.3.2	PPS	Primary Endpoint: Time to EFAD
14.3.5.4.1	FAS	Fatty Acid Profile
14.3.5.4.2	PPS	Fatty Acid Profile
14.3.5.5.1	FAS	Genetic Polymorphism
14.3.5.5.2	PPS	Genetic Polymorphism
14.3.6.1.1	FAS	Parenteral Nutrition-Associated Liver Disease
14.3.6.2.1	FAS	Hepatic Integrity
14.3.6.2.2	FAS	Shift Table of Hepatic Integrity for End of Treatment and Maximum Values
14.3.6.2.3	FAS	Hepatic Integrity: Days from Baseline to Maximum Value
14.3.6.3.1	FAS	Plasma Phytosterols, Cholesterol, and Squalene Levels
14.3.6.3.2	FAS	Plasma Phytosterols Correlation with Direct Bilirubin
14.3.6.4.1	FAS	Nutritional Intake from Parenteral Nutrition
14.3.6.4.2	FAS	Nutritional Intake from Enteral Nutrition
14.3.6.4.3	FAS	Nutritional Intake from IV Fluids
14.3.6.4.4	FAS	Overall Nutritional Intake
14.3.7.1	SS	Neonatal Morbidities at End of Treatment
14.3.8.1	SS	Vital Signs Summary and Change from Baseline
14.3.9.1	SS	Hematology Summary and Change from Baseline
14.3.9.2	SS	Liver Function Test Summary and Change from Baseline
14.3.9.3	SS	Serum Chemistry Summary and Change from Baseline

14.3.10	SS	Treatment Exposure

Listing Number	**Analysis Population**	**Listing Name**
16.2.1	N/A	Patient Disposition
16.2.2	FAS	Protocol Deviations
16.2.3.1	N/A	Patients Excluded from Efficacy Analyses
16.2.4.1	FAS	Demographic and Baseline Characteristics
16.2.4.2.1	FAS	Medical History
16.2.4.2.2	FAS	Diagnosis for Parenteral Nutrition
16.2.4.3.1	FAS	Concomitant Medications for Patient
16.2.4.3.2	FAS	Concomitant Medications for Mother
16.2.4.4	FAS	Concomitant Procedures
16.2.5.1	SS	Treatment Exposure
16.2.6.1	FAS	Growth Parameters
16.2.7.1.1	SS	Pre-Treatment Adverse Events
16.2.7.1.2	SS	Treatment Emergent Adverse Events
16.2.7.1.3	SS	Serious Pre-Treatment Adverse Events
16.2.7.1.4	SS	Serious Treatment Emergent Adverse Events
16.2.7.1.5	SS	Treatment Emergent Adverse Events of Special Interest
16.2.7.1.6	SS	Treatment Emergent AEs related to study treatment
16.2.7.1.7	SS	Serious Treatment Emergent AEs related to study treatment
16.2.7.1.8	SS	Treatment Emergent AEs leading to withdrawal
16.2.7.1.9	SS	Treatment Emergent AEs leading to death
16.2.7.2.1	SS	Neonatal Morbidities
16.2.8.1.1	FAS	Holman Index Measurements
16.2.8.1.2	FAS	Fatty Acid Profile
16.2.8.1.3	FAS	Genetic Polymorphism
16.2.8.2.1	FAS	Parenteral Nutrition-Associated Liver Disease (PNALD) Values
16.2.8.2.2	FAS	Hepatic Integrity Values
16.2.8.2.3	FAS	Drug Induced Liver Injury
16.2.8.2.4	FAS	Plasma Phytosterols, Cholesterol, and Squalene Levels
16.2.8.3.1	SS	Hematology Laboratory Values
16.2.8.3.2	SS	Liver Function Test Values
16.2.8.3.3	SS	Serum Chemistry Values
16.2.9.1	SS	Vital Signs
16.2.10.1	SS	Physical Examinations
16.2.11.1.1	FAS	Parenteral Nutrition Intake

16.2.11.1.2	FAS	Parenteral Nutrition Macronutrients
16.2.11.2.1	FAS	Enteral Nutrition Intake: Formula, Breast Milk, and Nutritional Shakes
16.2.11.2.2	FAS	Enteral Nutrition Intake: Additives and Fortifiers
16.2.11.2.3	FAS	Enteral Nutrition Intake: Oral Intake / Breastfeeding
16.2.11.2.4	FAS	Enteral Nutrition Macronutrients
16.2.11.3.1	FAS	IV Fluid Intake in addition to Parenteral Nutrition
16.2.11.3.2	FAS	IV Fluid Intake Macronutrients
16.2.11.4.1	FAS	Overall Nutritional Intake

Figure Number	**Analysis Population**	**Figure Name**
14.2.1	FAS	Box Plots of Growth Parameters by Treatment Group
14.3.5.2.1	FAS	Holman Index over Time
14.3.5.2.2	PPS	Holman Index over Time
14.3.6.1.1	FAS	Direct Bilirubin over Time
14.3.6.1.2	PPS	Direct Bilirubin over Time
14.3.6.2.1	FAS	Assessment of Drug Induced Liver Injury: ALT
14.3.6.2.2	FAS	Assessment of Drug Induced Liver Injury: AST
14.3.6.2.3	FAS	Time Course of Hy's Law Cases
14.3.6.3.2	FAS	Scatterplots of Plasma Phytosterols vs. Direct Bilirubin
14.3.6.4.1.1	FAS	Box Plots of Ordered Parenteral Nutrition Intake by Treatment Group
14.3.6.4.1.2	FAS	Box Plots of Administered Parenteral Nutrition Intake by Treatment Group
14.3.6.4.2.1	FAS	Box Plots of Ordered Enteral Nutrition Intake by Treatment Group
14.3.6.4.2.2	FAS	Box Plots of Administered Enteral Nutrition Intake by Treatment Group
14.3.6.4.3	FAS	Box Plots of Administered IV Fluid Intake by Treatment Group
14.3.6.4.4.1	FAS	Box Plots of Overall Ordered Nutritional Intake by Treatment Group
14.3.6.4.4.2	FAS	Box Plots of Overall Administered Nutritional Intake by Treatment Group