Clinical Trial Protocol: 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
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.
Investigators:	Multi-center
Sponsor:	Baxter Healthcare Corporation
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Amendment 5.6:	2022 FEB 22

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[redacted]

SYNOPSIS

Sponsor:
Baxter Healthcare Corporation

Name of Finished Product:
Clinolipid (lipid injectable emulsion, USP) 20%

Name of Active Ingredient:
Refined olive oil (80%) and refined soybean oil (20%)

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

Rationale:
Baxter plans to conduct a postmarketing, randomized, controlled clinical trial to evaluate the risk of developing essential fatty acid deficiency (EFAD) in pediatric patients, including neonates, receiving either Clinolipid or standard-of-care soybean oil-based lipid emulsion.

Primary Objective:
To evaluate the risk of developing EFAD in pediatric patients, including neonates, receiving either Clinolipid or standard-of-care soybean oil-based lipid emulsion (Intralipid) as a component of parenteral nutrition (PN) within the hospital setting from 7 to 90 days, inclusive.

EFAD will be defined using the 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.

1. Secondary Objective(s):
2. The secondary objectives are as follows:
3. To evaluate the risk of developing liver disease, including parenteral nutrition-associated liver disease (PNALD) as defined by direct bilirubin ≥2 mg/dL when no other etiology for liver dysfunction is present in patients receiving with intravenous lipid emulsion (ILE)
4. To evaluate the adequacy of nutritional intervention in patients receiving either ILE
5. To evaluate the safety profiles of Clinolipid and Intralipid, as assessed by adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)

Study Design:
This will be a descriptive study designed to evaluate the risk for pediatric patients treated adequately with Clinolipid in the hospital for up to a maximum of 90 days to develop EFAD.

Additionally, this study design will evaluate the safety and efficacy of using Clinolipid in a pediatric population.

A randomized, double-blind study is appropriate to decrease clinician and patient bias during study conduct.

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 (up to 1 month corrected age [CA]), 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).

The primary and secondary objectives will be determined based on, but not limited to, the following clinical and laboratory assessments:

- Plasma fatty acid (FA) profiles and Holman Index;
- Genetic polymorphisms in the FA desaturase genes FADS1 and FADS2 in a subset of patients (approximately 20%);
- Hepatic function tests including alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total and direct bilirubin to assess hepatic function and integrity;
- Plasma phytosterol (stigmasterol, campesterol, and sitosterol), cholesterol and squalene levels to determine potential correlation with the development of PNALD;
- Holman Index and fatty acid profiles will be evaluated. Select polymorphisms in the fatty acid desaturase genes, FADS1 and FADS2, will be determined in a subset of patients. The major plasma phytosterols found in the lipid emulsions (stigmasterol, campesterol, and sitosterol), cholesterol, and squalene also will be assessed.

After end of study treatment (maximum of 90 days), the patient will resume PN therapy as prescribed by their healthcare provider.

Study Population:
Key Inclusion Criteria:

1. Patients who are expected to require PN for at least 7 days;
2. Premature infants (born at 24 to <37 weeks of gestation with a birth weight ≥750 g) must require at least 80% of targeted energy requirements by PN at study entry (up to 1 month CA); full term infants and children must require at least 70% of targeted energy requirements by PN at entry into the study;
3. A patient, or legal representative, has signed a written informed consent form per 21 CFR Part 50.55(e).

Key Exclusion Criteria:

1. Patients who are not expected to survive hospitalization or with a severe critical unresponsive illness at time of initiation with foreseeable intercurrent events that could jeopardize the patient's participation in the study (i.e. unresponsive shock, sepsis, renal failure requiring dialysis, severe unresponsive metabolic acidosis, and/or severe unresponsive metabolic disorders), as judged by the Investigator;
2. Patients with a known hypersensitivity to lipid emulsion, egg or soybean proteins, or any of the active substances, excipients, or components of the container or who have a history of an adverse event due to ILE;

3. Patients with liver disease including cholestasis;
4. Patients with severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (i.e. triglyceride >400 mg/dL);
5. Premature infants born <24 weeks of gestation and patients ≥18 years;
6. Patient requires or is expected to require propofol for sedation;
7. Patient, born to a symptomatic mother diagnosed with COVID-19 at the time of birth or before birth;
8. Patient has received a diagnosis of COVID-19 (diagnosis <2 months prior and/or symptoms have not resolved);
9. Female patients who are pregnant. Note: 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.

Test Product: Clinolipid (lipid injectable emulsion, USP) 20%

Reference Therapy: Intralipid (lipid injectable emulsion, USP) 20%

Mode of Administration: The dosing schedule is the same for each of the injectable lipid emulsions (ILEs), Clinolipid and Intralipid (control).

Table 1. Dosing Schedule for Intravenous Lipid Emulsions (g/kg/d of lipid) [a]

	Day 1 of PN [b] (g/kg/day)	Targeted daily advancement rate (g/kg/day)	Maintenance [c] (g/kg/day)	Maximum (g/kg/day)
Preterm infants	1	1	2.5 to 3	3
Term infants (0-<1y)	1	1	2.5 to 3	3
Children (1-<10y)	1	1	2 to 3	3
Adolescents (10-<18y)	1	1	1 to 2	3

[a] Daily administration over 20-24 hours

[b] Randomization is recommended within 24 hours of signing consent but must occur within 3 days of signing consent. If patient is not randomized within 24 hours of informed consent, patient should be started on standard of care ILE on Day 1 of PN and transitioned to study drug once randomization has occurred.

[c] Unless there is a clinical reason to decrease the dose in the opinion of the Investigator

Duration of Treatment: from 7 days, up to 90 days

Statistical Methods:

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.

Analysis Sets:

The analysis sets in this study include: the Full Analysis Set (FAS), the Per Protocol Set (PPS), and the Safety Analysis Set. The FAS includes all patients who are randomized to receive either Clinolipid or standard-of-care (SOC) soybean oil-based lipid emulsion (Intralipid), consistent with the intention-to-treat principle. The PPS includes a subset of patients in the FAS who have Holman Index measurements taken at baseline and at least 1 other time point post-baseline, who have received a minimum of 7 days

of ILE treatment, and do not have a major protocol violation that potentially impacts the primary endpoint. The Safety Analysis Set includes all patients that have received treatment (Clinolipid or SOC).

Subgroup analyses of patients by age group (premature infants born <37 weeks of gestation (up to 1 month CA), full-term neonates born ≥37 weeks of gestation <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) and subgroup analyses according to gestational age and birth weight will be conducted.

The primary endpoint analysis and secondary endpoint analyses of the development of liver disease including parenteral nutrition-associated liver disease (PNALD) and the adequacy of nutritional intervention will be conducted for both the FAS and PPS. The safety analyses (secondary endpoint no. 3) will be conducted for the FAS.

Primary Endpoint:

The risk of developing EFAD (determined by Holman Index value >0.4) in pediatric patients will be summarized by treatment group as frequency and percentage, Time to developing EFAD will be analyzed using the Kaplan-Meier approach. Both incidence rate and proportion of EFAD will be computed for each treatment group.

Holman Index also will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) on an approximately 15-day basis in each of the 2 treatment groups (Clinolipid vs Intralipid).

FA profiles will be summarized using descriptive statistics in each of the treatment groups.

FA profile, Holman Index will be assessed in the pediatric patients at baseline and approximately every 15 days throughout the study up to end of study treatment.

Genetic polymorphisms in the FA desaturase genes FADS1 and FADS2 will be assessed in a subset of patients (approximately 20%) and the distribution assessed in the context of the FA profile.

- Genetic material will be obtained from buccal smears in all patients that 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 within FADS1 and FADS2 genes as the synthesis of ARA from linoleic acid (LA) requires both the delta-5 and delta-6 desaturase enzymes (coded for by FADS1 and FADS2).
- Distribution of the polymorphisms within FADS1 and FADS2 genes will be assessed in the context various FA findings 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).

Secondary Endpoints:

The 3 secondary endpoints of the study include 1) the development of liver disease including PNALD; 2) the adequacy of nutritional intervention; and 3) the safety profiles including AEs, SAEs and AESIs.

1. Liver disease, including development of PNALD

- The risk of developing PNALD (as defined by direct bilirubin ≥2 mg/dL when no other etiology for liver dysfunction is present in patients receiving ILE) in pediatric patients will be summarized by treatment group as frequency and percentage, as well as time to developing PNALD using the Kaplan-Meier approach. Both incidence rate and proportion of PNALD will be computed for each treatment group.
- To assess the relationship of phytosterol, cholesterol and squalene blood levels and the development of PNALD, plasma phytosterol, cholesterol, and squalene levels will be summarized using descriptive statistics at baseline, at the end of study treatment, and as well as maximal values during the study period in each of the 2 treatment groups. In addition, the correlations

between plasma phytosterol levels and direct bilirubin will be assessed by computing a Pearson's correlation coefficient or a Spearman correlation coefficient.

- Hepatic integrity (ALP, AST, ALT, GGT, total and direct bilirubin) will be evaluated by presenting descriptive summary statistics of individual values at different measurement time points from baseline to end of study treatment during the study period in each of the 2 treatment groups. Hepatic integrity parameters will also be summarized in shift tables comparing results from baseline to end of study treatment (max 90 days) and to maximal value during the study period in each of the 2 treatment groups. In addition, assessment for drug-induced liver injury will be conducted according to Hy's Law and eDISH criteria.[1,2]

2. Adequacy of nutritional intervention

The adequacy of nutritional intervention in patients receiving either Clinolipid or Intralipid will be assessed and results analyzed as follows:

- Prescribed and actual nutritional intakes (calories, protein, lipids and carbohydrates) from both PN and enteral/oral nutrition will be collected and recorded on a daily basis and summarized daily for the first 2 weeks of treatment and on an approximately every 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 infants <1 year) in each of the treatment groups as follows:
- Gain in weight (g/kg/day in infants and 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 growth standards for infants and children ages 0 to 2 years, or Center for Disease Control growth charts for children age ≥2 years).

3. Safety profiles of Clinolipid and Intralipid, including AEs, SAEs and AESIs.

The safety profiles will be assessed and analyzed as follows:

- Vital signs and laboratory tests will be summarized using descriptive summary statistics in each of the 2 treatment groups.
- 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 CA.
- All AEs, SAEs, and AESI will be tabulated by body system using the Medical Dictionary for Regulatory Activities (MedDRA) coded terms.
- Adverse events and SAEs will be presented by treatment group using frequencies and percentages. In addition, the AE rate per 100 patient days will be reported.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase (also SGPT)
ALP	alkaline phosphatase
ARA	arachidonic acid
AST	aspartate aminotransferase (also SGOT)
BMI	body mass index
BPD	bronchopulmonary dysplasia
BW	body weight
CA	corrected age
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CRF	case report form
CS	clinically significant
DHA	docosahexaenoic acid
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
EFAD	essential fatty acid deficiency
EPA	eicosapentaenoic acid
FA(s)	fatty acid(s)
FAS	full analysis set
FADS1	fatty acid desaturase 1 gene
FADS2	fatty acid desaturase 2 gene
GA	gestational age
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
hCG	human chorionic gonadotropin
IC	informed consent
ICF	informed consent form
ICH	International Council for Harmonisation
ILE	intravenous lipid emulsion
IP	investigational product
IRB	Institutional Review Board

IVH	intraventricular hemorrhage
LA	linoleic acid
MedDRA	Medical Dictionary for Regulatory Activities
NEC	necrotizing enterocolitis
OO	Olive oil
PN	parenteral nutrition
PNALD	parenteral nutrition-associated liver disease
PPS	per protocol set
PUFA	polyunsaturated fatty acid
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SDS	standard deviation score
SNP	single nucleotide polymorphism
SO	soybean oil
SOC	standard of care
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WHO	World Health Organization

1. INTRODUCTION

Although humans and other mammals can easily synthesize most fatty acids (FAs) from carbon groups in carbohydrates and proteins, they lack the desaturase enzymes necessary to insert a cis double bond at the n-6 and n-3 positions of a FA. As a result, the parent polyunsaturated fatty acid (PUFA) of the n-6 series, linoleic acid (LA, 18:2n-6), and the parent PUFA of the n-3 series, alpha-linolenic acid (ALA, 18:3n-3), are considered essential and indispensable for the synthesis of other long chain PUFAs of the n-6 and n-3 series.

It is currently estimated that essential fatty acid deficiency (EFAD) may occur in human when LA and ALA intake is less than 2-4% and 0.25-0.5% of energy intakes, respectively.[3] The clinical manifestations of EFAD are a flaky dry skin, hair loss, hair depigmentation, poor wound healing, increased susceptibility to infections, and poor growth in infants and children.[3] Biochemical characteristics include decreased blood and tissue PUFAs from the n-6 and n-3 series and an elevated triene:tetraene ratio (T:T, Holman Index). Other biochemical manifestations of EFAD are considered non-specific and can include elevated liver enzymes, hyperlipidemia, thrombocytopenia and altered platelet aggregation.[3,4]

EFAD is rare under usual circumstances in healthy humans who have access to a varied diet or have sufficient adipose tissue that allows fat store mobilization to prevent EFAD when exogenous supply is limited.[3,4] Thus, EFAD primarily occurs in clinical circumstances that severely limit fat intake, digestion, absorption and metabolism and in the setting of severely depleted fat stores. Due to their high requirements and limited fat stores, young infants are at increased risk for EFAD, especially premature infants.[4,5]

Parenteral nutrition (PN) is indicated for the supply of energy and essential nutrients when oral or enteral nutrition is not possible, insufficient, or contraindicated. Parenteral nutrition is essential for nutrient delivery in patients with gastrointestinal (GI) dysfunction who lack the capacity to absorb adequate nutrients for maintenance or recovery of tissue mass and function.

Intravenous lipid emulsions (ILEs) were developed in order to prevent and treat EFAD in patients who require PN, as well as to provide a high-density energy source. The first intravenous fat preparation used to any great extent in the United States was made from cottonseed oil and marketed under the tradename of Lipomul® and was withdrawn from the market in 1965 because of numerous reports of toxicity, including "the fat-overloading syndrome", hemorrhagic tendencies, and liver damage. The toxic accumulation of fat observed with Lipomul was attributed to its large particle size (1 nm

in diameter), and possibly the emulsifying agent, pluronic F-68.[6] Subsequently, for several years PN did not include the provision of any lipid and was associated with several reports of EFAD.[7-9]

The post-Lipomul ILEs were developed from soybean oil (SO) or safflower oil, both rich in LA and ALA. SO contains about 45–55 % LA, 6–9 % ALA, and very little saturated or monounsaturated FAs. Intralipid, a 100% SO based ILE, was invented by the Swedish physician and nutrition researcher Arvid Wretlind, and was approved for clinical use in Sweden in 1962 and 10 years later in the United States.

Experimental and clinical research suggests that these purely SO-based ILEs may exert an oxidative stress, may have a negative influence on immunological functions, and may play a role in PN-associated liver disease (PNALD). These findings were felt to be related to its absolute high PUFA content, favoring lipid peroxidation, and the relative excess of n-6 PUFAs, favoring pro-inflammatory effects.[10,11]

Several new ILEs were subsequently developed including other sources of FAs designed to decrease the proportion of SO. In addition to the classic 100% SO ILEs, new generation composite ILEs contained other lipids including medium chain triglycerides derived from coconut oil or other tropical nut oils, olive oil (OO), or fish oil, or a combination of several sources. These new generation ILEs potentially can provide advantages over pure SO ILEs and are widely available in Europe and Canada but not in the United States.[4,5,12-14]

Clinolipid is an ILE comprised of a mixture of 80% OO and 20% SO. It was formulated with a lower SO content than currently marketed emulsions in order to reduce LA levels, while still providing an adequate amount of EFAs to prevent and correct EFAD in adult and pediatric patients requiring PN.[15] This OO-based ILE is rich in oleic acid, an n-9 monounsaturated FA, that is considered immune neutral with potentially fewer adverse consequences on immunity compared to pure SO ILEs.[10]

Clinolipid has approximately one third of the LA content of a 100% SO ILE (fatty acid levels are provided in Table 1 and sterol composition is provided in Table 2). This reduction in the EFA supply could be a concern in a pediatric population, especially premature infants, who have higher EFA requirements than adults. Clinolipid has marketing authorization in approximately 50 countries. The current evidences of more than 20 years of clinical use suggest that Clinolipid is safe and can prevent EFAD.[15,16] However, the objective of this study is to evaluate the risk of developing EFAD when using 20% Clinolipid in pediatric patients requiring PN compared to the use of a 100%

SO ILE (Intralipid 20%) that is still the standard-of-care (SOC) in current United States hospital settings.

Table 1. Fatty Acid Levels (mean levels) for Intralipid and Clinolipid

Fatty Acid(s)	Intralipid 20%	Clinolipid 20%
Total Saturated Fatty Acids	15.6 %	16.6 %
Myristic acid (14:0)	0.1	0.0
Palmitic acid (16:0)	11.0	13.0
Stearic acid (18:0)	3.9	3.3
Total monounsaturated fatty acids	22.8 %	63.4 %
Palmitoleic acid (16:1n-7)	0.1	0.9
Oleic acid (18:1n-9)	20.9	59.7
Vaccenic acid (18:1n-7)	1.3	1.7
Gondoic acid (20:1n-9)	0.2	0.2
Total polyunsaturated fatty acids	61.7 %	20.0 %
Linoleic acid (18:2n-6)	54.7	18.6
γ-linolenic acid (18:3n-6)	ND	ND
α-linolenic acid (18:3n-3)	6.7	1.7
Arachidonic acid (20:4n-6)	0.2	0.2
EPA (20:5n-3)	ND	ND
DHA (22:6n-3)	0.1	0.1

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ND = not detected; values represent mean % and are rounded to nearest tenth

Adapted from Harvey K et al.[17]

Table 2. Sterol composition for Intralipid and Clinolipid (µg/mL ± SD)*

Sterols	Intralipid (Soybean Oil-Based)	Clinolipid (Olive Oil-based)
Squalene	7.43 ± 0.10	387.45 ± 2.30
Cholesterol	274.08 ± 3.55	109.70 ± 0.38
Campesterol	55.35 ± 0.48	13.33 ± 0.12
Stigmasterol	65.05 ± 0.52	12.15 ± 0.04
β-Sitosterol	302.64 ± 2.00	240.59 ± 2.08
β-Sitostanol	7.68 ± 0.25	4.57 ± 0.16
Lanosterol	8.35 ± 2.48	3.74 ± 0.20
Total sterols	713.15 ± 9.27	384.08 ± 2.98
Total phytosterols	439.07 ± 5.72	274.38 ± 2.60

Table 2. Sterol composition for Intralipid and Clinolipid (µg/mL ± SD)*

Sterols	Intralipid (Soybean Oil-Based)	Clinolipid (Olive Oil-based)
Phytosterols (mg) per 100 g of lipid	220 ± 2.86	137 ± 1.30

* All experiments were conducted in triplicate, and data are shown as mean ± SD; lipid emulsions analyzed are representative of only a single Lot number. Adapted from Xu et al.[18]

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the risk of developing EFAD in pediatric patients, including neonates, receiving either Clinolipid or SOC 100% SO-based ILE (Intralipid) as a component of PN within the hospital setting from 7 up to 90 days.

Complete 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 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%) 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 the10 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 FADS 1 and FADS2 genes.

2.2 Secondary Objective(s)

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 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 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).

3. INVESTIGATIONAL PLAN

3.1 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 SOC SO-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 up to 1 month corrected age (CA), 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) is signed and a Study Treatment Period starting when the patient receives study treatment (See Appendix 1, Schedule of Events Table). End of study treatment is defined as the last day of PN with Intralipid or Clinolipid; maximum 90 days of study treatment is allowed.

3.2 Rationale for Study Design and Control Group

This will be a descriptive study designed to evaluate the propensity for hospitalized pediatric patients treated adequately with Clinolipid or SOC (Intralipid) from 7 up to 90 days to develop EFAD. Additionally, this study design will evaluate the safety and efficacy of using Clinolipid or Intralipid in a pediatric population.

A double-blind study is appropriate to decrease clinician and patient bias during study conduct.

3.3 Study Duration

Enrollment for the study is anticipated to continue for approximately 22 months after initiation of the study.

4. STUDY POPULATION SELECTION

4.1 Study Population

Approximately 100 pediatric patients, including neonates, will be enrolled in the study.

The study will be conducted in approximately 15 study centers in the United States, focusing on institutions with neonatal and pediatric intensive care units.

A patient will be considered to be enrolled in the study after the signing of the ICF and confirmation of compliance with the study inclusion/exclusion criteria. Since this study is being conducted in a pediatric population, the patient's legal representative must provide IC (i.e. sign and date the ICF). An assent form (child's agreement to participate) will also be used following requirements of local or central Institutional Review Board (IRB) as applicable. The patient's legal representative must provide IC (i.e. sign and date the ICF). Screening failures will be documented. Screen failures may be re-screened once, if approved by the medical monitor. All re-screens must be fully re-consented and repeat all screening procedures.

4.2 Inclusion Criteria

Each patient must meet ALL of the following criteria to be enrolled in the study.

1. Patients and/or their legal representative must be able to understand the study and voluntarily sign the informed consent form (ICF) per 21 CFR Part 50.55(e)
2. Patients and/or their legal representative accept adherence to protocol requirements
3. Patients who are expected to require PN for at least 7 days
4. Premature infants (born at 24 to <37 weeks of gestation with a birth weight ≥750g) require at least 80% of targeted energy requirements by PN at study entry (up to 1 month CA); full term infants and children require at least 70% of targeted energy requirements by PN at study entry

4.3 Exclusion Criteria

Patients who meet ANY of the following criteria will be excluded from the study:

1. Patients who are not expected to survive hospitalization or with a severe critical unresponsive illness at time of initiation with foreseeable intercurrent events that could jeopardize the patient's participation in the study, as judged by the Investigator (e.g., unresponsive shock, sepsis, renal failure requiring dialysis, severe unresponsive metabolic acidosis, and/or severe unresponsive metabolic disorders);
2. Patients with a known hypersensitivity to lipid emulsion, egg or soybean proteins, or any of the active substances, excipients, or components of the container or who have a history of an adverse event due to ILE;
3. Patients with liver disease including cholestasis;
4. Patients with severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (triglyceride >400 mg/dL);
5. Patients who are unable to tolerate the necessary laboratory monitoring;
6. Patients who are enrolled in another clinical trial involving an investigational agent;
7. Patients with a known history of either severe hemorrhagic or severe hemolytic disease as judged by the investigator;
8. Premature infants born <24 weeks of gestation and patients ≥18 years;
9. Premature infants with a birth weight <750 g;
10. Patient requires or is expected to require propofol for sedation;
11. Patient, born to a symptomatic mother diagnosed with COVID-19 at time of birth or before birth;
12. Patient has received a diagnosis of COVID-19 (diagnosis <2 months prior and/or symptoms have not resolved);
13. Female patients who are pregnant. Note: 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.

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s) and Dosing

The PN guidelines for the provision of macronutrient in infants, children, and adolescents are provided in Table 3.

Micronutrients (electrolytes, minerals, trace elements and vitamins) should also be included in PN regimen based upon patient needs.

Table 3. General Pediatric Parenteral Nutrition Guidelines

	Energy (kcal/kg/d)	Amino acids (g/kg/d)	Glucose (g/kg/d)		Lipids (g/kg/d)	
	Target	Target	Start	Target	Start	Target
Preterm infants (<37wks)	90-120	3-4	6-8	10-14 (max.18)	0.5-1	3 (max.4)
Term infants (0-1y)	90-100	2.5-3	6-8	10-14 (max.18)	0.5-1	2.5-3 (max.3)
Children (1-10y)	55-80	1-2.5	3-6	8-10	1-2	2-3 (max.3)
Adolescents (10-18y)	30-55	0.8-2	2.5-3	5-6	1	1-2 (max.3)

Adapted from AAP 2014,[19] ASPEN 2015,[20] and ESPGHAN/ESPEN/ESPR/CSPEN 2018[21,22]

5.1.1 Clinolipid (lipid injectable emulsion, US Pharmacopeia) 20% - Investigational Product

Clinolipid is a sterile, non-pyrogenic ILE. Clinolipid contains a mixture of refined OO and refined SO in an approximate ratio of 4:1 (OO:SO). The lipid content is 0.20 g/mL. In Clinolipid, the mean composition of LA (n-6 EFA) is 35.8 mg/mL (range 27.6 to 44.0 mL) and ALA (n-3 EFA) is 4.7 mg/mL (range 1.0 to 8.4 mg/mL). The phospholipids provide 470 mg or 15 mmol of phosphorus per liter.

The total energy content, including fat, phospholipids, and glycerin is 2000 kcal/L.

5.1.1.1 Clinolipid Contraindications per US Prescribing Information

The use of Clinolipid is contraindicated in patients with the following:

- Known hypersensitivity to egg or soybean proteins or to any of the ingredients, including excipients.
- Severe hyperlipidemia (serum triglyceride concentrations above 1000 mg/dL) or severe disorders of lipid metabolism characterized by hypertriglyceridemia.

5.1.2 Intralipid 20% (lipid injectable emulsion, USP) – Active Control

Intralipid 20% (lipid injectable emulsion, USP) is the SOC 100% SO-based ILE. The lipid content of Intralipid 20% is 0.20 g/mL, with a LA content of 54.7% (approximately 0.11 g/ml).

The total energy content, including fat, phospholipids, and glycerin is 2000 kcal/L.

5.1.2.1 Intralipid Contraindications per US Prescribing Information

The administration of Intralipid 20% is contraindicated in patients with disturbances of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis or acute pancreatitis if accompanied by hyperlipidemia.

5.1.3 Dosing Schedule

In this study, the dosing schedule is similar for both ILE, Clinolipid or Intralipid (Table 4).

Table 4. Dosing Schedule from both Intravenous Lipid Emulsion[a]

	Day 1 of PN[b] (g/kg/day)	Targeted daily advancement rate (g/kg/day)	Maintenance [c] (g/kg/day)	Maximum (g/kg/day)
Preterm infants (<37wks)	1	1	2.5 to 3	3
Term infants (<1y)	1	1	2.5 to 3	3
Children (1-10y)	1	1	2 to 3	3
Adolescents (10-18y)	1	1	1 to 2	3

[a] Daily administration over 20-24 hours

[b] Randomization is recommended within 24 hours of signing consent but must occur within 3 days of signing consent. If patient is not randomized within 24 hours of informed consent, patient should be started on SOC ILE on Day 1 of PN and transitioned to study drug once randomization has occurred.

[c] Unless there is a clinical reason to decrease the dose in the opinion of the Investigator

5.2 Treatments Administered

Study treatment will be administered intravenously in the hospital setting from 7 up to 90 days using either a syringe pump or an infusion pump as appropriate for the daily volume of infusate. The flow rate will be prescribed by the Investigator to provide the daily dosage over 20 to 24 hours (maximum lipid infusion rate should not exceed 0.15 g/kg/hour).

5.3 Selection and Timing of Dose for Each Patient

Patients will be randomized to 1 of 2 treatment groups (Clinolipid vs. Intralipid). In case of multiple birth pregnancies, the infants will be assigned to the same treatment group. The selection of dose for each patient will be based on Table 4, Dosing Schedule for ILE (Table 4) and PN guidelines for other macronutrients (Table 3) as well as the patient's age, weight, and medical condition as judged by the investigator.

The administration of PN with SOC ILE may be initiated as per usual practice before Screening. In this situation, lipid dosing should be per Table 4, if possible.

If patients are not randomized on the same day as Screening and SOC PN is initiated, patients should receive SOC ILE using the dosing schedule per Table 4, starting on Day 1 of PN (until transition to study drug). Once patients transition to study drug, lipid dosing should continue progression per Table 4.

Study treatment will be administered as per the SOC in each study site. Intravenous lipid emulsion infusion may be administered over 20 to 24 hours daily, depending on hospital practice.

Any significant deviation (more than 3 consecutive days) to the Dosing Schedule and the reason for such violation should be recorded (e.g. hyperglycemia, hypertriglyceridemia, higher energy expenditure) in the case report form (CRF).

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 a clinical review of current patient status, assessment of any potential AE/SAEs, discussion/clarification with the investigator to resume or abort study treatment. If there is a likelihood that the patient will require a 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, as per Section 7.2.4 and Appendix 1 Schedule of Events.

5.4 Method of Assigning Patients to Treatment Groups

Randomization will be stratified by site and age group (premature infants born <37 weeks of gestation up to 1 month CA, 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 a 1:1 ratio to both treatment groups using a computer-generated central dynamic randomization schedule.

Preparation and labeling of treatment will be delegated by the Sponsor to the investigational site pharmacist(s). Patient numbers will be allocated according to the randomization code contained within the randomization schedule.

Study treatment will be prepared and dispensed by the investigational site pharmacist(s) or designee in accordance with the assigned treatment for that patient.

5.5 Blinding

The study will be double-blinded. The study treatment assignment will not be known by the Sponsor's or designee's data management, biostatistician (with the exception of an unblinded Sponsor's statistician who will have access to the randomization assignments), and medical functions; Investigator and site personnel; or by the personnel at the central laboratory. In order to prepare the study treatment, the designated pharmacist(s) will be aware of the study treatment (unblinded).

The unblinded pharmacist(s) will prepare the treatment according to the randomization schedule and will enter the required information on the study drug labels. These labels will not contain specific information pertaining to the identity of the study treatment. In addition, specified fields on the label will be blank so that the pharmacist(s) can enter the patient number, as well as other patient identifiers and information as applicable by local procedures. The labels will then be affixed to study treatment containers (either sterile syringes or flexible IV bags, as appropriate for the volume of infusate).

A Data and Safety Monitoring Board (DSMB) will be appointed by Baxter Healthcare Corporation to provide ongoing evaluation of safety data (refer to Section 10.8). Reports will be provided to the DSMB at pre-specified intervals.

Blinded data will be entered into the database and the treatment group assignments will be revealed after database lock.

5.6 Restrictions

5.6.1 Prior Therapy/Concomitant Medications

There are no restrictions on prior therapy or concomitant medications for this study.

All medications should be recorded in the source documents or equivalent. Prior medications, defined as those taken during the 30 days prior to Screening, will be recorded in the CRF. Concomitant medications, including dose, frequency, start and stop dates, and indication for use, will be recorded in the CRF throughout the study.

5.6.2 Concomitant Procedures

Invasive concomitant procedures, including the below list, must be documented in the eCRF:

- Chest tube
- Surgical procedure
- Surgical central line placement
- Blood/platelet/fresh frozen plasma or other colloid infusion
- Pericardiocentesis, pleural or peritoneal tap
- Lumbar puncture

5.6.3 Fluid and Food Intake

There are no restrictions on fluid or food intake during the course of this study. The inclusion criteria specifying that "Premature infants (<37 weeks of gestation) require at least 80% of targeted energy requirements by PN at study entry (up to 1 month CA); that full-term infants (≥37 weeks of gestation), children and adolescents who require at least 70% of targeted energy requirements by PN at study entry" is limited to Screening only.

All fluid and food intake will be recorded in the source document and the CRF.

5.6.4 Patient Activity Restrictions

Patients will remain hospitalized while enrolled in the study.

5.7 Treatment Compliance

Since all patients in this study will remain hospitalized, treatment compliance will be documented by investigational site personnel during the entire Study Treatment Period. Reasons for noncompliance and/or not meeting SOC targets will be tabulated and summarized.

5.8 Packaging and Labeling

Clinolipid is supplied in 100 mL and 500 mL CLARITY polyolefin bags (250 and 1000 mL bags may also be used). The CLARITY container is a lipid-compatible plastic container (PL 2401-1). The bag is packaged in an oxygen barrier overpouch, which contains an oxygen absorber/oxygen indicator sachet. Use only if the color of the oxygen indicator is within allowable range. Do not use unless emulsion has a homogeneous milky appearance.

Clinolipid will be labeled in accordance with the US Code of Federal Regulations 21 CFR 312.6 bearing the statement "Caution: New Drug- Limited by Federal (or United States) law to investigational use."

Intralipid will be packaged as a standard commercial product.

The following information will be recorded for both study treatments:

a. Lot number
b. Expiration date

5.9 Storage and Accountability

Clinolipid should be stored at 20 to 25°C (68 to 77°F) and should not be frozen. Excessive heat should be avoided. Clinolipid should be stored in its overpouch until ready to use.

Intralipid should be stored as per the product/package label, specifically Intralipid 20% should not be stored above 25°C (77°F). Do not freeze Intralipid 20%. If accidentally frozen, discard the bag.

5.9.1 Storage Requirements/Stability

Clinolipid will be shipped from the final manufacturing site to a clinical depot. Upon receipt, the clinical depot will segregate the product prior to order preparation. The product and supplies will be stored according to product label specifications, or other specific directions provided by the Sponsor. Clinolipid will be shipped from the clinical depot to the investigational site.

5.9.2 Investigational Product Accountability

The clinical depot personnel, Investigator, and investigational site personnel will be provided with written instructions on the handling and storage of investigational product and clinical supplies for the trial and appropriate documentation.

Accountability of all investigational product and clinical supplies will be performed by an unblinded study monitor during periodic site visits. The pharmacist will fill out a product accountability log to document all study product movement (i.e. receipt, dispensation, return, and disposition).

All unused product and supplies will be destroyed or returned to the Sponsor in accordance with applicable regulations. If needed, the Sponsor or its designee may

authorize an alternative disposition of unused investigational product and supplies; however, disposition can only occur after the Sponsor or its designee has been notified and has given written authorization. The Sponsor/designee will maintain a written record of any disposition of the investigational product and supplies in accordance with applicable regulations.

The Investigator shall not administer the investigational product to any person not authorized to receive it. The Investigator will be required to maintain adequate records of the disposition of the investigational product, including dates, quantities, batch/lot numbers, unique code numbers, expiration dates, as applicable, and use by study patients.

All of the investigational product will be reconciled and accounted for throughout the study. Additionally, at the conclusion of the study, records of all investigational product and supplies concerning delivery, inventory, dispensation, return and disposition will be collected from the clinical depot, and investigational site.

It is prohibited by law to use the investigational product outside the intent of this protocol.

6. STUDY PROCEDURES

Study assessments include the following:

6.1 Informed Consent

Informed consent (IC) is required prior to the initiation of any study related procedures or assessment. Since this study is being conducted in a pediatric population, the patient's legal representative must provide IC (i.e. sign and date the ICF). An assent form (child's agreement to participate) will also be used following requirements of local or central Institutional Review Board (IRB) as applicable.

6.2 Demographics

Demographic data including age, sex, race and ethnicity will be collected during Screening.

6.2.1 Neonates

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), and birth weight (BW) will also 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).[23]

6.3 Medical History and Prior Medications

Medical history information, including the diagnosis requiring PN, will be collected at Screening and updated as necessary at Baseline.

Diagnosis for requiring PN at Screening will be recorded (e.g. prematurity; congenital gastrointestinal malformation; gastrointestinal obstruction diseases; inherited gastrointestinal dysfunction and motility disorders; necrotizing enterocolitis; sepsis; short bowel syndrome, enteropathies including inflammatory gastrointestinal diseases; other gastrointestinal dysfunctions to be specified).

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). There are no restrictions for prior medications.

6.4 Physical Examination

Physical examinations will be conducted as per the SOC for the study site and documented for the study at Screening, Baseline and approximately every 15 days up to end of study treatment. In particular, clinical signs of EFAD (flaky dry skin, hair loss, hair depigmentation, poor wound healing, increased susceptibility to infections, growth status) will be considered as well as liver diseases specific symptoms (e.g. jaundice, hepatomegaly).

Any clinically significant (CS) new abnormal condition or worsening of a preexisting condition from Screening will be recorded in the CRF as AE.

6.5 Weight, Height or Length, and Head Circumference

As per Appendix 1, Schedule of Events Table, body weight (g) will be assessed and recorded daily from Baseline to end of study treatment while length or height (cm) (and head circumference (cm) in infants < 1 year of age) will be assessed and recorded on an approximately 15-day basis from Baseline to end of study treatment.

Standard deviation score (SDS) for weight, height or length and head circumference will be determined and recorded based on Fenton growth curve for premature infants, WHO growth standards for infants and children ages 0 to 2 years, and CDC growth charts for children age ≥2 years.

Body mass index (BMI, kg/m^2) will be determined and recorded in children and adolescents.

6.6 Vital Signs

Vital signs will be recorded once daily at approximately the same time each day (e.g. 8 AM), with a window of approximately 2-3 hours, as per Appendix 1, Schedule of Events Table. Vital signs include heart rate (beats/min), respiratory rate (breaths/min), systolic and diastolic blood pressure (mmHg), and body temperature (°C). The clinical significance of any abnormal vital sign values will be determined by the Investigator.

For clinically significant (CS) abnormal signs values, the Investigator will indicate if the value constitutes a new AE and record the associated signs, symptom, or medical diagnosis in the CRF as AE. Any abnormal value that persists should be followed at the discretion of the Investigator.

6.7 Clinical Laboratory Tests

6.7.1 Laboratory Parameters

Blood samples will be collected at Screening/Baseline and then as per the SOC for each investigational site and on an approximately 15-day basis as per Appendix 1, Schedule of Events Table. Baseline laboratory assessments do not need to be repeated if within ±24 hours of the Screening sample.

Laboratory data will be reviewed by the Investigator. For each abnormal laboratory value, the Investigator will determine whether the value is CS or not. For CS abnormal values, the Investigator will indicate if the value constitutes a new or a worsening AE and record the associated signs, symptoms, or medical diagnosis in the CRF. Any abnormal value that persists should be followed at the discretion of the Investigator.

Clinical laboratory tests will include the following (Table 5):

Table 5. List of Laboratory Tests

Tests Conducted at Local Laboratory	
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)
Tests Conducted at Central Laboratory	
Fatty Acid Profile and Holman Index[b] Genetic polymorphism testing for FADS1 and FADS2	Phytosterol Levels[b]: • Stigmasterol • Campesterol • Sitosterol Cholesterol Squalene

[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.

[b] Testing will be conducted with a minimal amount of blood volume per sample collected.

6.7.2 Sample Collection, Storage, and Shipping

Samples (Table 5) will be collected by site personnel as per Appendix 1, Schedule of Events Table.

6.7.2.1 Hematology and Chemistry

Hematology and Chemistry blood samples will be collected from all patients enrolled in the study. Blood samples should be collected at Screening/Baseline and then during SOC blood draws as well as on an approximately 15-day basis (ideally, blood should be collected at approximately the same time on each day the sample is to be drawn).

Samples will be processed and tested as per the investigational site's standard laboratory procedures.

6.7.2.2 Triglycerides

Blood samples for triglycerides will be collected from all patients enrolled in the study. Blood samples should be collected at Screening/Baseline and then during SOC blood draws as well as on an approximately 15-day basis (ideally, blood should be collected at approximately the same time on each day the sample is to be drawn).

Samples will be processed and tested as per the investigational site's standard laboratory procedures.

6.7.2.3 Liver function tests

Blood samples for liver function tests will be collected from all patients enrolled in the study. Blood samples should be collected at Screening/Baseline and then during SOC blood draws as well as on an approximately 15-day basis (ideally, blood should be collected at approximately the same time on each day the sample is to be drawn).

Samples will be processed and tested as per the investigational site's standard laboratory procedures.

6.7.2.4 Fatty acid profiles, Holman Index, and phytosterol, cholesterol, and squalene levels

Blood samples for the determination of FA profiles, Holman Index, and phytosterol (stigmasterol, campesterol, sitosterol), cholesterol, and squalene levels will be collected at Baseline from all patients enrolled in the study. Subsequent samples for FA profiles will be collected on an approximately 15-day basis at least 4 hours after interrupting ILE infusion in order to decrease the influence of infused ILE on FA profile. If a study site typically infuses ILE over 24 hours, the investigator should, to the best of their ability,

ensure a 4-hour lipid only infusion hold before obtaining samples for the FA profiles. Ongoing infusion of other macro- and micronutrients from PN are allowed as required for the best interest of the patient per the attending physician during the 4-hour ILE hold before obtaining samples for the FA profiles. Blood sample volumes will be kept to a minimum.

Blood samples for FA profiles, determining Holman Index, and quantifying the amount of phytosterols, cholesterol, and squalene in samples will be processed by an external laboratory. The FAs will be assessed according to the Mayo Clinic method, which is performed as a 2-step acid-base hydrolysis followed by hexane extraction and derivatization with pentafluorobenzyl bromide. Separation and detection are accomplished by capillary gas chromatography electron-capture negative ion-mass spectrometry. Quantitation is based on analysis in the selected ion-monitoring mode by using 13 stable isotope-labeled internal standards. Handling, labeling, and shipping procedures will be detailed in separate Laboratory Instructions provided by the Sponsor.

Reference values can be found in Appendix 2.

6.7.2.5 Genetic polymorphism for fatty acid desaturase genes

Buccal swab samples for the determination of genetic polymorphisms for FADS1 (rs174553) and FADS2 (rs174575, rs99780, rs174583) will be collected from all enrolled patients for whom consent is obtained. Buccal swabs can be collected at any time before the end of study treatment.

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 SNPs within FADS1 and FADS2 genes as the synthesis of ARA from LA requires both the delta-5 and delta-6 desaturase enzymes (coded for by FADS1 and FADS2) for synthesis. The level of these desaturase enzymes modulates the synthesis of ARA from LA.

Distribution of polymorphisms within FADS1 and FADS2 genes will be assessed in the context of various FAs derived from EFAs (LA and ALA):

- Gamma-LA and ARA from the n-6 PUFA pathway;
- Stearidonic acid, EPA, and DHA from the n-3 PUFA pathway.

Sample handling, labeling, and shipping procedures, as well as the name and address of the central laboratory conducting the testing, will be detailed in separate Laboratory Instructions provided by the Sponsor. Buccal swabs will be destroyed once all analyses have been completed.

6.8 Diagnosis and Management of Essential Fatty Acid Deficiency (EFAD)

EFAD will be suspected in all patients with abnormal plasma liver enzymes tests or any clinical signs of EFAD. The diagnosis will be confirmed by the planned FA profile analyses (see Appendix 1, Schedule of Events Table).

The Holman Index will be used for the diagnosis and management of EFAD.

The Holman Index, also called plasma triene:tetraene (T:T) ratio, is the ratio of the level of eicosatrienoic acid (Mead acid, n-9 FA) and the level of ARA (n-6 FA).

6.8.1 Holman Index <0.2

Patients with a Holman Index of <0.2 have normal EFA status and will be followed for possible development of EFAD as defined in the study protocol.

6.8.2 Index between 0.2 and 0.4

Patients with a Holman Index of 0.2-0.4 are considered to be at risk for EFAD. Values in this range are indeterminate and may be seen in patients with adequate LA intake to prevent EFAD or in patients with low LA intake that are evolving toward EFAD.

The management of these patients includes first the assessment for clinical features of EFAD (dermatitis, diarrhea, perianal irritation, growth and development failure, recurrent infections, irritability, and/or poor wound healing).

Second, it implies checking if the plasma ARA levels are within normal range and that the unblinded pharmacist preparing the ILE determine if LA intake is adequate (See Section 6.8.5 Calculating LA Intake from ILE).

- If no clinical features are present:
  - If the ARA levels are within normal range with LA intake within the normal range (1-4% of the total energy intake), continue to follow the patient and check FA levels and Holman Index regularly (approximately every 15 days) till the Holman Index is normalized. The investigator and the patient may remain blinded.

- If the ARA level is low, increase LA intake even if in the normal range (1-4% of total energy intake). For example, if the level of LA intake is less than normal requirement (<1% of total energy intake), lipid intake will be increased to supply LA within the normal range (1-4 % of total energy intake). If the patient is receiving a LA intake in the low normal range (1-2% of energy intake), it needs to be increased >2% of energy intake. If the patient is receiving a LA intake in the high normal range (3-4% of energy intake), it needs to be increased >4% of energy intake. The amount of the increase in LA intake should be determined by the clinician considering the clinical state of the patient and the safety of increasing the lipid intake. The monitoring of LA and ARA levels Holman Index and clinical features will persist regularly (every 15 days) till the Holman Index is normalized.

- If there are clinical features, increase LA intake even if in the normal range. For example, if the level of LA intake is less than normal requirement (<1% of total energy intake), lipid intake will be increased to supply LA within the normal range (1-4 % of total energy intake). If the patient is receiving a LA intake in the low normal range (1-2% of energy intake), it needs to be increased >2% of energy intake. If the patient is receiving a LA intake in the high normal range (3-4% of energy intake), it needs to be increased >4% of energy intake. The amount of the increase in LA intake should be determined by the clinician considering the clinical state of the patient and the safety of increasing LA intake. The monitoring of LA and ARA levels, Holman Index and clinical features will persist regularly (approximately every 15 days) until the Holman Index is normalized and clinical features disappear.

6.8.3 Holman Index >0.4

Patients with Holman index >0.4 will be considered as biochemical EFAD. It will be confirmed in the context of low LA, low ARA, and high eicosatrienoic acid (Mead acid).

Clinical EFAD is diagnosed in the presence of any clinical features of EFAD (dermatitis, diarrhea, perianal irritation, growth and development failure, recurrent infections, irritability, and/or poor wound healing).

The management of these patients includes the assessment, the record, and the increase of LA intakes until the Holman Index normalizes and clinical features, if present, disappear.

The daily monitoring of LA intakes, and the approximately every 15 day monitoring of LA and ARA levels and Holman Index will persist until the Holman Index normalizes and clinical features disappear. If the Holman Index does not reduce to <0.4 or if it continues to increase, lipid intake will be further increased. The amount of the increase in LA intake should be determined by the clinician considering the clinical state of the patient and the safety of increasing the total lipid intake.

Some patients may have higher requirements for EFAs due to an underlying disease (e.g. high demand for growth and wound healing). Total parenteral lipid intake should usually remain below the maximum intake (Table 4, Dosing Schedule), which is an amount that is normally adequate for prevention of EFAD in all patients. The patient should receive the increased LA intake for at least 1 week prior to repeating the FA profile with the Holman Index assessments to allow time for the physiologic effects of the FA to occur.

When EFAD persists despite maximal lipid intake, the ILE should be unblinded. If the patient is receiving Clinolipid, the patient should be switched to Intralipid to allow for greater delivery of LA.

Additional LA intakes may be supplied via intravenous and/or enteral/oral routes.

If severe hypertriglyceridemia (triglycerides >400 mg/dL) develops, the cause should be investigated. If it is determined to be related to the ILE, lipid intake may be adjusted using the ILE with the higher relative content of LA.

If direct bilirubin increases above 2.5 mg/dL suggestive of cholestasis, a reduction of total lipid intake may be considered while continuing to provide adequate LA. The adequacy of LA intake needs to be confirmed by the unblinded pharmacist(s).

6.8.4 Holman Index >0.4 at baseline

Some study patients (especially premature infants) may demonstrate FA profile and Holman index compatible with EFAD at baseline due to their limited fat stores. The treatment for these infants is to administer EFA via ILE as part of their PN as described in Table 4, Dosing Schedule and being sure to reach the maintenance dosage. Infants with EFAD at baseline are to be followed regularly (approximately every 15 days) while receiving ILE per study protocol for improvement in their FA profile and Holman Index.

- If the Holman Index does not decrease with lipid administration in accordance with Table 4, Dosing Schedule, the patient may have greater than normal

requirements for EFA and the LA intake should be increased to the maximum dosage according to Table 4, Dosing Schedule and at the investigator's discretion.

- If the patient still does not respond, the investigator will be unblinded to determine if the patient is receiving Clinolipid or Intralipid. If the patient is receiving Clinolipid, the patient should be switched to Intralipid (as Intralipid contains a higher concentration of LA than Clinolipid).
- If the patient does not respond to Intralipid at maximal lipid dosage, consider increasing the LA intake with an enteral/oral source of LA or some additional intravenous Intralipid intakes.

6.8.5 Calculating Linoleic Acid (LA) Intake from Intravenous Lipid Emulsion (ILE)

Clinolipid contains approximately 18.6% LA while Intralipid contains approximately 54.7% LA. Since both are 20% ILE (20 g/dL, 0.2 g/mL, 2 kcal/ml), the content of LA is approximately 0.11 g/mL for Intralipid (1.1 kcal/ml from LA) and 0.04 g/mL for Clinolipid (0.4 kcal/ml from LA) (Table 6).

Table 6. Intralipid and Clinolipid Linoleic Acid Content

Content	20% Intralipid	20% Clinolipid
Lipid, g/ml	0.2	0.2
Energy, kcal/ml	2	2
Linoleic acid, g/ml	0.11	0.04
Linoleic acid, kcal/ml	1.1	0.4

Sample Calculation:

If a 2 kg patient receives 16 mL of Intralipid per day, the patient receives 8 ml/kg/day of Intralipid. It corresponds to 1.6 g/kg/day of lipid and 0.88 g/kg/day of LA. The energy part of LA is 8.8 kcal/kg/day. If the total energy intake is 100 kcal/kg/day, it means that 8.8% of the energy intake comes from LA.

If a 2 kg patient receives 16 mL of Clinolipid per day, the patient receives 8 ml/kg/day of Clinolipid. It corresponds to 1.6 g/kg/day of lipid and 0.32 g/kg/day of LA. The energy part of LA is 3.2 kcal/kg/day. If the total energy intake is 100 kcal/kg/day, it means that 3.2% of the energy intake comes from LA.

The LA intake that normally prevents EFAD is 1-4% of total energy intake. The unblinded pharmacist determines if the patient has adequate LA intake for prevention of EFAD. The pharmacist communicates to the patient's nutrition clinician according to the protocol (see Sections 6.8.2, 6.8.3 and 6.8.4.).

6.9 Nutritional Intake

Prescribed and actual macronutrient intake (fluid, energy, protein, carbohydrates, and lipid) of both parenteral and enteral nutrition will be collected and recorded on a daily basis in the CRF from Baseline to end of study treatment for each of the treatment groups. See Appendix 1, Schedule of Events Table, for additional details.

Intravenous intakes (fluid, amino acid, dextrose/glucose, and lipid) from PN as well as any intravenous macronutrient additions to the PN solution will be collected and recorded as parenteral intakes.

For breast milk intake, the macronutrient content will be estimated from volume intakes using mean reference values in mature human milk (640 kcal, 12 g of protein, 67 g of carbohydrates, and 34 g of lipid per 1 Liter of milk).[23] When breastfeeding intakes cannot be measured, the best estimation (volume) of the investigator will be recorded. For commercial products including formula and human milk fortifiers, macronutrient intakes will be recorded from volume intake and calculated from manufacturer label. For oral food ingestion, energy and lipid intakes only will be recorded from best estimates.

6.10 Dispensing Study Treatment

Blinded study treatment will be provided to the pediatric/neonatal unit from the study site pharmacist(s). The pharmacist(s) will maintain accurate and complete records of study treatment dispensation. Study personnel in the pediatric/neonatal unit will administer study treatment to the patients intravenously using either a syringe pump or an infusion pump, as appropriate for the volume dispensed.

The amount of lipid emulsion (g/kg/day) delivered to the patient will be collected daily and recorded (volume, flow rate and infusion duration) for each administration of study treatment (See Section 6.9).

6.11 Concomitant Medications

Ongoing medications and nutritional supplements received by the patient and nursing mother (if applicable) will be recorded as concomitant medication once study treatment has been initiated. During treatment, concomitant medications and therapies (including

dose, frequency, start and stop dates, and indication for use), will be recorded in the CRF by study site personnel on a daily basis.

During treatment, both patients' and nursing mothers' concomitant medications (as documented in the patient's chart) will be recorded.

6.12 Concomitant Procedures

Invasive concomitant procedures, including the below list, must be documented in the eCRF:

- Chest tube
- Surgical procedure
- Surgical central line placement
- Blood/platelet/fresh frozen plasma or other colloid infusion
- Pericardiocentesis, pleural or peritoneal tap
- Lumbar puncture

6.13 Adverse Events Assessments

An AE is any untoward medical occurrence in a patient or clinical investigational patient administered a study product, and that does not necessarily have a causal relationship with the treatment or drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory function), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), organ dysfunction (e.g., cardiovascular failure, pancreatitis, etc.), systemic illness (e.g., sepsis), or outcome of death temporally associated with the use of the study product, whether or not the event is considered associated with the study product.

Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality, if the patient must be discontinued from the study due to the abnormality, or if the value exceeds specific limits defined by the SOC as qualifying it as an AE.

An elective procedure/surgery that occurs during the course of a study, but is being performed for a documented pre-existing condition and was pre-planned prior to study entry, will not qualify as an AE. If, however, the pre-existing condition unexpectedly deteriorates during the study requiring the procedure/surgery to be performed earlier than

planned, the condition for which the procedure/surgery is being performed will qualify as an AE.

In this study, AEs will be recorded in conjunction with the first study procedure (Screening). 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. Adverse events occurring during Screening but prior to the administration of study treatment will be considered as unrelated to study treatment.

6.13.1 Performing Adverse Events Assessments

During the course of the study, and maximum 30 days after the last dose of study drug, if hospital discharge has not occurred, the Investigator or designee will routinely monitor and solicit each patient for the occurrence of any AEs. If an AE occurs, a full description of the event, including the date and time of onset, duration, severity, actions taken, outcome, seriousness of the event, and causal relationship of the AE to the study treatment will be recorded in the patient's CRF. All AEs will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline.

6.13.2 Severity

The severity of an AE is defined as a qualitative assessment by the Investigator of the degree of intensity of the AE observed or reported by the patient. The assessment of severity will be made irrespective of treatment relationship or seriousness.

The severity of each AE will be recorded as mild, moderate, or severe according to the following definitions:

- Mild – The AE is a transient discomfort and does not interfere in a significant manner with the patient's normal functioning level and/or the AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate – The AE produces limited impairment of function and may require therapeutic intervention and/or the AE produces no sequela/sequelae.
- Severe – The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern and/or the AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

6.13.3 Relationship

Causality is a determination of whether there is a reasonable possibility that the investigational product/control is etiologically related to/associated with the AE. Causality assessment includes, for example, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiologic plausibility For each AE, the investigator will assess the causal relationship between the investigational product (IP) / control 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).

a. Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs.

b. Is not associated with the IP/control (i.e., does not follow a reasonable temporal relationship to the administration of IP/control or has a much more likely alternative aetiology).

- Unlikely related (either 1 or both circumstances are met).
  a. Has little or no temporal relationship to the IP/control.
  b. A more likely alternative aetiology exists.
- Possibly related (both circumstances must be met).
  a. Follows a reasonable temporal relationship to the administration of IP/control.
  b. An alternative aetiology is equally or less likely compared to the potential relationship to the IP/control.
- Probably related (both circumstances must be met).
  a. Follows a strong temporal relationship to the administration of IP/control, which may include but is not limited to the following:
     1. Reappearance of a similar reaction upon re-administration (positive re-challenge).
     2. Positive results in a drug sensitivity test (skin test, etc.).
     3. Toxic level of the IP/control as evidenced by measurement of the IP/control concentrations in the blood or other bodily fluid.
  b. Another aetiology is unlikely or significantly less likely.

6.13.4 Expectedness

A suspected unexpected serious adverse reaction (SUSAR) is any adverse reaction that is classified as serious and is suspected to be caused by the investigational drug but is not consistent with the information found in the current version of the Investigator's Brochure.

6.13.5 Clinical Significance

Clinical significance of AEs will be determined by the Investigator, based on his/her best medical judgement.

6.13.6 Clinical Laboratory Adverse Events

Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality, if patients must be discontinued from the study due to the abnormality or if the value exceeds specific limits qualifying it as an AE.

6.13.7 Serious Adverse Events

6.13.7.1 Definition

A SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.13.7.2 Reporting Serious Adverse Events

All SAEs or any pregnancy reports with or without an associated SAE must be reported to the sponsor within 24 hours of site's knowledge of the event. Further details are specified in the Safety Management Plan.

The Investigator will also report any SAEs to the Institutional Review Board (IRB) in writing based on the IRB's reporting requirements and provide the Sponsor with a copy of the notification.

All SAEs including follow-up information that occur from the date of signing of ICF until 30 days after the last dose of study treatment must be reported to Baxter Global Pharmacovigilance.

Baxter or designee will assess each SAE reported by the Investigator to determine if the event qualifies as an Expedited Report according to local regulations. Expedited reports will be submitted to the appropriate Authority by Baxter or designee. Per regulations, Investigators will receive a letter from Baxter or designee describing the expedited SAE. The Investigator should file this letter within their Investigator Site File. Additionally, the Expedited Report letter may need to be submitted by the Investigator to their IRB, as appropriate per local regulations.

6.13.8 Treatment-Emergent Adverse Events

A treatment-emergent AE is defined as any AE that occurs after the onset of study treatment administration through the end of the study.

6.14 Removal of Patients from the Study/ Discontinuation of the Study

Any patient/legal representative may voluntarily withdraw consent for continued participation and data collection at any time during the course of the study. The Investigator may terminate a patient's study participation at any time during the study if the Investigator judges it to be in the patient's best interest.

Patients may be withdrawn or prematurely discontinued from the study treatment/assessments for any of the following reasons:

- Adverse Event(s)
- Clinically significant change in a laboratory parameter
- Protocol violation (i.e. patient failed to meet protocol entry criteria or did not adhere to the protocol requirements)
- Pregnancy
- Patient or any legal representative requests to withdraw from the study
- Sponsor or Investigator terminates the study

All patients randomized to Clinolipid who must receive Intralipid for rescue therapy purposes will be discontinued from the trial.

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 a clinical review of current patient status, assessment of any potential AE/SAEs, discussion/clarification with the investigator to resume or abort study treatment. The outcome of the adjudication process will not preclude the monitoring for AE/SAEs for the subsequent 30 days and in the event of an AE, following the subject until the AE resolves, stabilizes or the subject returns to baseline. 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, as per Section 7.2.4 and Appendix 1 Schedule of Events.

If a patient's participation is discontinued, the reason(s) must be recorded in the source documents and in the CRF.

End of study treatment procedures should be performed when a patient withdraws or is discontinued from the study.

Patients who are withdrawn from the study will not be replaced.

The study may be discontinued:

- If new safety information becomes available indicating that continuing the study treatment or procedures may jeopardize the safety of the patients
- Because of an administrative decision by the Sponsor

6.15 Appropriateness of Measurements

Measurements to be performed during the course of the study (with the following exceptions) are standard for the indication or patient population under study: testing for phytosterols and genetic polymorphisms, while not standard, are appropriate for addressing the study endpoints.

7. STUDY ACTIVITIES

The details of the schedule of events are provided in Appendix 1, Schedule of Events Table.

7.1 Screening Period

After providing written IC, patients will enter the Screening Period. The Screening Period is defined as the period after the ICF is signed and dated until randomization. The maximum duration of this period is 3 days prior to dosing. Randomization is recommended within 24 hours of signing consent but must occur within 3 days of signing consent. If patient is not randomized within 24 hours of informed consent, patient should be started on SOC ILE on Day 1 of PN as per Table 4 and Section 5.3. Signing and dating of the ICF and the Screening visit may occur on the same day, if necessary; however, the ICF must be signed and dated before any Screening activities can be conducted.

The aim of the Screening Period is to determine the eligibility (inclusion/exclusion criteria) of patients for randomization.

Further assessments conducted during Screening include:

- Demographics
- Gestational age and birth weight for infants <1 years of age only
- Medical history (including diagnosis requiring PN)
- Physical examination, including weight and length or height (and head circumference for infants <1 year of age)
- Vital signs
- Laboratory evaluations including hematology and chemistry (refer to Appendix 1, Schedule of Events Table)
- Pregnancy test. Note: 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.
- Nutritional intakes
- Medication history
- Randomization to study treatment
- Adverse Events (AEs occurring during Screening but prior to administration of study treatment will be considered as unrelated to study treatment). Non-serious AEs during this time period will be collected as part of the medical history. Serious adverse events will need to be reported as per Section 6.13.7.2.

7.2 Study Treatment Period (Baseline to Day 90)

7.2.1 Baseline Procedures

Baseline is defined as the period within ±24 hours of first study treatment administration. The following procedures will be performed at Baseline (≤24 hours prior to administration of study treatment):

- Medical history will be updated as necessary.
- Physical examination including weight and length or height (and head circumference for infants <1 year of age)
- Vital signs
- Nutritional intakes
- Concomitant medications
- Concomitant procedures
- AEs

The following laboratory procedures will be performed at Baseline (±24 hours prior to administration of study treatment). Baseline laboratory assessments need not be repeated if completed within 24 hours of screening sampling:

- Laboratory evaluations including (refer to Appendix 1, Schedule of Events Table):
  - Hematology and chemistry
  - Hepatic function tests
  - Triglycerides
  - Fatty acid profile
  - Holman Index
  - Phytosterol, cholesterol, and squalene levels

Buccal swab samples for the determination of genetic polymorphisms for FADS1 (rs174553) and FADS2 (rs174575, rs99780, rs174583) will be collected from all enrolled patients for whom consent is obtained. Buccal swabs can be collected at any time before the end of study treatment.

7.2.2 Daily Procedures

The following procedures will be performed and recorded in the CRF on a daily basis during the Study Treatment Period.

- Weight
- Vital signs
- All nutritional intakes
- Concomitant medications
- Concomitant procedures
- AEs

7.2.3 Standard-of-Care Procedures

The following procedures will be performed at intervals determined by the SOC at each investigational site (refer to Appendix 1, Schedule of Events Table):

- Laboratory evaluations including:
  - hematology - complete blood count
  - chemistry - basic metabolic panel and electrolytes
- Diagnosis of 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 at 24 to <37 weeks of gestation up to 1 month CA with a birth weight ≥750g.

7.2.4 Days 15, 30, 45, 60, 75 and 90 or End of Study Treatment Procedures

The Study Treatment Period starts when 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.

The following procedures will be performed approximately every 15 days ±2 days for patients continuing on PN (days 15, 30, 45, 60, 75 and 90) and within ±2 days of the last day of study treatment (maximum 90 days on either Clinolipid or Intralipid) whenever that occurs:

- Physical examination including weight, length or height (and head circumference for infants <1 year of age)
- Vital signs
- Concomitant medications
- Concomitant procedures
- AEs
- Laboratory evaluations including:
  - Hematology parameters
  - Serum chemistry parameters
  - Hepatic integrity parameters
  - Total and direct bilirubin
  - Triglyceride levels
  - FA profile
  - Holman Index
  - Phytosterol, cholesterol, and squalene levels

In addition, the following data will be collected at end of study treatment:

- Diagnosis of 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 CA.

After end of study treatment (maximum of 90 days), the patient will receive nutritional intervention as prescribed by their healthcare provider as SOC if PN is still required.

8. QUALITY CONTROL AND ASSURANCE

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and that the data are generated, documented, and reported in compliance with the protocol and applicable regulatory requirements. Quality control will be applied to all stages of data handling to ensure reliability and correct processing. The Sponsor or designee is

responsible for securing agreement from all involved parties to ensure direct access to all study-related centers, source documents, and reports for the purpose of monitoring and auditing. Agreements made with the Investigator/institution will be in writing.

This study may be subject to an independent audit at the investigational study center, which will be conducted by the Sponsor's quality assurance personnel or designee. Full consultation with appropriate personnel will be made before and during such an audit. The Investigator must be available during the audit. If the Investigator is contacted by any regulatory authority regarding an audit for this study, the Investigator must contact the Sponsor immediately.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

A more detailed description of the statistical analysis will be presented in the Statistical Analysis Plan (SAP).

9.2 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.

For those patients who are discontinued from PN prior to 7 days due to adequate oral or enteral nutrition may be replaced at the discretion of the Sponsor.

9.3 Analysis Populations

The analysis sets in this study include: the Full Analysis Set (FAS), the Per Protocol Set (PPS), and the Safety Analysis Set. The FAS includes all patients who are randomized to receive either Clinolipid or SOC SO-based lipid emulsion (Intralipid), consistent with the intention-to-treat principle. The PPS includes a subset of patients in the FAS who have Holman Index measurements taken at baseline and at least 1 other time point 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). The Safety Analysis Set includes all patients that have received treatment (Clinolipid or SOC).

Subgroup analyses of patients by age group (e.g., premature infants born <37 weeks of gestation up to 1 month CA, full-term neonates born ≥37 weeks of gestation <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) and subgroup analyses for neonates according to GA and BW will be conducted.

The primary endpoint analysis and secondary endpoint analyses of liver disease including parenteral nutrition-associated liver disease (PNALD) and the adequacy of nutritional intervention will be conducted for both the FAS and PPS. All safety analyses will be conducted on the Safety Analysis Set.

Infants found to subsequently have baseline EFAD will not be considered to have treatment emergent EFAD and will be analyzed separately from infants with normal baseline EFAD status. Unblinded infants will be analyzed separately as well.

9.4 Demographics and Baseline Characteristics

Continuous demographic and baseline variables will be summarized using number of patients, mean, standard deviation, median, minimum, and maximum for each treatment group. Some variables such as sex, race, ethnicity, and age will be categorized and summarized by reporting the number and percentage of patients in each category for each treatment group.

9.5 Primary Endpoint

The primary endpoint is the risk of developing EFAD defined as defined by Figure in Appendix 3.

- The risk of developing EFAD in pediatric patients will be summarized by treatment group as frequency and percentage. Time to developing EFAD will be analyzed using the Kaplan-Meier approach.
- Both incidence rate and proportion of EFAD will be computed for each treatment group.
- The incidence rate of EFAD will be computed as the number of patients who develop EFAD during the Study Treatment Period divided by the corresponding person time (i.e. “person-day” which is computed as “total number of patients” times “treatment exposure period [day]” in the corresponding treatment group), and reported as per 100 patient days.
- The proportion of EFAD will be computed as the number of patients who develop EFAD during the Study Treatment Period divided by the corresponding total number of patients.

- The Holman Index will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) on an approximately 15-day basis in each of the 2 treatment groups (Clinolipid vs Intralipid).
- 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.

9.6 Secondary Endpoint(s)

The three secondary endpoints of the study include 1) the development of liver disease including PNALD; 2) the adequacy of nutritional intervention; and 3) the safety profile including AEs, SAEs and AESIs.

9.6.1 Liver Disease, Including Parenteral-Associated Liver Disease

9.6.1.1 Parenteral Nutrition-Associated Liver Disease

The risk of developing PNALD in pediatric patients by treatment will be summarized as frequency and percentage, as well as time to developing PNALD using the Kaplan-Meier approach. Both incidence rate and proportion of PNALD will be computed for each treatment group.

The incidence rate of PNALD will be computed as the number of patients who develop PNALD during the Study Treatment Period divided by the corresponding person time (i.e. “person-day” which is computed as “total number of patients” times “treatment exposure period [day]” in the corresponding treatment group), and reported as per 100 patient days. The proportion of PNALD will be computed as the number of patients who develop PNALD during the Study Treatment Period divided by the corresponding total number of patients.

9.6.1.2 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, median, 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).

Each hepatic integrity parameter will also be summarized in shift tables comparing end of study treatment and maximal values during the study intervention with those at baseline (mean, standard deviation, median, minimum, and maximum) including the delay (days) between baseline and maximal value in each of the 2 treatment groups (Clinolipid vs Intralipid). Shift categories will include normal and abnormal (>1 to 3 and >3-fold the upper limit of normal range). In addition, assessment for drug-induced liver injury (DILI) will be conducted according to Hy's Law and eDISH criteria,[1,2] with additional detail included in the SAP.

9.6.1.3 Plasma Phytosterol, Cholesterol, and Squalene Levels

Plasma phytosterol, cholesterol, and squalene levels will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) at baseline and the end of study treatment, as well as maximal value during the study and the delay (days) between study baseline and maximal value in each of the 2 treatment groups (Clinolipid vs Intralipid). In addition, the correlations 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.

9.6.2 Adequacy of Nutritional Interventions

9.6.2.1 Nutritional Intake

Prescribed and actual nutritional intake (fluid, energy, protein, carbohydrates, and lipids) from parenteral and enteral nutrition will be collected and recorded daily. They will be summarized 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.

9.6.2.2 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 (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 SDS from reference growth curves (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)

9.6.3 Safety Profile of Clinolipid and Intralipid

Vital signs and clinical laboratory tests will be summarized using descriptive summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) in each of the 2 treatment groups during the study period.

The following neonatal morbidities will be summarized by treatment group using n and percentage: BPD, ROP, IVH, PVL, NEC, and late-onset sepsis in enrolled premature infants born <37 weeks of gestation up to 1 month CA.

All AEs, SAEs, and AESIs will be tabulated by body system using the Medical Dictionary for Regulatory Activities (MedDRA) coded terms. They will be presented by treatment group using frequencies and percentage.

Adverse events of special interest are known AEs related to PN with ILEs, per Intralipid and Clinolipid USPIs and include the following: 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).

In addition, the AE rate will be estimated using person time (person-day) as the denominator, which is computed as “total number of patients” times “treatment exposure period [day]” in the corresponding treatment group. The AE rate per 100 patient days will be reported for the overall study period, and may be stratified into Weeks 1, 2, 3, and 4 as appropriate.

9.7 Interim Analysis

No interim analysis is planned for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The investigator will comply with the protocol (which has been approved/given favorable opinion by the IRB/), International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, and applicable regulatory requirements as described in the Clinical Study Agreement. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study center and verifies by signature the integrity of all data transmitted to the sponsor. Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

10.2 Institutional Review Board Approval

Before enrollment of patients into this study, the protocol, ICF and assent (when required), any promotional material/advertisements, and any other written information/recruitment aids will be reviewed and approved/given favorable opinion by the IRB and applicable regulatory authorities.

The IRB's composition or a statement that the IRB'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 IRB and, if required, upon the responsible party's notification of applicable regulatory authority(ies) approval.

The Investigator will promptly report to their IRB any unanticipated problems associated with the study treatment involving risks to patients or others, whether encountered at the investigative site or provided as a safety report by the Sponsor.

If the protocol or any other information given to the patient is amended, the revised documents will be reviewed and approved/given favorable opinion by the IRB 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.

10.3 Ethical Conduct of the Study

This study will be conducted in accordance with the following guidelines:

- Declaration of Helsinki (October 2013)
- Current ICH Guidelines (ICH E6) for GCP Guidelines
- Basic principles defined in US 21 CFR Part 312
- All applicable regulatory requirements and laws

10.4 Patient Information and Consent

The Investigator or his/her entitled designee will obtain written IC from each patient or from the patient's legal representative or designee as defined by local law. An assent form (child's agreement to participate) will also be used following requirements of local or central IRB as applicable. Consent and assent (where required) will be obtained before any study-specific procedures are performed.

Preparation of the ICF and assent form is the responsibility of the Investigator. The ICF must include all elements required by ICH, GCP, and applicable regulatory requirements, and must adhere to GCPs and to the ethical principles that have their origin in the Declaration of Helsinki. The ICF will be reviewed and approved by the Sponsor before IRB review.

The Investigator must provide the patient or the patient's legal representative with a copy of the ICF and written information about the study in the language in which the patient is most proficient. The language must be nontechnical and easily understood. The ICF will be reviewed with the prospective study patients or their legal representatives, and the Investigator will be available to answer questions regarding procedures, risks, and alternatives. The Investigator will allow sufficient time for the patient or the patient's legal representative to inquire about the details of the study and to decide whether or not to participate in the study. If the patient or the patient's legal representative wishes to participate, the ICF will be signed and personally dated by the patient or the patient's legal representative and by the person who conducted the IC discussion. The patient or the patient's legal representative will receive a copy of the signed ICF and any other written information provided to the patient before the patient's participation in the study. Before the commencement of the study, the Investigator must furnish the Sponsor with a copy of the IRB-approved ICF to be used in this study.

10.5 Patient Confidentiality

All patient information, medical records, and laboratory data will be kept confidential. Information and data may be discussed, analyzed, and reported; however, code numbers will identify the patient in the CRFs and in any reports, and the patient's identity will be kept confidential.

10.6 Study Monitoring

Monitoring visits will occur at regularly scheduled intervals at the investigational site to allow for verification of source documents and comparison of source data with the information recorded in the CRFs.

Representatives of the Sponsor, or its designee, must be allowed to visit the study site periodically to assess the data quality and the integrity of the study. These representatives will review study records on site and directly compare these with the source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. In addition, the study may be evaluated by Baxter's internal auditors or a designee, and/or by government inspectors, who must be allowed access to CRFs, source documents, and other study files. The Sponsor audit reports will be kept confidential.

The Investigator or a designated member of the Investigator's staff must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient's records (e.g. medical records, office charts, hospital charts, and study-related charts) for source data verification. The CRFs must be completed prior to each visit and be made available to the monitor so that their accuracy and completeness may be checked.

This study may be subject to an independent audit at the investigational site, which will be conducted by independent auditors. Full consultation with appropriate personnel will be made prior to and during such audit. The Investigator must be available during the audit. If the Investigator is contacted by any regulatory authority regarding an audit for this study or any other study, the Investigator will contact the Study Manager and Medical Director immediately.

10.7 Case Report Forms and Study Records

All patient medical records will be kept strictly confidential. Personally identifiable information will not be transmitted to Baxter, or its designee, or to any third parties. Patient CRFs will be maintained in an electronic data capture (EDC) system and will only be released to Baxter, its designee(s), or to appropriate government agencies. Code numbers will be used to identify the patient in CRFs and other study-related documents.

The Investigator is required to prepare and maintain adequate and accurate case histories for each patient. Source data will be entered in CRFs by the study coordinator/designee. Data should accurately reflect the data recorded in the source documents. The CRF must be reviewed by the Investigator and he/she will sign off in the EDC to verify that the CRF data is accurate, complete, and reflects the source documentation. This review and sign-off may be delegated to a qualified physician appointed as a Sub Investigator by the Investigator.

10.8 Data and Safety Monitoring Board

An independent DSMB will be established to review and analyze all safety data on a regular basis. Emerging efficacy data may be considered by the DSMB in evaluating the potential risks and benefits of the treatment under study. The DSMB will consist of an independent group of expert clinicians (a minimum of 2) who are not actively recruiting patients for this study, and a biostatistician. Reports will be provided to the DSMB at pre-specified intervals. The DSMB-associated biostatistician will be provided with the randomization code list and database transfers, (if requested).

Serious adverse events will be reviewed by the DSMB on an ongoing basis. The DSMB will review the frequency and severity of all AEs as well as demographic and bioactivity data. Ad hoc meetings may also be held for any safety concerns during the study. Based upon a review of the data, the DSMB will make recommendations to continue, modify, or stop the study if any of the stopping criteria are met (refer to Section 6.14). Further responsibilities and details of the DSMB will be included in the DSMB Charter.

10.9 Protocol Violations/Deviations

The Investigator will not deviate from this protocol without prior documented approval from the Sponsor or its designee and the IRB, except in cases of medical emergency. The Investigator may deviate from the protocol without prior approval only when the change is necessary to eliminate an apparent immediate hazard to the patient. In that event, the Investigator will notify the Sponsor immediately by phone, notify the IRB, and confirm notification to the Sponsor in writing as soon as possible, but within 5 working days after the change is implemented.

The Investigator is responsible for recording deviations from the protocol in the CRF.

10.10 Access to Source Documentation

The Sponsor or its designee will ensure that the protocol or other written agreement specifies that the Investigator/Institution provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection. The Sponsor

or its designee will verify that each patient has consented in writing to direct access to his/her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. The Sponsor or its designee is responsible for securing agreement from all involved parties to ensure direct access to all study-related centers, source documents, and reports for the purpose of monitoring and auditing.

10.11 Data Generation and Analysis

The Sponsor will utilize qualified individuals throughout all stages of the study process, from designing the protocol and CRFs, to supervising the overall conduct of the study, data handling and verification, conducting the statistical analyses, and preparation of final study reports.

The Sponsor will use an unambiguous patient identification code that allows for identification of all data reported for each patient.

A study database using EDC system will be created from the data in the CRFs using the MedDRA version 21.0 or higher for AE coding and the WHO Drug Dictionary (WHODRUG, version 201309) for concomitant medications coding.

Unless otherwise noted, all analyses will be performed using SAS®, SAS/GRAPH® and SAS/STAT® software, Version 9.4 of SAS for Windows, copyright © 2016 SAS Institute Inc, on a Microsoft Windows Server. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

10.12 Retention of Data

The Sponsor will retain the essential documents until at least 5 years have lapsed since the end of this clinical study for whatever reason.

The Investigator must retain all study records including investigational product disposition records and source documents for the maximum period required by applicable regulations and guidelines or institution procedures or for the period specified by the Sponsor (15 years), whichever is longer. The Investigator must contact the Sponsor or its designee before destroying any records associated with the study. The Sponsor or its designee will notify the Investigator when the study records are no longer needed. If the Investigator departs from the study site (e.g. relocation, retirement, death), the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator, IRB). The Sponsor must be notified in writing of any such transfer.

10.13 Financial Disclosure

The financial aspects of the study will be documented in an agreement between the Sponsor and the Investigator.

10.14 Publication and Disclosure Policy

Any information shared by the Sponsor regarding this study, including this protocol, is considered proprietary information and will be kept confidential.

The data generated by this clinical study are the property of the Sponsor. These data may be used by the Sponsor, now and in the future, for presentation or publication at the Sponsor's discretion or for submission to regulatory agencies.

The Sponsor recognizes the rights of the Investigators who qualify for authorship and want to publish the methods, results, and conclusions from the study. The Sponsor will allow the Investigator authors full access to data. The Sponsor has the right but not the obligation to review any publication or presentation from this study by any Investigator before publication or presentation to ensure intellectual property rights are respected. The Investigator or Institution will provide a copy of the proposed publication(s) to the Sponsor 60 days before submission for publication. The Sponsor will review such publications/presentations in a timely manner. Any differences in the interpretation or presentation of data will be resolved through a process of honest scientific debate.

The study will be published in a timely and responsible manner, with all articles and presentations conforming to good publication practice and other recognized standards. Premature and duplicate publications will be avoided. The Investigator agrees not to publish the results of the clinical study pertaining to his/her center before the publication of the overall clinical study results.

Authorship of publications resulting from the study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. The Uniform Requirements for Manuscripts state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version. Authors also agree to be accountable for all aspects of the publication. Refer to http://www.icmje.org/icmje-recommendations.pdf for current recommendations.

The Sponsor's support of the study and medical writing services will be acknowledged in all publications arising from the study.

10.15 Health Insurance Portability and Accountability Act

In connection with this research study, the Investigator and the institution may collect "protected health information" as defined in Title 45 CFR Section 164.501. The Investigator and/or the institution shall obtain the patient's legally authorized representative's authorization to allow the Investigator and the institution to disclose the protected health information in accordance with the standards as set forth in Title 45 CFR Section 164.514. The Sponsor may use and disclose the de-identified information as allowed by law.

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Appendix 1 Schedule of Events Table

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						
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

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	
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 (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 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 from all enrolled 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.

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	

[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.

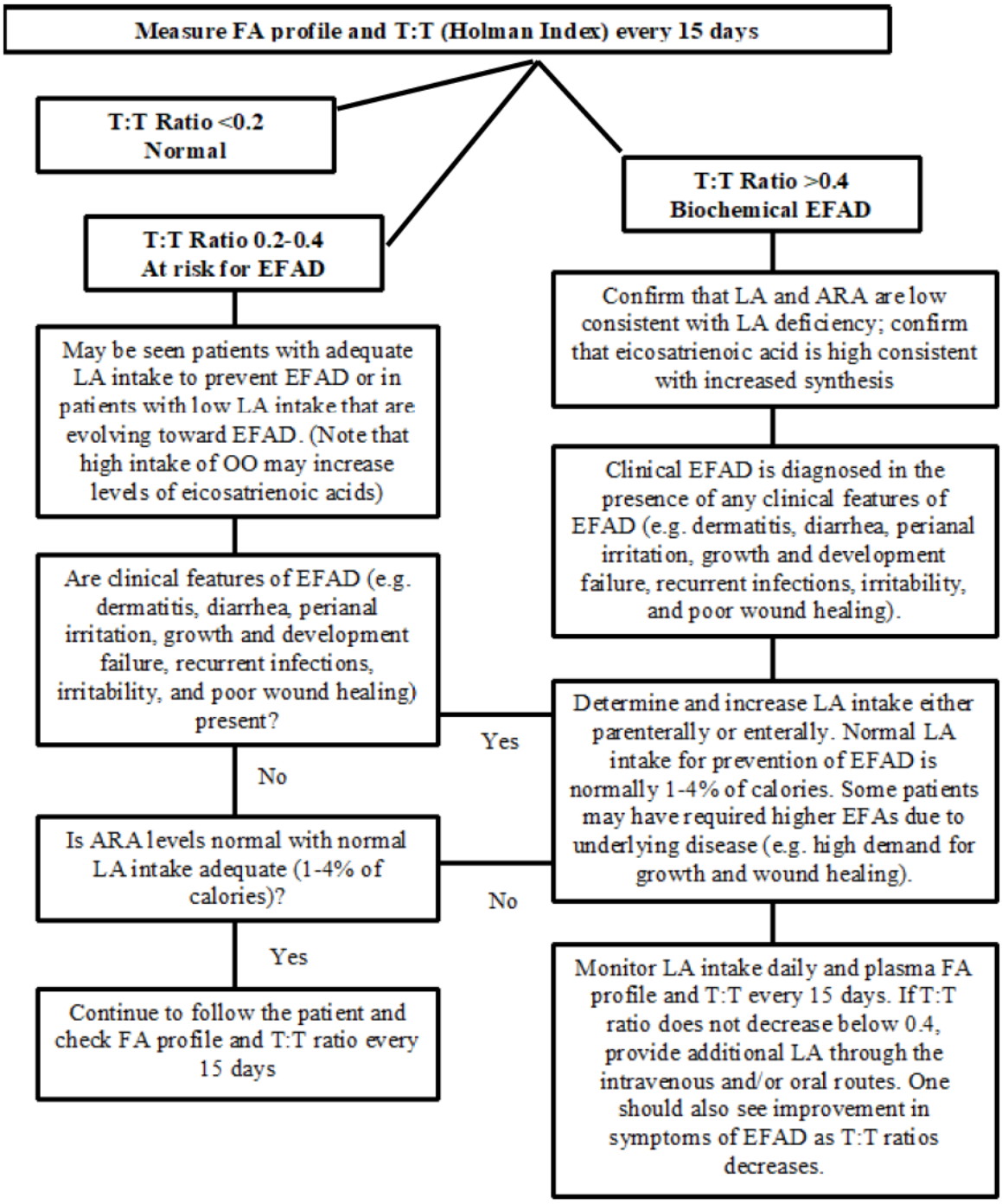
Appendix 2 Reference for Fatty Acid Profile Values (Mayo Clinic References)

Fatty Acid	Chain Length	Reference Values
Lauric Acid	C12:0	<1 year: 6-190 nmol/mL
		1-17 years: 5-80 nmol/mL
		> or =18 years: 6-90nmol/mL
Myristic Acid	C14:0	<1 year: 30-320 nmol/mL
		1-17 years: 40-290 nmol/mL
		> or =18 years: 30-450 nmol/mL
Hexadecenoic Acid	C16:1n-9	<1 year: 21-69 nmol/mL
		1-17 years: 24-82 nmol/mL
		> or =18 years: 25-105 nmol/mL
Palmitoleic Acid	C16:1n-7	<1 year: 20-1,020 nmol/mL
		1-17 years: 100-670 nmol/mL
		> or =18 years: 110-1,130 nmol/mL
Palmitic Acid	C16:0	<1 year: 720-3,120 nmol/mL
		1-17 years: 960-3,460 nmol/mL
		> or =18 years: 1,480-3,730 nmol/mL
Gamma-Linolenic Acid	C18:3n-6	<1 year: 6-110 nmol/mL
		1-17 years: 9-130 nmol/mL
		> or =18 years: 16-150 nmol/mL
Alpha-Linolenic Acid (ALA)	C18:3n-3	<1 year: 10-190 nmol/mL
		1-17 years: 20-120 nmol/mL
		> or =18 years: 50-130 nmol/mL
Linoleic Acid (LA)	C18:2n-6	1-31 days: 350-2,660 nmol/mL
		32 days-11 months: 1,000-3,300 nmol/mL
		1-17 years: 1,600-3,500 nmol/mL
		> or =18 years: 2,270-3,850 nmol/mL
Oleic Acid	C18:1n-9	<1 year: 250-3,500 nmol/mL
		1-17 years: 350-3,500 nmol/mL
		> or =18 years: 650-3,500 nmol/mL
Vaccenic Acid	C18:1n-7	<1 year: 140-720 nmol/mL
		1-17 years: 320-900 nmol/mL
		> or =18 years: 280-740 nmol/mL

Fatty Acid	Chain Length	Reference Values
Stearic Acid	C18:0	<1 year: 270-1,140 nmol/mL
		1-17 years: 280-1,170 nmol/mL
		> or =18 years: 590-1,170 nmol/mL
Eicosapentaenoic Acid (EPA)	C20:5n-3	<1 year: 2-60 nmol/mL
		1-17 years: 8-90 nmol/mL
		> or =18 years: 14-100 nmol/mL
Arachidonic Acid (ARA)	C20:4n-6	<1 year: 110-1,110 nmol/mL
		1-17 years: 350-1,030 nmol/mL
		> or =18 years: 520-1,490 nmol/mL
Eicosatrienoic Acid (Mead acid)	C20:3n-9	1-31 days: 8-60 nmol/mL
		32 days-11 months: 3-24 nmol/mL
		1-17 years: 7-30 nmol/mL
		> or =18 years: 7-30 nmol/mL
Homo-Gamma-Linolenic	C20:3n-6	<1 year: 30-170 nmol/mL
		1-17 years: 60-220 nmol/mL
		> or =18 years: 50-250 nmol/mL
Arachidic Acid	C20:0	<1 year: 30-120 nmol/mL
		1-17 years: 30-90 nmol/mL
		> or =18 years: 50-90 nmol/mL
Docosahexaenoic Acid (DHA)	C22:6n-3	<1 year: 10-220 nmol/mL
		1-17 years: 30-160 nmol/mL
		> or =18 years: 30-250 nmol/mL
DPA	C22:5n-6	<1 year: 3-70 nmol/mL
		1-17 years: 10-50 nmol/mL
		> or =18 years: 10-70 nmol/mL
DPA	C22:5n-3	<1 year: 6-110 nmol/mL
		1-17 years: 30-270 nmol/mL
		> or =18 years: 20-210 nmol/mL
DTA	C22:4n-6	<1 year: 2-50 nmol/mL
		1-17 years: 10-40 nmol/mL
		> or =18 years: 10-80 nmol/mL
Docosenoic Acid	C22:1	<1 year: 2-20 nmol/mL
		1-17 years: 4-13 nmol/mL

Fatty Acid	Chain Length	Reference Values
		> or =18 years: 4-13 nmol/mL
Nervonic Acid	C24:1n-9	<1 year: 30-150 nmol/mL
		1-17 years: 50-130 nmol/mL
		> or =18 years: 60-100 nmol/mL
Total Saturated Acid	N/A	<1 year: 1.2-4.6 mmol/L
		1-17 years: 1.4-4.9 mmol/L
		> or =18 years: 2.5-5.5 mmol/L
Total Monounsaturated Acid	N/A	<1 year: 0.3-4.6 mmol/L
		1-17 years: 0.5-4.4 mmol/L
		> or =18 years: 1.3-5.8 mmol/L
Total Polyunsaturated Acid	N/A	<1 year: 1.1-4.9 mmol/L
		1-17 years: 1.7-5.3 mmol/L
		> or =18 years: 3.2-5.8 mmol/L
Total n-3 Fatty Acids	N/A	<1 year: 0.0-0.4 mmol/L
		1-17 years: 0.1-0.5 mmol/L
		> or =18 years: 0.2-0.5 mmol/L
Total n-6 Fatty Acids	N/A	<1 year: 0.9-4.4 mmol/L
		1-17 years: 1.6-4.7 mmol/L
		> or =18 years: 3.0-5.4 mmol/L
Total Fatty Acids	N/A	<1 year: 3.3-14.0 mmol/L
		1-17 years: 4.4-14.3 mmol/L
		> or =18 years: 7.3-16.8 mmol/L

Appendix 3 Diagnosis and Management of EFAD



Appendix 4 Sponsor Signature

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
Original Protocol:	2014 MAY 20
Amendment 1:	2014 JUN 20
Amendment 2:	2014 SEP 03
Amendment 3:	2015 MAY 26
Amendment 4:	2019 MAR 22
Amendment 5:	2020 APR 13
Amendment 5.1:	2020 APR 21
Amendment 5.2:	2020 JUN 03
Amendment 5.3:	2020 JUN 25
Amendment 5.4:	2020 AUG 26
Amendment 5.5:	2022 FEB 03
Amendment 5.6:	2022 FEB 22

This clinical study protocol was subject to critical review and has been approved by the sponsor.

[redacted] Date: 22 FEB 22

Baxter Healthcare Corporation

Appendix 5 Investigator's Signature

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
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Amendment 5.3:	2020 JUN 25
Amendment 5.4:	2020 AUG 26
Amendment 5.5:	2022 FEB 03
Amendment 5.6:	2022 FEB 22

I have read Amendment No 5.6, which outlines the changes to the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the revised protocol in accordance with ICH guidelines and all applicable government regulations, including Part 54, Financial Disclosure by Clinical Investigators.

Signed:_____ Date:_____

Print Name:_____

Title:_____

Affiliation:_____

Address:_____

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Phone number:_____