Title:	Prospective, Randomized (1:1), Double-Blind, Parallel-Group, Active-Controlled, Multicenter Study to Compare Safety and Efficacy of Smoflipid® to Intralipid® 20% in Pediatric Patients of 3 Months to 16 Years of Age Requiring Parenteral Nutrition for at Least 90 Days and up to 1 Year
Authority Identification no.:	IND 102,137
Fresenius Kabi Study Identifier:	SMOF-028-CP4
Indication:	Smoflipid (lipid injectable emulsion) is indicated as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Study phase	4
Investigational drug:	Smoflipid (lipid injectable emulsion)
Control drug:	Intralipid 20% (a 20% I.V. fat emulsion)
Protocol status:	Final 2.0
Date:	19 February 2019
Sponsor:	Fresenius Kabi Deutschland GmbH [redacted] Else-Kröner-Straße 1 D - 61346 Bad Homburg Germany [redacted]

In case of emergency during out-of-office-hours please contact (Sponsor's medical expert according to ICH GCP):

[redacted]

The study will be carried out in accordance with the ICH – Guideline for good Clinical Practice (E6[R1] July 2002) including Explanatory Note and Comments, issued as CPMP/768/97, the Declaration of Helsinki, revised version (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the Code of Federal Regulations (CFR) Title 21 and the respective national laws and regulations.

The CSP and all subsequent amendments to the CSP are agreed upon between Fresenius Kabi as the sponsor of the clinical trial/investigation, the CRO, the Coordinating Investigator(s), if applicable and all Principal Investigators, and are recorded with a justification for each amendment.

Responsibilities (Signature Page)

The signatories confirm that this Clinical Study Protocol contains all information and regulations necessary for the conduct of this particular trial. We sign the protocol as an agreement of the details of the clinical trial and the means of data recording. We commit ourselves to comply with all instructions and regulations as laid down in this clinical trial protocol, in the current version of the Declaration of Helsinki, in the International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) Guideline, in the Code of Federal Regulations (CFR) Title 21, Part 312 and applicable national laws and regulations. Changes to this protocol require the written agreement of both the Investigator and Fresenius Kabi.

Coordinating Investigator

[redacted]

_____ _____

Date (DD_Month_YYYY) Signature

Chief Medical Officer Fresenius Kabi

[redacted]

_____ _____

Date (DD_Month_YYYY) Signature

Head of Divisional Medical, Clinical and Regulatory Affairs Fresenius Kabi

[redacted]

_____ _____
Date (DD_Month_YYYY) Signature

Director Global Safety Fresenius Kabi

[redacted]

_____ _____
Date (DD_Month_YYYY) Signature

Clinical Project Manager Fresenius Kabi

[redacted]

_____ _____
Date (DD_Month_YYYY) Signature

Contract Research Organization (CRO)

[redacted]

Date (DD_Month_YYYY) Signature

Biostatistics

[redacted]

Date (DD_Month_YYYY) Signature

Study outline

Title:	Prospective, Randomized (1:1), Double-Blind, Parallel-Group, Active-Controlled, Multicenter Study to Compare Safety and Efficacy of Smoflipid® to Intralipid® 20% in Pediatric Patients of 3 Months to 16 Years of Age Requiring Parenteral Nutrition for at Least 90 Days and up to 1 Year.
Authority Identification no.:	IND 102,137
Fresenius Kabi Study Identifier:	SMOF-028-CP4
Indication:	Smoflipid (lipid injectable emulsion) is indicated as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Study Phase:	4
Objectives:	Evaluate the safety and efficacy of Smoflipid (lipid injectable emulsion) compared to standard of care lipid emulsion Intralipid 20% (a 20% I.V. fat emulsion) administered via a central vein in pediatric patients 3 months to 16 years of age who require parenteral nutrition for at least 90 days and up to 1 year.
Study Hypothesis:	Smoflipid (lipid injectable emulsion) is safe and effective in pediatric patients when administered for 90 days or up to 1 year.
Study Drugs:	Investigational drug: Smoflipid (lipid injectable emulsion), referred to as Smoflipid in the following text. Control drug: Intralipid 20% (a 20% I.V. fat emulsion), referred to as Intralipid 20% in the following text.
Dosage of Study Drugs:	Dosage of Smoflipid and Intralipid 20% The dosing of the study drugs depends on the patient's individual energy requirements, age, body weight, tolerance, clinical status, and the ability to eliminate and metabolize lipids. A titration phase is necessary in patients with a new indication for PN treatment. Age groups are classified according to ICH (ICH 2000).

Study drugs will be started and advanced according to ASPEN pediatric nutrition recommendations (A.S.P.E.N. 2015) and center standards. Maximum dosage is according to the US Prescribing Information for Intralipid 20%, i.e., for pediatric patients up to 3 g/kg/d, and up to 2.5 g/kg/d for adolescents according to maximum dosage for adults.

A) Patients who start PN:

Infants 3 months to < 2 year of age:

start	0.5 to 1 g/kg/d lipid
advanced by	0.5 to 1 g/kg/d lipid
maximum	up to 3 g/kg/d lipid

Children 2 to < 12 years of age:

start	1 to 2 g/kg/d lipid
advanced by	0.5 to 1 g/kg/d lipid
maximum	up to 3 g/kg/d lipid

Adolescents 12 to 16 years of age:

start	1 g/kg/d lipid
advanced by	1 g/kg/d lipid
maximum	up to 2.5 g/kg/d lipid

B) Patients who already receive PN:

Infants 3 months to < 2 years of age:
up to 3 g/kg/d lipid

Children 2 to < 12 years of age:
up to 3 g/kg/d lipid

Adolescents 12 to 16 years of age:
Up to 2.5 g/kg/d lipid

Study drugs will be dosed at a weight-based infusion rate according to each patient's lipid needs and clinical condition. Investigational and control drug should be infused at constant rate for 10 to 24 h/d. Infusions should be given 5 to 7 days per week. Maximum infusion rate should not exceed 0.125 g/kg/h lipid.

Serum triglycerides and direct bilirubin will be monitored monthly to monitor lipid administration (see below, Study Treatment, Intravenous lipid dose management).

Route of Administration: The study drugs will be infused into a central vein via central venous catheter or peripherally inserted central catheter.

Dosage of Other PN Components: For total PN, amino acids, dextrose, electrolytes and micronutrients will be administered according to center standards taking into account the ASPEN recommendations for PN in pediatric patients (A.S.P.E.N. 2015). Age groups are classified according to ICH (ICH 2000). Energy needs will be estimated using equations for calculation (A.S.P.E.N. 2015).

The following dosages for amino acids and dextrose are recommended in the age groups. Dosage of dextrose will be adjusted to reach the target parenteral calories taking into account the calories from prescribed lipids and amino acids.

A) Patients who start PN:

Infants 3 months to < 2 years of age:

Age 3 months to < 1 year

• Amino Acids:	start	2.5 to 3 g/kg/d
	goal	2.5 to 3 g/kg/d
• Dextrose:	start	6 to 8 mg/kg/min (8.6 to 11.5 g/kg/d)
	advanced by	3.5 mg/kg/min) (5 g/kg/d)
	maximum	14 to 18 mg/kg/min (20.2 to 25.9 g/kg/d)

Age 1 year to < 2 years:

• Amino Acids:	start	1.5 to 2.5 g/kg/d
	goal	1.5 to 2.5 g/kg/d
• Dextrose:	start	3 to 6 mg/kg/min (4.3 to 8.6 g/kg/d)
	advanced by	2 to 3 mg/kg/min (2.9 to 4.3 g/kg/d)
	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Children 2 to < 12 years of age:

• Amino Acids:	start	1.5 to 2.5 g/kg/d
	goal	1.5 to 2.5 g/kg/d

• Dextrose:	start	3 to 6 mg/kg/min (4.3 to 8.6 g/kg/d)
	advanced by	2 to 3 mg/kg/min (2.9 to 4.3 g/kg/d)
	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Adolescents 12 to 16 years of age:

• Amino Acids:	start	0.8 to 2 g/kg/d
	goal	0.8 to 2 g/kg/d
• Dextrose:	start	2.5 to 3 mg/kg/min (3.6 to 4.3 g/kg/d)
	advanced by	1 to 2 mg/kg/min (1.4 to 2.9 g/kg/d)
	maximum	5 to 6 mg/kg/min (7.2 to 8.6 g/kg/d)

B) Patients who already receive PN:

Infants 3 months to < 2 year of age:

Age 3 months to < 1 year

• Amino Acids:	goal	2.5 to 3 g/kg/d
• Dextrose	maximum	14 to 18 mg/kg/min (20.2 to 25.9 g/kg/d)

Age 1 to < 2 years

• Amino Acids:	goal	1.5 to 2.5 g/kg/d
• Dextrose:	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Children 2 to < 12 years of age:

• Amino Acids:	goal	1.5 to 2.5 g/kg/d
• Dextrose:	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Adolescents 12 to 16 years of age:

• Amino Acids:	goal	0.8 to 2 g/kg/d
• Dextrose:	maximum	5 to 6 mg/kg/min (7.2 to 8.6 g/kg/d)

Other parenteral nutrients (e.g., L-cysteine hydrochloride, carnitine) will be administered according to hospital practice and applicable guidelines (A.S.P.E.N. 2015).

Oral or Enteral Nutrition: Patients are included if 60% or more of their calorie needs are provided by PN (see below, Inclusion Criteria). If a patient can partially be nourished orally or enterally, the energy intake will be calculated and the dosage of PN will be reduced correspondingly.

Study Treatment: Patients will be randomized 1:1 to receive either Smoflipid (investigational group) or Intralipid 20% (control group).

The blinded study drugs will be administered simultaneously with the other prescribed PN components. The patients will receive the study drugs according to their individual prescription on 5 to 7 days per week. Parenteral nutrition can be administered overnight (as usual in home care patients) or continuously over 10-24 h/day (mainly in hospital setting). The maximum infusion rate for the study drug must not be exceeded.

During the course of the study, dosage reductions of the study drug can be necessary as consequence of laboratory analyses. Serum triglyceride (TG) levels should be kept < 250 mg/dL throughout treatment with a study drug. If higher levels develop, the dosage of the lipid emulsion will be reduced. Persisting higher levels can lead to the decision that a patient is removed from the study. Also, direct bilirubin levels in plasma will be used to decide about dosage reduction or cessation of the study drug infusions. The procedures will be as follows:

<u>Serum triglycerides for intravenous lipid dose management:</u>

A) Patients who start PN:

During dose titration, levels of TG will be monitored daily. Should TG exceed 250 mg/dL, the study drug will be held until analysis of another blood sample on the following morning. If TG are ≤ 250 mg/dL the study drug is restarted. If not this procedure has to be repeated on each subsequent morning. If after 3 days TGs still exceed 250 mg/dL, the patient will be removed from the study.

Once the target dose has been reached at level of serum TG ≤ 250 mg/dL, TG will be assessed monthly.

B) Patients who already receive PN:

Triglycerides levels will be monitored monthly. Should TG exceed 250 mg/dL, a confirmatory analysis must be performed after 7 days. If the confirmatory analysis reveals that TG still exceed 250 mg/L, the study drug dosage should be reduced, or the patient should be removed from the study, at discretion of the Investigator.

Direct bilirubin for intravenous lipid dose management:

Direct bilirubin levels will be assessed monthly. If at any point direct bilirubin exceeds 2.0 mg/dL (> 2.0 mg/dL), a confirmatory analysis must be performed after 7 days. If the confirmatory analysis reveals that direct bilirubin is still > 2.0 mg/dL, the lipid dose has to be decreased to 1 g/kg/day; dextrose dose should be increased accordingly to maintain adequate energy provision. Lipid dose will be maintained at 1 g/kg/d and not be increased again even if direct bilirubin levels decrease again to 2.0 mg/dL or lower.

If at any point direct bilirubin exceeds 4 mg/dL (> 4 mg/dL), the patient must be taken off study treatment. In this case, further PN treatment is at the discretion of the Investigator.

Duration of Treatment: Study treatment will last for a minimum of 90 consecutive days and as long as PN is indicated, up to 365 consecutive days. The study ends after the Final Study Visit, latest on Day 366 (see Section 1, Study Schedule). If the indication for PN continues after Study Day 365, PN will continue per normal institution policy. Study drugs will no longer be used.

Early termination of study treatment (Before Study Day 91)

The study treatment will stop if infusion of the study drug cannot be continued because TG or direct bilirubin levels remain above the defined limits (see above, Intravenous lipid dose management) after reduction of the dosage.

The study treatment will also be stopped if the Holman Index of a patient (biochemical marker for essential fatty acid deficiency (EFAD)) reaches or exceeds 0.4 or if any clinical symptoms of EFAD appear or when the patient's growth is inadequate (drop of 1 in z-score in a time period of 2 consecutive months).
The study treatment will also stop if enteral food tolerance increases and in consequence, less than 60% of the patient's

energy requirements are provided by PN for at least one month. If PN is still indicated after termination of the study treatment, it will continue per normal institution policy.

In case of early termination, patients will be replaced by randomizing additional patients unless the decision to terminate was made for safety reasons (including intravenous lipid dose management).

Late termination of study treatment (Study Days 91 to 365)

After Study Day 90 the study treatment will be terminated as soon as nutritional needs can be fully covered from enteral or oral nutrition or PN is continued without a lipid emulsion (i.e., PN, or at least the lipid emulsion, is no longer indicated).

After Study Day 90 the study treatment will also stop if infusion of the study drug cannot be continued because TG or direct bilirubin levels remain above the defined limits (see above, Intravenous lipid dose management) after reduction of the dosage. In case of termination between Day 90 and Day 365, patients will not be replaced.

The study treatment will also be stopped if the Holman Index of a patient (biochemical marker for essential fatty acid deficiency (EFAD)) reaches or exceeds 0.4 or if any clinical symptoms of EFAD appear or when the patient's growth is considered inadequate (drop of 1 in z-score in a time period of 2 consecutive months).

The study is terminated on Day 366 at the latest, after the Final Study Visit (see Section 1, Study Schedule). If the indication for PN continues after study Day 365, study drugs will not be continued. PN will be prescribed per normal institution policy.

Patients: Pediatric patients who are expected to require PN for at least 90 consecutive days, both in hospital or home care setting. For patients who remain on PN, treatment will be continued for up to 1 year. Patients will be randomized into one of three age group cohorts:

48 patients 3 months to < 2 years of age
48 patients 2 years to < 12 years of age
48 patients 12 to 16 years of age

Inclusion Criteria:

1. Male or female patients 3 months to 16 years of age.
2. Patients who require PN for at least 5 days/week.
3. Patients who receive 60% or more of their total energy requirements as PN at enrollment and who are expected to receive 60% or more of their total energy requirements as PN for at least 90 days.
4. Written informed consent from parent(s) or legal representative(s). If possible, patient assent must also be obtained (according to local law).

Exclusion Criteria:

1. Known hypersensitivity to fish, egg, soybean, or peanut proteins, or to any of the active ingredients or excipients of Smoflipid or Intralipid 20%.
2. Hyperlipidemia or disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentration > 250 mg/dL).
3. Inborn errors of amino acid metabolism.
4. Cardiopulmonary instability (including pulmonary edema, cardiac insufficiency, myocardial infarction, acidosis and hemodynamic instability requiring significant vasopressor support).
5. Hemophagocytic syndrome.
6. Liver enzymes (either AST, or ALT, or GGT) exceeding 5 x upper limit of normal range
7. Direct bilirubin ≥ 2.0 mg/dL
8. INR > 2.
9. Any known hepatic condition outside of IFALD that will increase direct bilirubin ≥ 2.0 mg/dL.
10. Clinically significant abnormal levels of any serum electrolyte (sodium, potassium, magnesium, calcium, chloride, phosphate).
11. Active bloodstream infection demonstrated by positive blood culture at screening.
12. Severe renal failure including patients on renal replacement therapy.
13. Abnormal blood pH, oxygen saturation, or carbon dioxide.
14. Pregnancy or lactation.
15. Participation in another clinical study.
16. Unlikely to survive longer than 90 days.

Target Variables:

<u>Efficacy:</u>

- Body weight (weight velocity as z-score change from baseline).
- Body length/height (growth velocity as z-score change from baseline).

- Head circumference (patients < 36 months of age [z-score change from baseline]).
- Fatty acid profiles including linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid and Mead acid, analyzed in total plasma and in red blood cell membranes.
- Triene/tetraene ratio (Holman Index) in total plasma to assess essential fatty acid deficiency (EFAD).

Safety:

- Incidence of PNALD/PNAC[1]: Number of patients in each treatment group with direct bilirubin levels > 2 mg/dL, confirmed by a second sample collected 7 days after the first sample (incidence of PNALD/PNAC[1]).
- Time from Study Day 1 until reaching direct bilirubin levels > 2 mg/dL, followed up by a second sample collected 7 days after the first sample (time until developing PNALD/PNAC).
- Sterols in plasma including phytosterols: β-sitosterol, campesterol, stigmasterol, brassicasterol, ergosterol, cholesterol, desmosterol, lanosterol, β-sitostanol, lathosterol, squalene (a sterol precursor).
- Laboratory values (blood, plasma, or serum): triglycerides, direct bilirubin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), creatinine, urea nitrogen, electrolytes (Na, K, Mg, Cl, Ca, Phosphate), trace elements (ferritin, Zn, Se, Cu, Mn, Cr), glucose, total protein, C-reactive protein (CRP), white blood cells (WBC), red blood cells (RBC), and platelet counts, hemoglobin (hgb), hematocrit (hct), international normalized ratio (INR).
- Vital signs: blood pressure, heart rate, body temperature.
- All adverse events (AEs).
- The relation between genetic polymorphisms in the fatty acid desaturase genes FADS1 and FADS2 and plasma concentrations of linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and Mead acid, as well as relation to EFAD (triene/tetraene ratio).

[1] In this study protocol, the terms PNAC and PNALD are used synonymously and are defined by direct bilirubin levels > 2 mg/dL.

Statistics:

Sample Size:
Defined as 144 patients (48 patients per age group cohort), having completed Study Day 90 to ensure that at least 23 subjects are randomized to each treatment group within each age group cohort.

Statistical evaluation:
All target variables will be analyzed in an exploratory manner presenting descriptive statistics. Binary, categorical and ordinal parameters will be summarized by means of absolute and percentage numbers. Numerical data will be summarized by means of standard statistics. Confidence intervals (CI) will be determined for all outcome parameters for which mean and standard deviation will be calculated. The detailed list will be included in the Statistical Analyses Plan (SAP).

Analysis sets:
Safety population: all patients having received at least one dose of a study drug and at least one post-baseline safety evaluation – used for analysis of safety variables.
Intention-to-treat (ITT) population: all randomized patients.
Per-protocol (PP) population: all randomized patients having received study drug at least until Study Day 90, with 5 to 7 infusions per week, and without any major protocol deviations.
ITT and PP populations will be used for analysis of efficacy variables.

Evaluations/Follow up:

All data will be collected according to the study schedule (see Section 1).
After obtaining a signed and dated informed consent form (ICF) and before administering the first dose of study drug, baseline assessments will be completed including:

- Review of inclusion and exclusion criteria. Eligibility of a patient can be assessed from existing laboratory data if the data are not older than one week.
- Collection of demographic data.
- Recording the patient's medical history, vital signs, physical examination, nutritional status (anthropometric: head circumference [< 3 years]) length [< 2 years], height, weight, BMI (body mass index) [> 2 years]), concomitant medications, duration and composition of current PN.
- After patient eligibility is confirmed, baseline blood samples will be withdrawn for analyses of safety and efficacy laboratory parameters.

Once the ICF is signed and dated, AEs will be documented throughout the study and followed after receiving the first dose of treatment until resolved.

Study Day 1 is the day on which the first administration of the study drug starts. Baseline assessments are performed, and the patient is randomized, earlier on the same day. Alternatively, baseline assessments and randomization can be performed on study Day -1, i.e., the day before Day 1. Home care patients will stay overnight in the hospital for the first study drug infusion and can leave on Day 2. Alternatively, home care patients that are stable on home parenteral nutrition (HPN) prior to study participation can also be trained and receive the first dose of study treatment at the hospital, returning to their home on the same day (Day 1).

Volumes of administered study drugs, brands and volumes of administered parenteral amino acids and dextrose and, if applicable, brands and volumes administered of enteral formulas, volumes of human milk or milk formulas, and as far as possible, type and amount of ingested oral food, will be documented for each Study Day.

Blood samples for safety and efficacy laboratory analysis, analyses of fatty acids and sterols will be taken monthly. Samples for trace elements will be taken every 3 months (see 1. Study Schedule). All blood samples will be taken at the hospital during the monthly visit. Other measurements and examinations will be performed monthly as well during the hospital visits. One blood sample is taken during the treatment phase for genetic analysis (FADS1, FADS2) (see 1. Study Schedule).

After cessation of the last infusion of study drug, a Final Study Visit will be performed (see 1. Study Schedule).

Coordinating Investigator:

[redacted]

Other Investigators/Sites: [redacted] sites are planned, all in the USA

Final Protocol Submission to FDA: [redacted]

1. Study Schedule

Daily procedures and assessments during treatment phase (starting on Day 1):
Study drug administration, study drug administered, other PN products administered, EN administered and oral food intake, adverse events, concomitant medication.

Table 1: Study Schedule of Assessments and Procedures

Assessments/ Procedures \ Study Days	Screening / Baseline Visit Prior to Start of PN with Study Drugs	Treatment Phase Study Drug Administration Day 1 to Day 365§				Final Study Visit / After End of Last Study PN
	Day 1 or Day -1 *	Day 1 Visit *	Weekly Call (± 1 day)	Monthly Visit (± 5 days)	Every 3 months, (during a monthly visit)	End + 1 Day **
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographics incl. race and ethnicity	X					
Pregnancy test, if applicable	X					
Randomization	X					
Medical history, demographic data	X					
Prior/concomitant medication	X			X		X
Body weight, length/height, head circumference	X			X		X
Physical examination incl. Tanner stage	X			X		X
Vital signs [a]	X			X		X
Blood sampling for standard laboratory [b]	X			X		X
Blood sampling for special laboratory [c]	X			X		X
Blood sampling for trace element analysis [d]	X				X	
Start of study drug infusion		X				
Prior / concomitant nutrition [e]	X		X			X
Adverse events [f]	X	X	X	X		X
Blood sampling for genetic analysis (FADS1, FADS2) [g]				(X)		

* Screening, baseline assessments and randomization are performed on Day 1, prior to the start infusion of study PN, or alternatively on Day -1, i.e., the day before Day 1. Study drug infusion starts on Day 1.

** One day after last day of study drug administration.

§ During the treatment phase, study drug will be administered 5 to 7 days per week. A break of 1 or 2 days per week is allowed and will not lead to prolongation of the treatment phase.

[a] Blood pressure, heart rate, body temperature.

[b] Triglycerides, direct bilirubin, total bilirubin, ALT, AST, GGT, ALP, creatinine, urea nitrogen, electrolytes (Na, K, Mg, Cl, Ca, Phosphate), glucose, total protein, CRP, WBC, RBC, and platelet counts, hgb, hct, INR.

[c] Fatty acid profiles (linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid and Mead acid, analyzed in total plasma, and in red blood cell membranes);

sterols in plasma including phytosterols (β-sitosterol, campesterol, stigmasterol, brassicasterol, ergosterol, cholesterol, desmosterol, lanosterol, β-sitostanol, lathosterol, squalene)

[d] Trace elements (Ferritin, Zn, Se, Cu, Mn, Cr).

[e] Prescribed daily dose, actual daily dose, infusion rates of PN products; type and quantity of enteral nutrition products and oral food.

[f] Recording of AEs starts after signature of informed consent.

[g] In all patients genetic polymorphism of two desaturase encoding genes (FADS1 and FADS2) will be determined. Only one blood sample is required which can be taken any time during the treatment period.

2. Contents

LIST OF TABLES

3. List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	Aspartate aminotransferase
BMI	Body mass index
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DEHP	di-2-ethylhexyl phthalate
DSMB	Data Safety Monitoring Board
CFR	Code of Federal Regulations
eCRF	Electronic case report form
EFAD	Essential Fatty Acid Deficiency
FADS1/2	Fatty Acid Desaturase (Genes) 1 and 2
FDA	Food and Drug Administration (United States)
FDCA	United States Federal Food, Drug, and Cosmetics Act
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
hgb	Hemoglobin
hct	Hematocrit
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFALD	Intestinal Failure-Associated Liver Disease
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IVLE	Intravenous Lipid Emulsion
MCT	Medium Chain Triglycerides
MedDRA	Medical Dictionary for Regulatory Affairs
PDF/A	Portable Document Format/A (Adobe Systems Inc.)
PN	Parenteral nutrition
PNAC	Parenteral Nutrition-Associated Cholestasis
PNALD	Parenteral Nutrition-Associated Liver Disease
PP	Per protocol
PREA	Pediatric Research Equity Act
Q	Quarter

RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TG	Triglycerides
US	United States
WBC	White blood cells

4. Introduction

4.1 Background

Parenteral nutrition (PN) is a life-saving procedure enabling adequate nutritional substrates to be provided to a patient whenever the nutritional needs cannot be met with oral or enteral nutrition. Total PN provides amino acids, dextrose, lipids, electrolytes, vitamins, trace elements, and water. Within PN regimens, intravenous lipid emulsions (IVLEs) have two main functions: 1) to supply calorie-dense energy and 2) to provide essential fatty acids (Hamilton et al 2006, Krohn and Koletzko 2006, Mascioli et al 1996, Waitzberg et al 2006). Intravenous lipid emulsions have now routinely been used in PN for more than 50 years, since Intralipid® was first registered in Sweden in 1962. In the USA, Intralipid 20% was approved in 1975.

Smoflipid® was first approved in Sweden in 2004 and is currently available in more than 65 countries worldwide. The US Food and Drug Administration (FDA) approved Smoflipid for use in adults in July 2016.

Smoflipid has been developed to optimize the fatty acid profile of the IVLE used in PN, providing a mixture of essential and non-essential fatty acids, including n-3, n-6, and n-9 fatty acids. Smoflipid is a fixed physical mixture of 4 different oils: soybean oil (30%), medium-chain triglycerides (MCT) (30%), olive oil (25%), and fish oil (15%). Compared to pure soybean oil emulsions, Smoflipid has a reduced amount of n-6 fatty acid linoleic acid which is partially replaced by n-9 and n-3 fatty acids. Smoflipid contains 200 mg/L α-tocopherol, which protects unsaturated fatty acids against lipid peroxidation. Furthermore, Smoflipid contains only approximately 30% of amount of phytosterols contained in Intralipid 20%.

The 2014 clinical guidelines of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) on support of pediatric patients with intestinal failure at risk of PNALD (Wales et al 2014) states that no recommendation can be made for use of a fat emulsion with soy oil, medium-chain triglycerides, olive oil, and fish oil (Smoflipid) until it is approved for use in the United States. In 2016, (A.S.P.E.N.) and the Society of Critical Care Medicine (SCCM) issued updated guidelines for nutrition support in critically ill adult patients, which have stated that alternative (oil-based) IVLEs may provide an outcome benefit over soy-based IVLEs, and should be considered in critically ill patients who require PN (McClave et al 2016).

Prolonged use of PN in the setting of long-term intestinal failure has been associated with hepatic complications reflected by elevated bilirubin levels after approximately 2 to 3 weeks of PN (Christensen et al 2007). In this context, elevated bilirubin levels are considered to be a marker for evolving PN-associated cholestasis (PNAC) which can lead to PN-associated liver disease (PNALD)[2] (Colomb et al 2000, Javid et al 2011, Koseesirikul et al 2012, Pichler et al

[2] In this study protocol, the terms PNAC and PNALD are used synonymously and are defined by direct bilirubin levels > 2 mg/dL.

2012). Parenteral nutrition-associated liver disease is considered to be multifactorial, and various aspects of PN may promote cholestasis (Wales et al 2014). In recent years, investigators focused on the role of the soybean oil-based IVLEs in the development of PNALD due to their high content of the ω6 fatty acid linoleic acid (C18:2ω6, 52% to 54% in Intralipid) and plant sterols (phytosterols) and their low content of α-tocopherol (Burrin et al 2014, Clayton et al 1998, Ng et al 2015, Wales et al 2014).

Three company-sponsored studies comparing Smoflipid to Intralipid 20% in the pediatric population were completed in 2005 and 2006. The studies included preterm neonates, infants, and children up to 11 years of age (Goulet et al 2010, Rayyan et al 2012, Tomsits et al 2010). The data from these studies showed that the use of Smoflipid was safe and effective. A beneficial effect on liver parameters was found, although liver function was not the primary endpoint in these studies. In two studies, significantly greater decreases from baseline values were seen in total and direct bilirubin in the Smoflipid versus Intralipid 20% group (Goulet et al 2010, Rayyan et al 2012). In the third study, lower gamma-glutamyl transferase levels were noted in the Smoflipid group versus the Intralipid 20% group (Tomsits et al 2010). In these studies, PN was administrated for up to 2 weeks or for up to 4 weeks.

Another company-sponsored study in the pediatric population was started in December 2015 in the USA and is currently ongoing. This prospective, randomized, controlled, double-blind, parallel-group trial compares safety and efficacy of Smoflipid to Intralipid 20% in hospitalized neonates and infants requiring at least 28 days of PN. The targeted maximal lipid dose is 3.0 g/kg/day. The primary objective of the study is to show the superiority in safety of Smoflipid over Intralipid 20% as measured by the number of patients in each treatment group who develop conjugated bilirubin > 2 mg/dL during the first 28 days of study treatment. This ongoing US Smoflipid study, and the study outlined in this clinical study protocol, will provide a substantial database for the short-term and long-term pediatric use of Smoflipid in the USA.

4.2 Rationale and Purpose of the Study

Smoflipid was approved by the FDA for use in adult patients in July 2016. As required by section 505B(a) of the US Federal Food, Drug, and Cosmetic Act (FDCA), the safety and effectiveness of the new product for the claimed indications in pediatric patients must be assessed. For this reason, Fresenius Kabi will conduct this postmarketing study in pediatric patients 3 months to 16 years of age.

The present protocol describes a prospective, randomized, double-blind, parallel-group, active-controlled, multicenter study to evaluate the safety and efficacy of Smoflipid administered for at least 90 days, and continued for all patients who remain on PN for up to 1 year, compared to standard of care soybean oil based lipid emulsion (Intralipid 20%) administered for the same duration. Per the request of the FDA, the study's efficacy assessments will include anthropometric measures and evaluation of the risk of developing essential fatty acid deficiency (EFAD). Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS 2 should be determined in at least a subset of patients. The study's safety assessments will include evaluation of the risk of developing PNALD/PNAC. Plasma

phytosterol levels will be included as well.

4.3 Benefit/Risk Assessment

Parenteral nutrition is a lifesaving treatment if oral or enteral intake is impossible or not sufficient for a prolonged time. In this study only patients with indication for long-term PN suffering from reversible or irreversible intestinal failure will be included, e.g., patients with short bowel syndrome, intestinal atresia, abdominal surgical procedures due to gastroschisis or omphalocele closure, necrotizing enterocolitis, gastrointestinal motility disorder, or mucosal enteropathy.

Patients will receive the study drugs as part of their PN support for at least 90 days either during their hospitalization or in the home care setting. It is standard clinical practice to incorporate lipid emulsions into the PN protocol to ensure an adequate supply of essential fatty acids and energy. It is not possible to supply these calories with dextrose alone, because the excess dextrose intake that would be required is associated with metabolic complications and liver damage (Koletzko et al 2005).

Both study drugs, Smoflipid and Intralipid 20%, are approved in more than 60 countries for both adult and pediatric populations. In the USA, the comparator drug Intralipid 20% has been approved since 1975 for adult and pediatric use. Smoflipid was approved by the FDA for use in adults in July 2016. The present pediatric study is requested by the FDA as a post-marketing requirement for Smoflipid.

According to the latest "Periodic Safety Update Report" for Smoflipid, approx. 1.0 million patients were treated with Smoflipid from February 2015 to January 2018. Approx. 2.2 million patients received Smoflipid since the first registration in February 2004.

According to the latest "Periodic Safety Update Report" for Intralipid 10%, 20%, 30%, approx. 4,159,000 patients have received Intralipid 20% from March 2014 to September 2018. Since July 1999 approx. 10 million patients have received Intralipid 20%.

During these reporting intervals of both drugs, no actions have been taken or have been proposed for safety reasons. Based on the available safety data for Intralipid 20% and Smoflipid no change of the risk-benefit ratio of both products was identified. For both drugs the risk benefit balance was stated to remain positive.

According to the Smoflipid Prescribing Information (Appendix 1), the adverse reactions in > 1% of 229 patients treated in clinical studies with Smoflipid were nausea (9%), vomiting (7%), hyperglycemia (5%), flatulence, pyrexia, abdominal pain (4% each), increased blood triglycerides, hypertension (3% each), sepsis, dyspepsia, urinary tract infection, anemia, and device related infection (2% each). Furthermore, the components of Smoflipid may cause hypersensitivity reactions. Parenterally administered lipid emulsions are an independent risk factor for the development of catheter-related bloodstream infections.

According to the Prescribing Information of the standard-of-care emulsion Intralipid 20%

(Appendix 2), the most frequent adverse reactions are inseparable from the PN procedure with or without Intralipid 20%; these are adverse reactions due either to contamination of the I.V. catheter or to vein irritation by concurrently infused hypertonic solutions. Immediate or early adverse reactions more directly related to Intralipid 20% reported to occur in an incidence of < 1% in clinical trials are dyspnea, cyanosis, allergic reaction, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, and others. Among delayed adverse reactions are hepatomegaly, jaundice due to central lobular cholestasis, splenomegaly, thrombocytopenia, leukopenia, and transient increases in liver function tests.

In general, it can be concluded that study patients treated with either Smoflipid or Intralipid 20% are not exposed to higher risk than patients who are not included in the study and would receive PN according to institutional policy. In fact, study patients might even benefit from participating in the study as they will be more intensively monitored than under standard medical care.

5. Objectives

The objective of the study is to evaluate the safety and efficacy of Smoflipid compared to standard of care lipid emulsion Intralipid 20% administered via a central vein in pediatric patients 3 months to 16 years of age who require PN to meet their nutritional needs for at least 90 days and up to 1 year.

5.1 Study Hypothesis

The study hypothesis is that Smoflipid is safe and effective in pediatric patients when administered for 90 days or up to 1 year.

5.2 Target Variables

Efficacy variables:

- Body weight (weight velocity as z-score change from baseline).
- Body length/height (growth velocity as z-score change from baseline).
- Head circumference for patients who are < 36 months of age (z-score change from baseline).
- Fatty acid profiles including linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and Mead acid in total plasma (according to Mayo Medical Laboratories standards) and in red blood cell membranes.
- Triene/tetraene ratio (Holman Index) in plasma to assess essential fatty acid deficiency (EFAD). Severity of EFAD will be graded based on triene/tetraene ratio, as suspected ≥ 0.05, moderate ≥ 0.20 and severe ≥ 0.40 (Cober et al 2012).

Safety variables:

- Incidence of PNALD/PNAC[3]: Number of patients in each treatment group with direct bilirubin levels > 2 mg/dL, confirmed by a second sample collected 7 days after the first sample (incidence of PNALD/PNAC). Time from Study Day 1 until reaching direct bilirubin levels > 2 mg/dL, followed up by a second sample collected 7 days after the first sample (time of developing PNALD/PNAC). (i.e., presented as the Study Day on which for the first time the direct bilirubin level was found > 2 mg/dL.)
- Sterols in plasma including phytosterols: β-sitosterol, campesterol, stigmasterol, brassicasterol, ergosterol, cholesterol, desmosterol, lanosterol, β-sitostanol, lathosterol, squalene (a sterol precursor).
- Laboratory values: (blood, plasma, or serum): triglycerides, direct bilirubin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), creatinine, urea nitrogen, electrolytes (Na, K, Mg, Cl, Ca, Phosphate), trace elements (ferritin, Zn, Se, Cu, Mn, Cr), glucose, total protein, C-reactive protein (CRP), white blood cells (WBC), red blood cells (RBC), and platelet counts, hemoglobin (hgb), hematocrit (hct), international normalized ratio (INR).
- Vital signs: blood pressure, heart rate, body temperature.
- All adverse events (AEs).
- The relation between genetic polymorphisms in the fatty acid desaturase genes FADS1 and FADS2 and plasma concentrations of linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and Mead acid, as well as relation to EFAD (triene/tetraene ratio).

6. Study Design

6.1 Description of the Study Design

This is a prospective, randomized, double-blind, parallel-group, active-controlled, phase 4 multicenter study to assess safety and efficacy of Smoflipid compared to Intralipid 20% in pediatric patients requiring long-term PN.

Treatment group 1: Smoflipid (investigational drug)
Treatment group 2: Intralipid 20% (control drug)

The study drugs, Smoflipid and Intralipid 20%, are lipid emulsions for infusion and will be provided in bags containing100 mL, 250 mL, or 500 mL. Detailed information on packaging,

[3] In this study protocol, the terms PNAC and PNALD are used synonymously and are defined by direct bilirubin levels > 2 mg/dL.

labelling, and dose of study drug is provided in Section 10.

The study population will be pediatric patients of 3 months to 16 years of age with indication for PN that is expected to continue for 90 days at minimum, as consequence of reversible or irreversible intestinal failure. This condition can be present in patients with, e.g., short bowel syndrome, intestinal atresia, abdominal surgical procedures due to gastroschisis or omphalocele closure, necrotizing enterocolitis, gastrointestinal motility disorder, or mucosal enteropathy. Study patients will be hospitalized or treated in the home care setting, and the study will also continue during transmission from hospital to home PN or during re-hospitalization. During the first 90 days, study treatment will last as long as PN is required to cover 60% or more of the patient's total energy requirement. Unless terminated in the first 90 days, study treatment will last as long as any PN including intravenous lipids is required, but at maximum for 1 year in total.

If a patient is found to be potentially eligible for participation in the study, a signed and dated informed consent form (ICF) will be obtained from the patient's parent(s) or legal representative(s) prior to the performance of any study-specific procedures or assessments. If possible, patient assent must also be obtained.

Randomization into the 3 age group cohorts will be distributed evenly so as to have 48 subjects in each age group with at least 23 subjects in each treatment group per cohort (see Section 6.3):

Randomization group 1: 48 patients 3 months to < 2 years of age
Randomization group 2: 48 patients 2 years to < 12 years of age
Randomization group 3: 48 patients 12 to 16 years of age

Before initiation of study treatment, demographics, including medical history, race and ethnicity, starting date and composition of current PN, current medications, physical examination findings, vital signs, body weight and length/height, BMI (> 2 years) and head circumference (< 3 years) will be documented, and blood samples will be obtained for the assessment of baseline laboratory values.

During the treatment phase, concomitant medications and all safety and efficacy parameters will be recorded according to the study schedule (see Section 11). All I.V. energy sources (study drugs, other PN components, propofol, dextrose from drug carrier solutions), enteral formulas, and oral intake will be documented daily to assure that total energy content from all sources does not exceed the prescribed caloric target. Changes in dosage of the study drugs or other PN components, and the reason for these changes will be recorded.

Study treatment will last for a minimum of 90 consecutive days and, as long as PN including lipids is indicated, up to 365 consecutive days. The study will be terminated if infusion of the study drug cannot be continued because of increased TG or direct bilirubin levels (see 10.3.4 Intravenous lipid dose management).

Up to Study Day 90 the study treatment will be terminated (i.e., early termination of study treatment) if less than 60% of the patient's energy requirements are provided by PN for at least

one month. If PN is still indicated after termination of the study treatment, it will continue per normal institution policy. Study drugs will no longer be used.

Between study Day 91 and Study Day 365, the study treatment will be terminated (i.e., late termination of study treatment) as soon as nutritional needs can be fully covered from enteral or oral nutrition, or is continued without a lipid emulsion (i.e., PN, or at least the lipid emulsion, is no longer indicated).

Whenever a patient has received his/her last dose of study drug, a Final Study Visit will be performed the following day to perform the end-of-study procedures. If after the last dose of study medication PN is still indicated, it will continue per normal institution policy.

To ensure safety of the patients during their study participation, medical monitoring will be performed on all safety relevant information collected during the trial. A medical safety officer will be available for safety related questions throughout the study.

6.2 Rationale of Study Design, Including Choice of Control Group

The FDA requested that Fresenius Kabi perform a postmarketing study in pediatric patients 3 months to 16 years of age to evaluate the safety and efficacy of Smoflipid administered for at least 90 days, and continued for all patients who remain on PN for up to 1 year, compared to standard of care soybean oil based lipid emulsion (Intralipid 20%) administered for the same duration. Per the request of the FDA, the study's efficacy assessments will include anthropometric measures and evaluation of the risk of developing essential fatty acid deficiency (EFAD). Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS 2 should be determined in a subset of patients. The study's safety assessments will include evaluation of the risk of developing PNALD and PNAC. Plasma phytosterol levels will be included as well.

The current multicenter study to evaluate safety and efficacy of Smoflipid for nutrition in pediatric patients 3 months to 16 years of age was designed to meet Pediatric Research Equity Act (PREA) requirements, i.e. to provide:

- Evidence-based information on the correct dosing for these pediatric age groups,
- Evidence-based information on nutritional efficacy and
- Evidence-based information on pediatric safety issues as indicated by possible adverse events

Smoflipid and the comparator, Intralipid 20%, will be dosed according to each patient's caloric needs and clinical condition. The maximum lipid dosage for the age groups (see Section 10.3) is according to the US Prescribing Information for Intralipid 20%, i.e., for pedatric patients up to 3 g/kg/d, and up to 2.5 g/kg/d for adolescents according to maximum dosage for adults. The dose infused will be assessed for safety and efficacy in pediatric patients. The same maximum dosage for lipids in infants and children, i.e., 3 g/kg/day, applies for Smoflipid in countries

where the pediatric use is approved.

The specific outcome measures selected to evaluate nutritional efficacy in the current Smoflipid protocol are:

- Body weight and length/height and head circumference (patients < 36 months of age)
- Fatty acid profiles including linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid and Mead acid, analyzed in total plasma and in red blood cell membranes
- Triene/tetraene ratio (Holman Index) in total plasma to assess essential fatty acid deficiency (EFAD)

PREA requirements are designed to obtain evidence-based safety information on pediatric patients to help the prescribing physicians understand what adverse events can be anticipated. In the current study protocol, specific safety outcomes as listed below were selected to capture changes in standardized safety assessment, and safety assessment particularly referring to safety aspects of different parenteral lipid components:

- Number of patients in each treatment group with direct bilirubin levels > 2 mg/dL, (incidence of PNALD/PNAC)
- Time until reaching direct bilirubin levels > 2 mg/dL (time until developing PNALD/PNAC)
- Sterols in plasma including phytosterols
- Laboratory values
- Vital signs
- Adverse events
- The relation between genetic polymorphisms in the fatty acid desaturase genes FADS1 and FADS2 and plasma concentrations of linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and Mead acid, as well as relation to and EFAD (triene/tetraene ratio).

As Smoflipid and its components have been used widely and given world-wide with a very rare incidence of adverse drug reactions (ADRs)/serious adverse events (SAEs), no confirmatory hypotheses will be tested. All target variables will be analyzed in an exploratory manner presenting descriptive statistics. The trial will not be powered. To power this trial, selection of one single parameter would be required as a primary safety endpoint to show a clinically meaningful difference between the treatment groups (the treatment effect) in a reasonable sample size and trial duration. As mentioned above, both Smoflipid and Intralipid 20% provide parenteral lipids. Selecting a single parameter to power the study as a superiority study or as a non-inferiority study with a reasonable non-inferiority margin would be difficult because the similar treatment concept would require more patients than could be obtained under any reasonable circumstances due to very low incidence of adverse drug reactions.

6.3 Randomization, Allocation of Patients

Eligible subjects will be randomized into 3 cohorts based on their age:

Randomization Cohort 1: 48 patients 3 months to < 2 years of age
Randomization Cohort 2: 48 patients 2 years to < 12 years of age
Randomization Cohort 3: 48 patients 12 to 16 years of age

Within each cohort, subjects will be randomized at baseline in a 1:1 ratio to receive either Smoflipid or Intralipid 20%. Randomization will be implemented by the unblinded site pharmacist using [redacted] interactive web response system. Appropriate randomization codes will be provided on the screen immediately after randomization for a subject is requested. The assigned treatment code will be stored in [redacted].

[redacted] is a web based platform that integrates the most important functions of this clinical study, including patient enrollment, randomization and unblinding procedure, study drug management and accountability, eCRF and safety reporting. All individual functions of the platform are validated and CFR 21 Part 11 compliant.

Patients will be identified using a sequential numbering system. During the course of screening, the subject will be given a seven-digit number having an underscore following the first four digits. The first four digits of this number will be the site number. The last three digits will refer to the individual subject according to his/her sequence of entry into the study. For example, the first subject screened at site 0402 will be number 0402-001.

The unblinded site pharmacist will pick the study drug (either Smoflipid or Intralipid 20% in adequate bag size) as indicated by [redacted] for each randomized subject. The correctness of the picked study drug will be checked and confirmed by [redacted] based on the individual bag number, which the pharmacist will be required to type into the system. The unblinded site pharmacist will affix an additional label with the subject (randomization) number onto the bag of the study drug when dispensing.

6.4 Blinding and Decoding

As this is a double-blind study, the allocation to the treatment groups will not be known by the Investigator and staff, patients and their relatives, or members of the Fresenius Kabi Clinical Research Department until completion of the study.

A bag ID list will be prepared and provided to Fresenius Kabi manufacturing operations for the production of uniquely numbered bag labels. Bag ID numbers from 000 001 to 100 000 will be randomly assigned to Smoflipid or Intralipid 20% to ensure that numbers are not indicative of study treatment.

Smoflipid and Intralipid 20% will be delivered to the hospital pharmacists in 100 mL, 250 mL, and 500 mL infusion bags, together with the appropriate documentation (e.g., Certificates of Analysis).

The bags will have a blinded label in accordance with the requirements of Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP), and each bag will be labeled with an individual bag number. Both study drugs are white emulsions which precludes unblinding by visual inspection.

The bags are packed in cartons, with 10 bags containing the same product and bag size in one carton. The cartons will have unblinded labels attached identifying the product. They are delivered to the hospital research pharmacy; the pharmacist will be the only unblinded study team member (The pharmacist can delegate the study procedures to his/her staff; they also would be unblinded).

For the individual patient, the pharmacist will receive the randomization information from the system (group allocation: Smoflipid or Intralipid 20%) as described in Section 6.3. Information about the individual daily dosage will be provided from the prescription, and the pharmacist will choose the appropriate bag size for the individual patient to ensure that the daily lipid dosage can be administered from 1 bag per day.

The pharmacist will dispense the appropriate study drug bags to the blinded site personnel. For patients in the home care setting, study drugs will be provided for a full month, i.e., until the next site visit of the patient. In this case, the pharmacist will also hand out a study medication log and the corresponding dispensing labels to the patient. The dispensing labels have to be applied to the study medication log immediately when a bag is prepared for infusion.

Emergency subject unblinding will be managed in [redacted]. In the event an Investigator needs to unblind a study subject, authorized study personnel at the site will log into the appropriate [redacted] unblinding workflow, to request access to the unblinded randomization code for the subject in question. In order to do so, the Investigator will have to acknowledge the serious nature of unblinding. Upon taking these steps, [redacted] will then provide the Investigator the specific treatment arm for that subject. Upon exiting the unblinding workflow, an email notification of this action will automatically be sent to appropriate management and safety officials acknowledging the subject unblinding without providing the specific treatment arm. Note that this information will also be captured in the study audit trail, so it will be more secure than other forms of unblinding.

7. Data Management and Statistics

7.1 Data Management

This study will be monitored regularly by a Clinical Research Associate (CRA) as described in the Monitoring Manual and Electronic Case Report Form (eCRF) Completion Guidelines. The CRA will check for completion of the entries on the eCRFs, their compliance with the study protocol and GCP, and will compare the eCRF entries with the source data. A 100% source data verification and ICF check will be performed. In case of any data discrepancies,

queries will be generated automatically by the system or manually by Data Management, the Medical Monitor, or the CRA. All eCRFs that have been completely monitored by the CRA will be signed electronically by the Investigator when all data queries have been resolved and Data Management has confirmed the eCRF is clean.

Data Management will process the data according to the Data Management Plan. The procedure of eCRF handling from the source up to submission to Data Management is described in Section 11.4.1.

7.2 Statistics

7.2.1 Sample Size Estimation

Sample size was defined as 144 patients (48 patients 3 months to < 2 years of age, 48 patients 2 years to < 12 years of age, and 48 patients 12 to 16 years of age), having completed Study Day 90. This is to ensure that at least 23 subjects are randomized to each treatment group within each age group.

Based on a presentation at the FDA's Pediatric Clinical Investigators Training in 2014, where it was noted that the minimum of 100 pediatric subjects is required to assess safety (Lewis 2014), the planned patient numbers (24 in each arm within each age group, or 144 total) are adequate to provide sufficient information on safety of pediatric dosing considering the low risk safety profile of Smoflipid in adults. The current study will enroll approximately 72 patients in the investigational group. Additional data for pediatric patients (neonates and infants) receiving Smoflipid will come from the clinical study started in December 2015 in the USA (see Section 4.1).

An exploratory study using descriptive statistical analysis of the target variables will be performed. There is no primary outcome parameter and the study is not powered. Reasons for this study design are explained in Section 6.2.

7.2.2 Analysis sets

Safety Set
The safety population will consist of all patients having received at least one dose of a study drug and at least one post-baseline safety evaluation. The safety population will be used for analysis of safety variables.

Intention-to-Treat Set
The intention-to-treat (ITT) population will consist of all randomized patients.

Per-Protocol Set
The per-protocol (PP) population will consist of all randomized patients having received study drug at least until Study Day 90, with 5 to 7 infusions per week, and without any major protocol deviations (see Section 15.2).

ITT and PP populations will be used for analysis of efficacy variables.

7.2.3 Statistical Analysis

The study outcome measures were selected in order to assess the safety and nutritional efficacy of the PN lipid emulsion. No primary and secondary measures are defined. Outcome measures will be evaluated as they are documented. Laboratory values will be transformed into SI (Système International d'Unités) if necessary.

A comprehensive Statistical Analysis Plan (SAP), covering details of all methods used to analyze the various parameters will be prepared. It will also include information on the handling of missing values. The SAP will be reviewed, and if needed, updated before data analysis. The SAP will be approved and signed off prior to unblinding the study.

All target variables will be analyzed in an exploratory manner presenting descriptive statistics. Binary, categorical and ordinal parameters will be summarized by means of absolute and percentage numbers (including 'missing data' as valid category). Numerical data will be summarized by means of standard statistics (e.g., number of available data, mean, standard deviation, minimum, median, maximum, and lower and upper quartile). Confidence intervals (CI) will be determined within treatment for all outcome parameters for which mean and standard deviation will be calculated.

Wherever useful, the summary statistics will be presented by Study Day. Results will be presented stratified by study drug and age group, and overall. In addition, appropriate figures (e.g., bar charts, Box-Whisker-Plots) may be presented to summarize the results for some parameters also in a graphical way.

7.3 Replacement of Patients

Patients withdrawn from study after randomization but before receiving any study drug will be counted as "early drop-outs". These patients will be replaced (i.e., by randomizing additional patients) and will not undergo procedures of the Final Study Visit.

Early termination of study treatment (Before Study Day 91)

Patients who received study drug at least once (i.e., first study infusion was at least started) but who didn't complete at least 90 days of study treatment, will be counted as "late-drop-outs".

The study treatment will stop if infusion of the study drug cannot be continued because TG or direct bilirubin levels remain above the defined limits (see 10.3.4 Intravenous Lipid Dose Management). The study treatment will also stop if less than 60% of the patient's energy requirements need to be covered from PN for at least one week.

In case of early termination patients will undergo final examination. They will be replaced unless the decision to terminate was made for safety reasons. Patients who were withdrawn

from study treatment due to a safety issue (including intravenous lipid dose management), will be counted as "withdrawals". These patients will not be replaced.

Late termination of study treatment (Study Days 91 to 365)

Between Study Day 91 and Study Day 365 the study treatment will be terminated as soon as nutritional needs can be fully covered from enteral or oral nutrition or is continued without a lipid emulsion (i.e., PN, or at least the lipid emulsion, is no longer indicated). After Study Day 90 the study treatment will also stop if infusion of the study drug cannot be continued because TG or direct bilirubin levels remain above the defined limits (see 10.3.4 Intravenous Lipid Dose Management).

In case of late termination, independent of the reason, patients will not be replaced.

8. Study Duration

End of the study is defined as completion of last visit of the last patient undergoing the study.

9. Patient Selection

9.1 Study Population

The current study will be performed in infants, children and adolescents, male or female, 3 months to 16 years of age. This study population was selected to fulfill Pediatric Research Equity Act (PREA) requirements (Section 505B(a) of the FDCA). It will evaluate the safety and efficacy of Smoflipid administered for at least 90 days in pediatric patients 3 months of age or older.

9.2 Inclusion Criteria

1. Male or female patients 3 months to 16 years of age.
2. Patients who require PN for at least 5 days/week.
3. Patients who receive 60% or more of their total energy requirements as PN at enrolment and who are expected to receive 60% or more of their total energy requirements as PN for at least 90 days.
4. Written Informed Consent from parent(s) or legal representative(s). If possible, patient assent must also be obtained (according to local law).

9.3 Exclusion Criteria

1. Known hypersensitivity to fish, egg, soybean, or peanut proteins, or to any of the active substances or excipients of Smoflipid or Intralipid 20%.

2. Hyperlipidemia or disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentration > 250 mg/dL).
3. Inborn errors of amino acid metabolism.
4. Cardiopulmonary instability (including pulmonary edema, cardiac insufficiency, myocardial infarction, acidosis and hemodynamic instability requiring significant vasopressor support).
5. Hemophagocytic syndrome.
6. Liver enzymes (either AST or ALT or GGT) exceeding 5 x upper limit of normal range
7. Direct bilirubin ≥ 2.0 mg/dL
8. INR > 2.
9. Any known hepatic condition outside of IFALD that will increase direct bilirubin levels ≥ 2.0 mg/dL .
10. Clinically significant abnormal levels of any serum electrolyte (sodium, potassium, magnesium, calcium, chloride, phosphate).
11. Active bloodstream infection demonstrated by positive blood culture at screening.
12. Severe renal failure including patients on renal replacement therapy.
13. Abnormal blood pH, oxygen saturation, or carbon dioxide.
14. Pregnancy or lactation.
15. Participation in another clinical study.
16. Unlikely to survive longer than 90 days.

9.4 Exclusion after Study Admission

Once a patient has received any amount of a study drug, the Investigator will make every reasonable effort to keep the patient in the study. However, the Investigator may withdraw a patient, in his/her clinical judgment, if it is either in the best interest of the patient or if the patient cannot comply with the study protocol. More specifically, the patient can be withdrawn from the study by any of the points as follows:

- Withdrawal of Informed Consent by the patient's parent(s) or legal representative(s) (or of patient assent if it was obtained according to local law).
- Severe or deliberate violation of the study protocol.
- Failure or success of therapeutic efficacy causing an unacceptable risk/benefit ratio.
- Discontinuation of study treatment for other reasons (e.g., up to Study Day 90, if less than 60% of the patient's energy requirements need to be covered from PN for at least one month, or after Study Day 90 if PN, or at least the lipid emulsion, is no longer indicated because of recovery of gastrointestinal function).

The patient's parent(s) or legal representative(s) may voluntarily withdraw the patient from participation in the study or prevent the administration of study medication at any time without needing to provide any reason.

If the Investigator has to withdraw a patient from the study, or if the patient´s parent(s) or legal representative(s) refuse(s) to have the patient continue with study participation, a complete final examination should be performed after cessation of the last dose of study drug. If consent

is withdrawn, the final examination can only be performed legally if there is permission from the patient's parent(s) or legal representative(s) to do it.

The reasons for withdrawal must be recorded in the eCRF.

Patients who are withdrawn from the study due to AEs/SAEs will be treated and followed according to established medical practice to evaluate the course of the AE and to ensure resolution or stabilization (see also Section 12). Any attempts of contacting a patient who is lost for follow up should be documented in the source notes.

Fresenius Kabi reserves the right to discontinue the entire study for internal reasons at any time (see 15.3 Premature Termination of the Study).

10. Study Drugs

10.1 Characterization of the Investigational Drug

Smoflipid is a sterile, nonpyrogenic, white, homogenous lipid emulsion for intravenous infusion. The lipid content of Smoflipid is 0.20 g/mL, and comprises a mixture of soybean oil, MCT, olive oil, and fish oil. Smoflipid belongs to the pharmacotherapeutic group: "Solutions for parenteral nutrition, fat emulsions" (ATC-code: B05BA02). Smoflipid is indicated as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

The mean essential fatty acid content of Smoflipid is 35 mg/mL (range of 28 to 50 mg/mL) linoleic acid (omega-6) and 4.5 mg/mL (range of 3 to 7 mg/mL) α-linolenic acid (omega-3). Further description of the fatty acids contained in Smoflipid is provided in the Prescribing Information of Smoflipid (Appendix 1).

Each 100 mL of Smoflipid contains approximately 6 g soybean oil, 6 g MCT, 5 g olive oil, 3 g fish oil, 1.2 g egg phospholipids, 2.5 g glycerin, 16.3 to 22.5 mg all-rac-α-tocopherol, 0.3 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9).

The phosphate content is 15 mmol/L.

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

Smoflipid has an osmolality of approximately 380 mOsm/kg water (which represents an osmolarity of 270 mOsm/L).

10.2 Characterization of the Control Drug

Intralipid 20% is a sterile, non‑pyrogenic fat emulsion intended as a source of calories and essential fatty acids. Intralipid belongs to the pharmacotherapeutic group: "Solutions for

parenteral nutrition, fat emulsions" (ATC-code: B05BA02). Intralipid 20% is indicated as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days) and as a source of essential fatty acids for prevention of essential fatty acid deficiency.

The major component fatty acids are linoleic acid (44-62%), oleic acid (19-30%), palmitic acid (7-14%), α-linolenic acid (4-11%) and stearic acid (1.4-5.5%). Further description of the fatty acids contained in Intralipid 20% is provided in the Prescribing Information of Intralipid 20% (Appendix 2).

Intralipid 20% is made up of 20% soybean oil (20 g/100 mL), 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection. In addition, sodium hydroxide is added to adjust the pH so that the final product pH is 8 (pH range is 6 to 8.9).

The phospholipids present contribute 47 milligrams or approximately 1.5 mmol of phosphorus per 100 mL of the emulsion.

The total caloric value, including fat, phospholipid and glycerin, is 2.0 kcal per mL of Intralipid 20%.

Intralipid 20% has an osmolality of approximately 350 mOsmol/kg water (which represents 260 mOsmol/L of emulsion).

10.3 Preparation, Administration, and Dosage of Study Drugs

10.3.1 Preparation of the Study Drugs

Smoflipid and Intralipid 20% will be delivered to the hospital pharmacists in 100 mL, 250 mL, and 500 mL infusion bags, together with the appropriate documentation (e.g., Certificates of Analysis). Each bag is wrapped in an overpouch that contains the infusion bag, an integrity indicator sachet (Oxalert®) and an oxygen absorber.

The study drugs will have a blinded label, and each bag will be labeled with an individual bag number. The bags are packed in cartons, with 10 bags containing the same product and bag size in one carton. The cartons will have unblinded labels identifying the product. They are delivered to the hospital research pharmacy; the pharmacist will be the only unblinded study team member.

For the individual patient, the pharmacist will receive the randomization information from the system: (group allocation: Smoflipid or Intralipid 20%), and information about the adequate bag size from the prescription. The pharmacist will dispense the appropriate study drug bags for the individual patient, as described in Section 6.4.

10.3.2 Administration Instructions

The bags have to be stored in overpouch until ready for use. After removing the overpouch, the

lipid emulsion should be infused immediately.

Prior to infusion, the study drug bags should be inspected visually to ensure that the emulsion has not separated. The emulsion should be a homogenous liquid with a milky appearance. Any bag in which there appears to be an oiling out on the surface of the emulsion must not be used. The bag has to be discarded as well if any signs of discoloration, particulates, or leakage are observed or if the integrity indicator (Oxalert®) is black.

The study drugs will be infused via a dedicated line for PN into a central vein using a central venous catheter or a peripherally inserted central catheter.

The study drugs can be infused concurrently into the same vein as dextrose-amino acid solutions (as part of PN) by a Y-connector located near the infusion site; flow rates of each solution should be controlled separately by infusion pumps.

A 1.2 micron in-line filter should be used. Filters of less than 1.2 micron pore size must not be used.

To prevent air embolism, a non-vented infusion set should be used or on a vented set, the vent should be closed. Multiple connections should be avoided and flexible bags should not be connected in series. Residual gas in the bag has to be fully evacuated prior to administration. Flexible bags are not to be pressurized to increase flow rates, and if administration is controlled by a pumping device, the pump has to be turned off before the bag runs dry.

Administration sets and lines that contain di-2-ethylhexyl phthalate (DEHP) must not be used. Administration sets that contain polyvinyl chloride (PVC) components have DEHP as a plasticizer.

The intravenous tubing used to infuse the study drugs must be changed every 24 hours to prevent catheter related blood stream infections.

Fresenius Kabi will provide detailed handling instructions for study drugs. The caregivers of home care patients (usually the child's parents) will be trained on the study drug administration and documentation during the Screening Visit (see 11.2.1).

The hospital pharmacist will provide the necessary tubing for infusion via Y-connector to home care patients together with the study drugs.

10.3.3 Dosage of the Study Drugs

The dosing of the study drugs depends on the patient's individual energy requirements, age, body weight, tolerance, clinical status, and the ability to eliminate and metabolize lipids. A titration phase is necessary in patients with a new indication for PN treatment.

When determining dose, energy supplied by dextrose and amino acids from PN, as well as energy from oral or enteral nutrition, has to be taken into account. Energy and lipid provided

from lipid-based medications should also be taken into account (e.g., propofol).

Prior to administration of the study drugs, or any PN product, severe fluid and electrolyte disorders should be corrected.

Study drugs will be started and advanced according to ASPEN pediatric nutrition support guidelines and center standards. Maximum lipid dosage is according to the US Prescribing Information for Intralipid 20%, i.e., for pediatric patients up to 3 g/kg/d, and up to 2.5 g/kg/d for adolescents according to maximum dosage for adults (Appendix 2). Age groups classified according to ICH (ICH 2000).

The study drugs are given concurrently with amino acids and dextrose containing PN products.

A) Patients who start PN

The initial rate of infusion should be no more than 0.05 mL/minute for the first 10 to 15 minutes. If no untoward reactions occur, the rate can be changed to permit infusion of 0.5 mL/kg/hour.

Infants 3 months to < 2 year of age:

start	0.5 to 1 g/kg/d lipid
advanced by	0.5 to 1 g/kg/d lipid
maximum	up to 3 g/kg/d lipid

Children 2 to < 12 years of age:

start	1 to 2 g/kg/d lipid
advanced by	0.5 to 1 g/kg/d lipid
maximum	up to 3 g/kg/d lipid

Adolescents 12 to 16 years of age:

start	1 g/kg/d lipid
advanced by	1 g/kg/d lipid
maximum	up to 2.5 g/kg/d lipid

B) Patients who already receive PN:

Infants 3 months to < 2 years of age:
up to 3 g/kg/d lipid

Children 2 to < 12 years of age:
up to 3 g/kg/d lipid

Adolescents 12 to 16 years of age:
up to 2.5 g/kg/d lipid

The individual dosage of study drug should be infused at a constant rate for 10 to 24 h/d. The

administration flow rate is determined by dividing the volume of study drug by the duration of the infusion. Maximum infusion rate for lipid should not exceed 0.125 g/kg/h lipid.

Study drug infusions should be given 5 to 7 days per week.

Serum triglycerides and direct bilirubin will be monitored to adjust or stop lipid administration if necessary (see 10.3.4 Intravenous Lipid Dose Management).

During the course of the study, dosage reductions of the study drugs can be necessary as consequence of laboratory analyses as follows.

10.3.4 Intravenous Lipid Dose Management

Serum TG levels should be kept < 250 mg/dL throughout treatment with a study drug. If higher levels develop, the dosage of the lipid emulsion will be reduced. Persisting higher levels can lead to the decision that a patient is removed from the study. Also direct bilirubin levels in plasma will be used to decide about dosage reduction or cessation of the study drug infusions. Furthermore, cessation of study drug infusion will be obligatory in case EFAD or inadequate growth is observed.

The procedures will be as follows:

Serum TG levels for intravenous lipid dose management:

A) Patients who start PN:

During dose titration, levels of TGs will be monitored daily. Should TGs exceed 250 mg/dL (> 250 mg/dL), the study drug will be held until analysis of another blood sample on the following morning. If TGs are ≤ 250 mg/dL the study drug is restarted. If not this procedure has to be repeated on each subsequent morning. If after 3 days TGs still exceed 250 mg/dL, the patient will be removed from the study.

Once the target dose has been reached at level of serum TG ≤ 250 mg/mL, TG levels will be assessed monthly.

B) Patients who already receive PN:

Triglycerides levels will be monitored monthly. Should TGs exceed 250 mg/dL (> 250 mg/dL), a confirmatory analysis must be performed after 7 days. If the confirmatory analysis reveals that TGs still exceed 250 mg/L (> 250 mg/dL), the study drug dosage should be reduced, or the patient should be removed from the study, at discretion of the Investigator.

Direct bilirubin for intravenous lipid dose management:

Direct bilirubin levels will be assessed monthly. If at any point direct bilirubin exceeds 2.0 mg/dL (> 2.0 mg/dL), a confirmatory analysis must be performed after 7 days. If the

confirmatory analysis reveals that direct bilirubin is still > 2.0 mg/dL the lipid dose has to be decreased to 1 g/kg/day immediately; dextrose dose should be increased accordingly to maintain adequate energy provision. Lipid dose will be maintained at 1 g/kg/d and not be increased again even if direct bilirubin levels decrease again to 2.0 mg/dL or lower).

If at any point direct bilirubin exceeds 4 mg/dL (> 4 mg/dL), the patient has to be taken off study treatment. In this case, further PN treatment is at the discretion of the Investigator.

For each Study Day, the prescribed dose, the dose actually infused, and the infusion time of study drug administration will be recorded in the eCRF.

Stopping study drug infusion due to EFAD:

At each of the monthly visits blood samples will be drawn for the analysis of fatty acids in plasma and red blood cells. Based on the results the triene-tetraene ratio (Holman Index) will be calculated to assess EFAD. Severity of EFAD will be categorized according to Cober et al 2012:

Suspected EFAD: Triene/tetraene ratio ≥ 0.05 and < 0.20
Moderate EFAD: Triene/tetraene ratio ≥ 0.20 and < 0.40
Severe EFAD: Triene/tetraene ratio ≥ 0.40

The site will be informed immediately as soon as severe EFAD is observed according to the Holman Index result and the patient must be permanently taken off study medication immediately. The investigators will also have to permanently discontinue study medication infusion in case clinical symptoms of EFAD are observed.

Stopping study drug infusion due to inadequate growth:

At each visit the patient's height, length or head circumference will be assessed and the z-score of the patient's growth will be obtained. If an absolute drop of 1 in the z-score is observed in a time period of 2 consecutive months, then the patient will have to be taken off study treatment.

In all cases where study medication infusion needs to be permanently discontinued, the further PN treatment is at the discretion of the Investigator.

10.4 Combination with Other Nutrition Components

10.4.1 Parenteral Nutrition

The study drugs will be given concomitantly with other PN components. For total PN, amino acids, dextrose, electrolytes and micronutrients will be administered according to center standards taking into account the ASPEN recommendations for PN in pediatric patients

(A.S.P.E.N. 2015). Age groups are classified according to ICH (ICH 2000). Energy needs will be estimated using equations for calculation (A.S.P.E.N. 2015).

For home care patients, the other PN components will be compounded in the home care pharmacy and delivered and stored according to the usual routine (e.g., delivered weekly by the home care provider as part of their normal standard of care, and kept in a fridge).

The following dosages for amino acids and dextrose are recommended in the age groups. Dosage of dextrose will be adjusted to reach the target parenteral calories taking into account the calories from prescribed lipids and amino acids.

A) Patients who start PN:

Infants 3 months to < 2 year of age:

Age 3 months to <1 year

• Amino Acids:	start	2.5 to 3 g/kg/d
	goal	2.5 to 3 g/kg/d
• Dextrose:	start	6 to 8 mg/kg/min (8.6 to 11.5 g/kg/d)
	advanced by	3.5 mg/kg/min) (5 g/kg/d)
	maximum	14 to 18 mg/kg/min (20.2 to 25.9 g/kg/d)

Age 1 year to < 2 years:

• Amino Acids:	start	1.5 to 2.5 g/kg/d
	goal	1.5 to 2.5 g/kg/d
• Dextrose:	start	3 to 6 mg/kg/min (4.3 to 8 .6 g/kg/d)
	advanced by	2 to 3 mg/kg/min (2.9 to 4.3 g/kg/d)
	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Children 2 to < 12 years of age:

• Amino Acids:	start	1.5 to 2.5 g/kg/d
	goal	1.5 to 2.5 g/kg/d
• Dextrose:	start	3 to 6 mg/kg/min (4.3 to 8.6 g/kg/d)
	advanced by	2 to 3 mg/kg/min (2.9 to 4.3 g/kg/d)
	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Adolescents 12 to 16 years of age:

• Amino Acids:	start	0.8 to 2 g/kg/d
	goal	0.8 to 2 g/kg/d
• Dextrose:	start	2.5 to 3 mg/kg/min (3.6 to 4 .3 g/kg/d)
	advanced by	1 to 2 mg/kg/min (1.4 to 2.9 g/kg/d)
	maximum	5 to 6 mg/kg/min (7.2 to 8.6 g/kg/d)

B) Patients who already receive PN:

Infants 3 months to < 2 year of age:

Age 3 months to < 1 year

• Amino Acids:	goal	2.5 to 3 g/kg/d
• Dextrose:	maximum	14 to 18 mg/kg/min (20.2 to 25.9 g/kg/d)

Age 1 to < 2 years:

• Amino Acids:	goal	1.5 to 2.5 g/kg/d
• Dextrose:	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Children 2 to < 12 years of age:

• Amino Acids:	goal	1.5 to 2.5 g/kg/d
• Dextrose:	maximum	8 to 10 mg/kg/min (11.5 to 14.4 g/kg/d)

Adolescents 12 to 16 years of age:

• Amino Acids:	goal	0.8 to 2 g/kg/d
• Dextrose:	maximum	5 to 6 mg/kg/min (7.2 to 8.6 g/kg/d)

Other parenteral nutrients (e.g., carnitine, L-cysteine hydrochloride) will be administered according to hospital practice and applicable guidelines (A.S.P.E.N. 2015).

The prescribed dosages, the dosages actually infused, and the infusion times of all PN products will be recorded in the eCRF.

10.4.2 Oral or Enteral Nutrition

Patients are included if 60% or more of their calorie needs are provided by PN, i.e., up to < 40% of energy can be covered from enteral formulas or oral intake. Oral food intake or enteral nutrition is not limited by the study procedures but will be decided by the Investigator

depending on the underlying disease and gastrointestinal tolerance.

If a patient can be partially nourished orally or enterally, the energy intake will be calculated and the dosage of PN will be reduced correspondingly.

If before Study Day 90 enteral nutrition or oral food intake covers 40% or more of the energy requirements during at least one month, the study will be terminated. Between Study Day 90 and Study Day 365 the study will be terminated as soon as nutritional needs can be fully covered from enteral or oral nutrition or PN is continued without a lipid emulsion (i.e., PN, or at least the lipid emulsion, is no longer indicated) (see 9.4 Exclusion after Study Admission).

10.5 Supply, Packaging, Labeling and Storage

10.5.1 Supply of Study Drugs

Fresenius Kabi will provide the Investigator's Pharmacy with a sufficient amount of study medication in the 3 bag sizes together with the respective Certificates of Analysis. A temperature recording device will document the temperature of the study medication during the transport to site.

The medication is the property of Fresenius Kabi and must not be passed on to third parties.

10.5.2 Packaging and Labeling

The blinded study drugs, Smoflipid and Intralipid 20%, will be provided in 3 bag sizes (100 mL, 250 mL, 500 mL) as ordered by the site pharmacies. The bags will be labeled in accordance with the requirements of GCP and GMP. Each bag wears a uniquely numbered label with a bag ID numbers from 000 001 to 100 000, randomly assigned to Smoflipid or Intralipid 20% to ensure that numbers are not indicative of study treatment.

The unblinded pharmacist will provide the study personnel with the appropriate blinded bags, as described in Section 6.4.

10.5.3 Storage Conditions

Throughout the study and until distribution, the study drugs will be stored in a securely locked area, only accessible to authorized personnel, at 20° to 25°C (68° to 77°F). Excessive heat has to be avoided and study drugs must not freeze. If accidentally frozen, bags have to be discarded.

Storage conditions (e.g., temperature) of the final blinded product should follow the instructions of the pharmacist. Independent from the pharmacy instructions, the final product is not allowed to be frozen or stored > 25°C. For the transportation of study drugs, home care patients will be provided with isothermic containers equipped with temperature data loggers. If required, appropriate cabinets for temperature control (20 to 25°C) will be provided to the patients' homes.

The bags have to be stored in overpouch until ready for use. After removing the overpouch, the lipid emulsion should be infused immediately.

10.6 Study Drug Accountability

Receipt of study drugs as well as return of any unused bag will be documented by the Investigator on a form provided by Fresenius Kabi. The study drugs are property of Fresenius Kabi and must not be passed to third parties.

Study drugs will be stored separately and safely and will be used exclusively for this study as described in this protocol. Any use of a study drug is documented on each patient's eCRF. For each bag the bag size, batch number, prescribed volume, and infused volume will be specified.

At the end of the study, the Investigator will explain any discrepancies between delivery, use, and return of the study drugs (drug accountability).

10.7 Return and Destruction of Study Drugs and Materials

Unused study drugs and unused study documentation forms will be returned to Fresenius Kabi for destruction at the end of the study or earlier. Alternatively, after written notice from Fresenius Kabi, unused forms and study drugs may be destroyed at the investigational site. Destruction will be documented.

In home care patients, the use of study drugs is documented on the medication log where the dispensing label for each used bag has to be attached (see 6.4 Blinding and Decoding). The study medication logs and unused products have to be returned to the clinical site at the next study visit. Any used bag can be discarded by the home care provider; they will provide a respective certificate of destruction.

10.8 Concomitant Medication and Nutrition

From the time of inclusion and throughout the trial period, the use of concomitant medications will be allowed as clinically needed with the exception of:

- Beta-carotene, lutein, lycopene, vitamin A, vitamin C and vitamin E as sole parenteral additives or food supplements
- Any IV lipid emulsion other than the study medication or propofol
- Enteral administration of fish oil (except as component of milk formulas)

The use of concomitant medication must be documented in the eCRFs (type, start date, end date, dosage, frequency, route, indication for use). Prior and concomitant volume replacement with blood, plasma, or colloid transfusions will be recorded.

Concomitant nutrition, including micronutrient and electrolyte additions to PN, enteral formulas, human milk or milk formulas, food and food supplements, and total energy intake (including energy intake from non-nutritional sources, e.g., propofol), will be documented in

the eCRFs during the entire treatment period.

11.Study Schedule

11.1 Summary of Procedures

A complete overview of all study procedures to be performed at the individual study visits is presented in Section 1. All procedures must be documented in the eCRF.

11.2 Detailed Description of Investigations

11.2.1 Screening Visit (Day -1 or Day 1)

The Screening Visit has to take place on Study Day 1, or alternatively on Study Day -1, i.e., the day before Day 1. The Screening Visit is performed at the Investigator's clinical site.

The procedures of the Screening Visit have to be executed in the following sequence:

A. Informed consent process

A signed/dated informed consent form must be obtained from the patient's parent(s) or legal representative(s) prior to the performance of any study related procedures or evaluations. If possible, patient assent must also be obtained (according to local law).

The parent(s) or legal representative(s) of the child or adolescent will be informed of the nature of the study by the Investigator or a designated Sub-Investigator of the study team as documented on the study responsibility log. The parent(s) or legal representative(s) will also receive a copy of the "parent information sheet".

The Investigator will inform the parent(s) or legal representative(s) of the patient on following aspects of the study:

- Voluntary participation
- Description of the clinical investigation
- Risks
- Benefits
- Alternative procedures or treatments
- Confidentiality
- Medical treatment in event of injury
- Contact person for any questions or study-related issues

In addition, the parent(s) or legal representative(s) of the child or adolescent will be given the opportunity to discuss the study, ask questions about the study, and have those questions answered by the Investigator. The parent(s) or legal representative(s) of the patient will be

allowed sufficient time to consider this information.

Two copies of the ICF will need to be signed and dated by the parent(s) or legal representative(s) and the Investigator; one copy will be provided to the parent(s) or legal representative(s) of the patient. The other copy will be kept in the patient's medical file. The patient's medical file must also document that the parent(s) or legal representative(s) provided consent prior to participation in the study.

B. Assignment of subject number and completion of the screening log

C. Review of inclusion and exclusion criteria

Patients will be assessed for eligibility (see 9.2 Inclusion Criteria, and 9.3 Exclusion Criteria). The patient can only be considered as eligible if all inclusion criteria are met and none of the exclusion criteria apply. Otherwise the patient will be considered a screening failure and will not be randomized.

Existing laboratory analyses will be accepted for assessment of eligibility if they are not older than one week. A pregnancy test will be performed in female patients who have had their menses.

If a patient is erroneously randomized into the study without meeting all of the enrolment criteria, the patient will be withdrawn from the study and replaced.

D. Randomization

If the patient meets all enrolment criteria, randomization according to age group cohort will be performed as described in Section 6.3.

E. Baseline documentation

These procedures will be performed or assessed during Screening Visit prior to the first dose of study medication:

- Recording of demographic data:
  - date of birth
  - age
  - sex
  - race
  - ethnicity

- Recording of physical examination findings and body measurements
  - physical inspection
  - body weight
  - body length (patients < 2 years of age) or body height

- head circumference (patients < 36 months of age)
- BMI (patients > 2 years of age)
- Tanner stage

- Recording of vital signs
  - blood pressure
  - heart rate
  - body temperature

- Recording of the patient medical history
- Results of a pregnancy test (only in female patients who have had their menses)
- Recording of prior medication and prior nutrition support (i.e., medication and nutrition support at obtaining the signed/dated ICF)
- After the ICF is signed and dated: recording of AEs/SAEs, if applicable

F. Blood sampling

Blood is sampled for laboratory analysis of the following parameters:

- From blood, plasma, or serum:
  - triglycerides
  - urea nitrogen
  - ALT
  - AST
  - direct bilirubin, total bilirubin
  - GGT
  - ALP
  - creatinine
  - electrolytes: sodium, potassium, calcium, magnesium, chloride, phosphate
  - trace elements: ferritin, zinc, selenium, copper, manganese, chromium
  - glucose
  - total protein
  - CRP
  - hematology: WBC count, RBC count, platelets count, hgb, hct
  - coagulation: INR
  - sterols: β-sitosterol, campesterol, stigmasterol, brassicasterol, ergosterol, cholesterol, desmosterol, lanosterol, ß-sitostanol, lathosterol, squalene.
  - fatty acids: alpha linolenic acid, linoleic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and Mead acid, in total plasma, and in red cell membranes.

11.2.2 Baseline Visit (Day 1)

Study Day 1 is per definition the day on which the first study drug infusion starts. All other Visits and Study Days are relative to the Baseline Visit. The Baseline Visit is performed at the

Investigator's clinical site.

The first study drug infusion will be started during Baseline Visit. In new home care patients it will usually be in the evening of Day 1 as these patients will stay overnight in the hospital for the first study drug infusion and leave on Day 2. Patients that have been stable on HPN prior to study participation can receive the first dose during Day 1 and leave the hospital on the same day.

Patients will be trained on handling and administration of study drug and on documentation of daily nutrition intake of all sources.

The procedures of the Baseline Visit have to be executed in the following sequence:

A. Completion of baseline documentation

Before start of the first administration of the study drug on Day 1, all baseline documentation has to be completed (see 11.2.1 Screening Visit). Furthermore, the Investigator has to confirm that all eligibility criteria are still fulfilled.

B. Administration of Study Drug as Part of PN

If none of the exclusion criteria, and all inclusion criteria, related to the baseline documentation are met, the Investigator can proceed with the procedures of administration of the study drug.

Start of infusion of the study drug in the prescribed individual dosage with dosage titration in patients who did not receive PN before (see Section 10.3). In these patients who start PN, the initial rate of infusion of the study drug should be no more than 0.01 g fat/minute (0.05 mL/min of the study drug) for the first 10 to 15 minutes.

The study drug will be infused concomitantly with the other PN components as prescribed.

Warnings and precautions included in the Prescribing Information of both Smoflipid (Appendix 1) and Intralipid 20% (Appendix 2) will be considered before and during each administration of a Study Drug.

C. Recording

- Recording of medication, nutrition, and adverse reactions
  - concomitant medication
  - parenteral nutrition
  - oral or enteral nutrition
  - adverse events (AEs)

11.2.3 Treatment Phase

During treatment phase, the patients will receive the study drug 5 to 7 times per week as part

of their PN regimen.

The frequency of Treatment Phase weekly calls is 7 ± 1 days up to Day 365. In addition, monthly visits will take place at the Investigator's clinical site. The monthly site visits will be performed in a time window of 30 ± 5 days.

During Treatment Phase Visits, the following procedures will be executed:

A. Recording of therapies and adverse events

During each weekly call and each monthly visit, the following will be recorded for each study day in the interval between the last and the current visit:

- Recording of therapies and adverse reactions
  - concomitant medication
  - new AEs and outcome of formerly recorded AEs (see Section 12)
  - in home care patients: hospital readmission (date, reason)
  - in hospitalized patients: transition to home care (date)

- Recording of nutrition per study day
  - study drugs: dose prescribed, dose administered, timing
  - other PN products: dose prescribed, dose administered, timing
  - oral or enteral nutrition: products, dose prescribed, dose administered amounts and energy content; if possible, type of food and beverages,
  -

B. Measurements and examination

The following parameters will be measured and examinations performed monthly:

- body weight, body length/height, head circumference (patients < 36 months of age)
- physical examination including Tanner stage
- vital signs: blood pressure, heart rate, body temperature

C. Blood sampling

- Blood is sampled monthly for the following laboratory analyses (in blood, plasma or serum)
  - triglycerides
  - urea nitrogen
  - ALT
  - AST
  - direct bilirubin, total bilirubin
  - GGT
  - ALP
  - creatinine

- electrolytes: sodium, potassium, calcium, magnesium, chloride, phosphate
- glucose
- total protein
- hematology: WBC count, RBC count, platelets count, hgb, hct
- coagulation: INR

- fatty acids: alpha linolenic acid, linoleic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and Mead acid, in total plasma, and in red cell membranes.

- sterols: β-sitosterol, campesterol, stigmasterol, brassicasterol, ergosterol, cholesterol, desmosterol, lanosterol, ß-sitostanol, lathosterol, squalene.

In case of a suspected blood stream infection CRP will be assessed in addition.

- Blood is sampled <u>every 3 months for the assessment of</u>
  - trace elements: ferritin, zinc, selenium, copper, manganese, chromium

- Blood is sampled <u>once during the treatment phase</u> for the following laboratory analyses:
  - In all patients genetic polymorphism of two desaturase encoding genes (FADS1 and FADS2) will be determined. The Investigator will decide the time point at which the blood sample is withdrawn.

According to the specific situation of a patient, blood samples can be drawn during the infusion of the study drug and/or other PN products (hospitalized patients with PN over 24 h/day) or between two infusions (mainly home care patients). The sampling time and the time of the last or current study drug infusion will be documented.

D. Revision of dose of Study Drug and other PN components

Dosage of the study medication and the other PN products will be checked and, if necessary adapted to changes in the clinical or metabolic condition of the patient (e.g., possible higher infusion volume as consequence of weight gain, or possible dosage reduction due to proceeding gastrointestinal adaptation).

Any changes in the prescription of the study drug or other PN products, and their reasons, will be recorded. If no changes are made, the continuation of the current dosage has to be confirmed.

Warnings and precautions included in the Prescribing Information of Smoflipid (Appendix 1) and of Intralipid 20% (Appendix 2) will be considered before the dosing of the study drug is changed or confirmed.

11.2.4 Final Study Visit

The Final Study Visit will take place after cessation of the last study drug infusion. Study

treatment can last up to 365 consecutive days, i.e., for one year after randomization. No patient will receive study medication beyond Study Day 366.

Up to Study Day 90, study treatment will be terminated if enteral food tolerance increases and in consequence, if less than 60% of the patient's caloric requirements are provided by PN for at least one week (see 9.4 Exclusion after Study Admission).

After Study Day 90 the study treatment will be terminated as soon as nutritional needs can be fully covered from enteral or oral nutrition or PN is continued without a lipid emulsion (i.e., PN, or at least the lipid emulsion, is no longer indicated).

The study will be terminated at any time, if infusion of the lipid emulsion cannot be continued because TG or direct bilirubin levels remain above the defined limits (cf. 10.3.4) after reduction of the study drug dosage.

During Final Study Visit, the same procedures will be executed as in the monthly Treatment Phase Visits (see above, 11.2.3). Additionally, the reason for study termination will be recorded if it takes place before Study Day 365.

Note: Should the Final Study Visit be performed between Day 90 and Day 365 and less than 1 week after the collection of the last blood samples, then the blood sampling will not be repeated at the Final Study Visit.

If a patient is withdrawn from the study at any time due to an AE, the patient should be followed until an outcome of the AE can be defined.

In case the study participation is terminated because of withdrawal of the informed consent, the Final Study Visit, or single procedures of this visit, will only be executed if allowed by the patient's parent(s) or legal representative(s).

If the termination occurs before Study Day 365 because of cessation of PN, and PN is restarted later, a re-treatment with study drug is not allowed.

11.2.5 Early Termination Visit

There is no specific definition of an Early Termination Visit because the study can be terminated for various reasons and at any time point. Independent of the reason and the time point of termination, a Final Study Visit (see above, 11.2.4) will be performed unless it is refused by the patient's parent(s) or legal representative(s).

11.3 Experimental and Analytical Methods

11.3.1 Anthropometric Measurements

Assessment of body weight:
Scales used for measuring body weight of the patients must be calibrated and revised according

to applicable local requirements. The relevant documentation must be updated and available on request.

Assessment of body length/height:
Body length/height of the patients will be assessed in lying/standing position with the help of a length board/stadiometer.

Assessment of head circumference (patients < 3 years of age):
An accurate head circumference measurement is obtained with a non-stretchable measuring tape. The measurement should be made around the widest possible circumference of the head, i.e., over the most prominent part on the back of the head (occiput) and just above the eyebrows (supraorbital ridges).

11.3.2 Laboratory Variables

Laboratory analyses will be performed in the local laboratories or in central laboratories (only fatty acids, sterols, and FADS1 and FADS2 genes).

All blood sample volumes will be specified and included in the ICFs and IRB submission documents.

Analyses in local laboratories

Determination of the laboratory values will be assessed using established validated techniques at the local laboratory of the clinical site. Valid normal ranges for the age groups and certifications from all laboratories will be obtained before start of the study.

Blood samples which are drawn at home (home care patients) will be sent to the clinical site for analysis. An exact description of the methodology for drawing, handling and shipping of the samples for the analysis will be provided to the home care providers.

The Investigators will review all laboratory results. Laboratory values outside the normal range will be assessed concerning their clinical significance by the Investigator. If the out-of-range value is considered clinically significant, it will be recorded as an AE (see Section 12) and documented in the eCRF (see Section 11.4.1).

Analyses of fatty acids and sterols

Analysis of fatty acids (linoleic acid, α-linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid and Mead acid, analyzed in total plasma and in red blood cell membranes and of sterols (β-sitosterol, campesterol, stigmasterol, brassicasterol, ergosterol, cholesterol, desmosterol, lanosterol, β-sitostanol, lathosterol, squalene) in plasma will be performed at the following specialized laboratory:

[redacted]

[redacted]

An exact description of the methodology for drawing, handling and shipping of the samples for the analysis of fatty acids and sterols at the central lab will be provided to the clinical sites.

Fatty acid profiles will be used for assessment of EFAD. Severity of EFAD will be graded based on triene/tetraene ratio, e.g., as suspected ≥ 0.05, moderate ≥ 0.20 and severe ≥ 0.40 (Cober et al 2012).

Analysis of fatty acid desaturase encoding genes (FADS1 and FADS2)

Analysis is performed only once for each patient, at the following specialized laboratory:

[redacted]

An exact description of the methodology for drawing, handling and shipping of the blood sample for the genetic analysis at the central lab will be provided to the clinical sites.

11.4 Documentation of Patient Data

All patient data generated during the study will be documented in the patient's medical records (source data). Source data is defined as all information in original records and certified copies of original records regarding clinical findings, including observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Only the Investigator and authorized co-workers (as listed on the form "Site Delegation of Authority Log" provided by Fresenius Kabi) will transcribe patient data from the source data into the eCRF.

All evaluations reported in the eCRF must be supported by source documents.

11.4.1 The Electronic Case Report Form

All patient data generated during the study will be recorded in the eCRFs provided by Fresenius Kabi/Clinipace. The eCRF is specifically designed to meet the data recording requirements of the Clinical Study Protocol and the requirements of FDA 21 CFR Part 11. Clinical Trial Data will be captured in the validated [redacted] system designed and tested to exceed FDA 21 CFR 11 standards, and to support the study specific protocol specifications. All completed documentation of the Operational Qualification, User Acceptance Testing, and Installation Qualification will be maintained by Clinipace. The completed project specific Data Management Plan (DMP) will further describe, in detail, how the [redacted] Study instance will be utilized to manage this Clinical Trial.

Only the Investigator and authorized co-workers (as listed on the form "Site Delegation of

Authority Log" provided by Fresenius Kabi and trained appropriately on the eCRF system) will complete eCRFs or make corrections to the eCRF entries, and will have access to the data or may change data, without the possibility of deleting the original entries. All study personnel involved in data entry or data review will have to adhere to the eCRF completion guidelines. After completion, each eCRF will be electronically signed and dated by the Investigator.

For all laboratory data, the units or any transformation of units must be clearly defined. Transformation of data during the data processing will be documented.

This study will be monitored regularly by a CRA from Clinipace. The CRA will check for completion of the entries in the eCRFs, their compliance with the study protocol and with GCP, and will compare the eCRF entries with the source data. Source data verification will be performed for all patients and 100% of the data. A 100% accuracy and completeness check will be performed on the ICFs. A detailed list of all monitoring activities to be performed during the study will be included in the Monitoring Manual (see Section 13).

12. Adverse Events and Serious Adverse Events

12.1 Definitions

12.1.1 Adverse Event (Adverse Experience, AE)

Adverse event (AE) means any untoward medical occurrence in a patient administered a pharmaceutical/medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical/ medicinal product, whether or not considered related to the pharmaceutical/medicinal product.

An AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant (pre-existing) illness
- An effect of the study medication
- An effect of a comparator drug
- Unrelated to participation in the clinical study
- A combination of such factors

12.1.2 Adverse Drug Reaction (Adverse Reaction, ADR)

For marketed products, all noxious and unintended responses to a pharmaceutical/medicinal product related to doses normally used in human for prophylaxis, diagnosis, or therapy of disease or for modification of physiological functions should be considered as Adverse Drug

Reactions.

12.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An SAE or SAR is any untoward medical occurrence (effect, reaction) that at any dose:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is of medical importance**

* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** Important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered as serious. Important medical events should also usually be considered serious (21 CFR 312.32(a)).

Events that do not fit in any of the above categories are to be considered non-serious AEs or non-serious ADRs.

12.1.3.1 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug (21 CFR 312.32(a)).

12.1.4 Unexpected (Serious) Adverse Reaction

An Unexpected (Serious) Adverse Reaction is a reaction, where the nature or severity or outcome is not consistent with the applicable reference safety information. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented (serious) adverse reaction constitute unexpected events.

The reference safety information for assessment of expectedness is the current version of the Prescribing Information for Smoflipid (Appendix 1) and Intralipid 20% (Appendix 2).

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are all ADRs that are considered to be both:

- Serious, and

- Unexpected

12.2 Assessment of Adverse Events

For each AE, the Investigator will assess:

- Seriousness (as defined in section 12.1.3)
- Intensity/Severity
- Causality (to study drugs and study procedures)
- Outcome
- Action taken

12.2.1 Intensity/Severity

For the intensity/severity assessment of AEs based on clinical signs and symptoms, abnormal laboratory parameters or vital signs, the "Common Terminology Criteria for Adverse Events" (CTCAE) V4.03, should be used as far as reasonable (see Appendix 3). The Common Terminology Criteria for AEs is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

If these criteria are not reasonably applicable to an AE, the event's intensity/severity should be classified according to the Investigator's discretion as close as possible to CTCAE V4.03 based on the comparison with the most severe case encountered in past training and clinical experience. For such events the following general category descriptions may be used (Table 2).

Table 2: Intensity/Severity Definitions for Adverse Events and Serious Adverse Events

Grade	Category	Definition/Explanation
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
4	Life-Threatening/Disabling*	Life-threatening consequences; urgent intervention indicated.
5	Fatal**	Death related to the AE.

*Life-threatening/disabling or **fatal AEs will also meet the identical seriousness criteria and

thus will qualify as SAEs.

12.2.2 Causality/Relationship to Study Drug

For all AEs, the causal relationship to study drug and to study procedures is to be assessed by the Investigator (regardless of whether they occurred under investigational drug or control drug).

Related:
A causal relationship between a drug and an AE can be assumed if there is at least a reasonable possibility for such a causal relationship. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. A causally related AE is equal to an ADR.

Not related:
Not related with the use of a drug means that the criteria mentioned above are not met, or that a causal relationship is ruled out.

Each causality assessment should be substantiated by the Investigator; in case of "not related" at least one (e.g. the most probable) alternative cause should be provided with the assessment.

12.2.3 Relationship to Study Procedures

Relationship to Study Procedures means that there is a reasonable possibility that the event is caused by specific circumstances of the protocol such as diagnostic or administration procedures.

12.2.4 Outcome

The outcome of the AE (and NOT the patient's outcome) is to be assessed at the time of documentation of the AE based on the following categories:

1. Resolved (i.e., complete resolution of AE)
2. Resolved with sequelae
3. Not resolved (includes AEs which are improving but not yet resolved completely, AEs which are ongoing at time of documentation, and AEs which are still present when a patient dies due to other causes or due to another AE).
4. Fatal (= death due to the AE).
5. Unknown (e.g., if patient is lost to follow-up).

12.2.5 Action Taken

The action taken to study drugs by the Investigator as a result of the AE will be classified in one of the following categories:

1. None (= continuing according to protocol)

2. Dose reduced; this could mean:
   a) Reducing the dose of the study drug
   b) Maintaining the dose level, despite required increase as per protocol
   c) Reducing the frequency of administration
3. Study drug discontinued and restarted
4. Study drug discontinued permanently

In addition, the Investigator needs to provide information on other therapy or countermeasures, such as:

a) Drug therapy was initiated to counteract the AE
b) Dose of concomitant medication was changed
c) Non-drug remedial therapy was initiated

If considered necessary, the Investigator may decide to withdraw patients from the study as a consequence of AEs.

12.3 Reporting and Documentation Procedures

In this study, all AEs – except AEs based on abnormal laboratory parameters or vital signs with an intensity/severity grade 1 (see Table 2) that has no clinical relevance – have to be documented and reported.

If the same AE occurs frequently during the study and all episodes have the same main AE characteristics (intensity, causal relationship, outcome), this should be documented as one AE with multiple episodes.

All other AEs, including those known to be associated with the study drugs, are to be completely documented and reported.

12.3.1 Documentation of (Serious) Adverse Events

All AEs including SAEs must be documented by the Investigator on the AE page of the eCRF.

Adverse events based on clinical signs and symptoms are to be assessed according to the CTCAE V4.03 intensity criteria (Appendix 3) or – if CTCAE is not applicable – according to the general intensity/severity criteria provided in the Table 2 in Section 12.2.1.

Adverse events based on abnormal laboratory parameters or vital signs are to be assessed according to the CTCAE V4.03 intensity/severity criteria and their clinical relevance as outlined in Table 3 below. For such AEs the clinical picture should be described, if applicable, rather than the laboratory parameter or vital sign only (e.g., “hypertension” instead of “increased systolic and diastolic blood pressure” or “hyperthyroidism” instead of “elevated thyroid hormones”).

Table 3: Documentation of AEs (Laboratory parameters and vital signs)

Severity Grade*	Clinically relevant	Documentation as
1	Yes	AE in eCRF
	No	No documentation necessary
2	Yes/No	AE in eCRF
3	Yes (typical)	AE in eCRF; if serious, additionally on SAE report form
4	Yes	AE in eCRF; additionally on SAE report form
5	Yes	AE in eCRF; additionally on SAE report form

*According to CTCAE V4.03 (Appendix 3) as far as possible

If a patient is withdrawn due to an AE at the end of the study treatment period, the patient should be followed-up until an outcome of the event can be defined. If this is not possible due to clinical or organizational reasons, an outcome assessment has to be performed by the Investigator. A final examination should be performed.

AEs are generally coded according to Medical Dictionary for Regulatory Affairs (MedDRA). At the end of the study before the clinical data base is closed, all AEs will be re-coded according to the latest MedDRA version available.

12.3.2 Reporting of Serious Adverse Events

The Investigator should not delay initial SAE report entry due to missing data. As soon as the minimum information is available the initial SAE report will be entered into the eCRF, in any case, no later than 24h after becoming aware of the SAE. The eCRF will automatically generate a notification e-mail that will inform the safety associate at Clinipace and the Director Global Safety at Fresenius Kabi that an SAE has been reported.

Each initial SAE report should contain at least the following information:

- Study number
- Patient number
- Patient's date of birth (or age)
- Investigator's name and address
- AE (description, start date, outcome on the day of the report)
- Investigator's assessment of seriousness and intensity/severity
- Investigator's assessment of causal relationship to study drug and study procedures
- Action taken to the study drug

If necessary, the Investigator will provide follow-up reports immediately after knowledge of further relevant information.

12.3.3 Documentation and Reporting of Other Safety-Relevant Information and Unanticipated Problems

Any:

- Pharmaceutical quality issue regarding study medication
- Report of overdose
- Report of misuse
- Report of use outside the scope of this clinical study protocol
- Report of pregnancies or drug exposure via parent

must be documented and reported immediately but within 24 hours at the latest of awareness on a "Serious Adverse Event Form" or "Drug Exposure via Parent Data Collection Form" form to the e-mail address provided below (see 12.3.4, Safety Contact at Fresenius Kabi).

For instance, a report of overdose has to be completed if the total administered dose of the study drug exceeds the maximal dosage as defined in this protocol.

For studies conducted under 21 CFR part 312, Investigators are required to promptly report "to the IRB … all unanticipated problems involving risk to human subjects or others," including AEs that should be considered unanticipated problems requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure (§§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1)). For this purpose, Investigators must report all unanticipated problems immediately to the Safety Contact at Fresenius Kabi (see 12.3.4).

Accordingly, to satisfy the Investigator's obligation to notify the IRB of unanticipated problems, Fresenius Kabi will process and analyze AE information and other safety relevant information for the entire study and assess whether an AE occurrence is both *unanticipated* and a *problem* for the study. Fresenius Kabi will provide the Investigator with the report for submission to IRB.

An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. Therefore, FDA recommends that there should be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. Fresenius Kabi will conduct ongoing safety evaluations, including periodic review and analyses of its entire safety database, not only for IND safety reporting purposes, but also to update Investigator Brochures, protocols, and consent forms with new safety information.

12.3.4 Safety Contact at Fresenius Kabi

The Safety Associate of Clinipace Worldwide will contact the site for clarification of data entered onto the eCRF, or to obtain missing information. In the event of questions regarding SAE reporting the site may contact:

[redacted]

[redacted]

In case of urgent questions regarding any safety aspect of this study, the Global Safety, Fresenius Kabi, OR Global Medical Affairs Officer at Clinipace Worldwide can be reached as follows:

[redacted]

12.3.5 Reporting to FDA, Institutional Review Boards, and Investigators

Fresenius Kabi as the Sponsor of this trial will inform the FDA and IRBs about unanticipated problems involving risk to human subjects or others, including AEs that should be considered unanticipated problems on an expedited basis (21 CFR 312.66).

Fresenius Kabi will also provide Periodic Safety Update Reports or line listings to the IRBs as required. General and local requirements will be followed. All Investigators participating in the study will receive Safety Reports and information on unanticipated problems.

12.3.6 Period of Observation

The period of observation will begin the day the patient's parent(s) or legal representative(s) has/have signed the ICF. The end of the observation period is defined as the time of the last Final Study Visit. The Final Study Visit takes place after cessation of the last infusion of study drug.

All unresolved AEs will be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the SAE is otherwise explained.

When the patient has been discharged from the hospital, or has been in home care, the Investigator should instruct the patient's personal physician (only if patient's legal representative/s allow/s) to report any SAE and any AE that this physician believes might reasonably be related to participation in this study. The Investigator should notify Fresenius Kabi immediately of any such SAE.

12.4 Unblinding of Treatment for Emergency Reasons

In case of a medical emergency requiring identification of the study lipid emulsion administered to the patient, the treatment code may be unblinded. For unblinding procedure see Section 6.4.

After completing the unblinding procedure, an email notification of this action will automatically be sent to appropriate management and safety officials acknowledging the subject unblinding without providing specific treatment arm.

If an emergency unblinding becomes necessary, the Investigator should notify the Sponsor/Medical Monitor, if possible, prior to unblinding.

If an Investigator, patient, or parent/legal representative is unblinded, the patient must be withdrawn from the clinical study and procedures accompanying withdrawal are to be performed.

Serious and Unexpected Suspected Adverse Reactions, which are subject to expedited reporting, should be unblinded before submission to the FDA.

In case of unblinding, the blindness of Fresenius Kabi's (and the CRO's) clinical study team must be maintained wherever possible, i.e., no information with regard to a broken treatment code must be communicated to any blinded member of the study team. The unblinding must be notified immediately to the CRA responsible for the site.

12.5 Data Safety Monitoring Board (DSMB)

In this study an independent DSMB will be involved. The DSMB is a multidisciplinary group consisting of clinical study scientists and statisticians experienced in managing PN in pediatric patients as well as conducting and analysing randomized clinical trials. The DSMB members are not otherwise participating in the trial. The DSMB will be responsible for the monitoring of patient safety. The DSMB can request any analysis during the course of the study on either a blinded or unblinded basis.

The working principles will be defined in a DSMB charter describing the composition of the DSMB, responsibilities, organization, flow of information, evaluation and decision principles, and interactions.

13.Monitoring

13.1 Monitoring Procedures and Responsibilities

Site monitoring is conducted to ensure the patient protection, compliance with the study protocol, study progress, adherence to study procedures, study interventions, and

administration of study drugs. The monitoring and collection of data will be performed in high quality manner in compliance with ICH/GCP, valid Standard Operating Procedures (SOPs), and other regulatory guidelines, if appropriate.

This study will be monitored regularly by a CRA from the CRO. The CRA will check all inform consent documents and the appropriate documentation as well as the completion of the entries in the eCRFs, their compliance and accuracy with the study protocol and will compare the eCRF entries with the source data. This source data verification will be performed for all patients on all data. Administration of study drugs and the investigator site file will be monitored as well. Further details will be defined in the Monitoring Manual.

In addition, the monitor will check whether all AEs and SAEs have been documented and reported appropriately within the required time periods.

The Investigator and his staff will be expected to cooperate with the CRA, to be available during a sufficient portion of the monitoring visit to answer questions and to provide any missing information.

In addition the Investigator is required to:

- Have all data properly recorded in the eCRF and the patient file before each monitoring visit.
- Have the source documents available at the monitoring visits.
- Record all study drugs dispensed in the eCRF and drug accountability records.
- Provide investigator site file for verification of completeness and accuracy.

All patients who were screened, but not enrolled into the study will be listed on the patients screening log and will be monitored as well.

Monitoring will also be conducted to detect any misconduct or fraud.

Monitoring will be performed by:

[redacted]

13.2 Frequency of Monitoring

During the treatment phase of the study, each site will be visited by the monitor as soon as possible after first patient of each site has been screened and ICF was signed, followed by visits approximately every [redacted] weeks, or as appropriate.

14. Audits and Inspections

14.1 Audits

14.1.1 Auditing Procedures

Audits (quality assurance) may be performed to ensure compliance of the study with GCP requirements. The Auditor will work on behalf of Fresenius Kabi, but will be independent from the operational departments within Fresenius Kabi. The Investigator and Clinipace will permit the respective person direct access to source data/documents.

At the study site, the Auditor will check the following:

- Preconditions to start the study
- Completeness and correctness of the ICFs
- Compliance of study with study protocol
- Source data check
- Drug accountability
- General compliance of the study with GCP and national law
- Organization of the study and delegation of staff responsibilities
- Patient recruitment, screening, enrolment and treatment allocation/randomization
- Changes in study or routine hospital procedures, if any
- Handling of (Serious) AEs inclusive reporting and follow-up

14.1.2 Frequency of Audits

Audits will be performed according to an audit plan.
At least one on-site audit is planned for this trial, but audits may be performed at any time at any site during the study as considered necessary.

14.1.3 Documentation of Audits

After each audit the Auditor will compile an audit report including an audit certificate. A copy of the certificate will be sent to the Investigator to be filed in the Investigator's site file.

14.2 Inspections

The Investigator will permit study related IRB review, and regulatory inspection(s), providing direct access to source data/documents.

15.Modifications during the Study

15.1 Protocol Amendments

If both Fresenius Kabi and the Coordinating Investigator agree upon a change or addition in the study protocol during the course of the study, this will be documented in a written protocol amendment. These amendments will become part of the study protocol.

Minor modifications, minor deviations, or specifications of the study protocol can be described in a non-substantial amendment.

Substantial amendments must be submitted to the IRBs and the FDA. In case of substantial amendments that affect information submitted to both the FDA and the IRBs, Fresenius Kabi will make arrangements to submit the notifications in parallel. For substantial amendments to information that only the FDA assesses, Fresenius Kabi will not only submit the amendment to the FDA, but also make arrangements to inform the IRBs about this application. Similarly, Fresenius Kabi will inform the FDA of any substantial amendment to information for which only the IRB is responsible (e.g. facilities for the trial).

Examples for substantial amendments, but not limited to these, are:

- Change in study design
- Changes in measures of efficacy
- Changes of inclusion or exclusion criteria
- Changes of safety reporting or evaluation
- Changes likely to have an impact on the safety of study patients
- Changes in the interpretation of the scientific documents in support of the conduct of the study
- Changes deemed otherwise significant

15.2 Protocol Deviations

No deviation from the study protocol will be allowed unless a formal amendment is made to the protocol. However, in case a deviation has occurred the Investigator must document it in the eCRF.

Major protocol deviations are those protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or may affect the patient's rights, safety, or well-being. In case of any potential major deviation the Investigator has to notify the CRA immediately.

Protocol deviations will be assessed and graded in the blinded data review meeting prior to the final analysis of the study data.

15.3 Premature Termination of the Study

Fresenius Kabi has the right to terminate the study at a specific study site or completely at any time. Reasons which may require termination include:

- Patient enrolment is too slow
- The Investigator fails to comply with the study protocol or legal requirements
- Data recording is not accurate (e.g., eCRFs are not completed appropriately)
- The incidence or severity of AEs/SAEs in this or in parallel studies indicate a potential health hazard caused by treatment with a study drug
- Fresenius Kabi is requested by the FDA to terminate the study
- Fresenius Kabi decides to terminate the study due to internal reasons

In case of premature termination of the study, Fresenius Kabi will notify the FDA and IRBs within 15 days and give reasons for termination, which should clearly be explained. Additionally, the Investigators will be notified by Fresenius Kabi and will receive instruction, if necessary, as to what final examinations are required.

16. Final Clinical Study Report

Fresenius Kabi is responsible for compilation of the final clinical study report (CSR). The final CSR will be submitted to the Coordinating Investigator and all Principal Investigators for approval and signature. A copy of the final signed CSR will be sent to each Investigator for the study site file.

17. Administrative Requirements

The trial will be carried out in accordance with the current version of ICH E6 - Guidelines for Good Clinical Practice (June 2017), the Declaration of Helsinki, revised version (64th WMA General Assembly, Fortaleza, Brazil, October 2013), and the Code of Federal Regulations (CFR) Title 21.

17.1 Public Trials Registry

Fresenius Kabi will obtain a Clinical Trials Registry Number for the clinical study from the ClinicalTrials.gov database, via internet, by filling in an application form. This number identifies a study unambiguously.

17.2 Institutional Review Board

Fresenius Kabi will submit the study protocol including the ICF to the responsible IRBs for review. Approval by the IRB is a pre-requisite for initiation of the study. Fresenius Kabi will provide the Investigator with a copy of the approval letter and a list of the names and occupations of the committee members.

Amendments that are substantial must be notified to the FDA and the IRBs; Fresenius Kabi will make arrangements to submit the notifications in parallel. For substantial amendments to information that only the FDA assesses, Fresenius Kabi will not only submit the amendment to the FDA but also make arrangements to inform the IRBs that they have made the application. Similarly Fresenius Kabi will inform the FDA of any substantial amendment to information for which only the IRB is responsible (e.g., facilities for the study).

During the study the IRBs will be informed of any ADRs which are both serious and unexpected and any other SAEs as required by the IRB. Changes increasing the risk to patients or affecting significantly the conduct of the study will also be reported to the IRBs.
Fresenius Kabi will notify the IRBs of the end of the study within 90 days.

17.3 Submission to the Food and Drug Administration

Fresenius Kabi is responsible for submission of study-related documents to the FDA (Center for Drug Evaluation and Research, Division of Gastroenterology Products) before study start. Approval by the FDA is a pre-requisite for initiation of the study.
Fresenius Kabi will notify the FDA of the end of the study within 90 days.

17.4 Notification of Local Authority

Not applicable in the USA.

17.5 Patient Information and Informed Consent

It is the responsibility of the Investigator to give each legal representative of the patient full and adequate verbal and written information regarding the objective and procedures of the study and the potential benefits, discomforts and risks involved prior to inclusion in the study. The Investigator has to inform the legal representative(s) about appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient. The legal representative(s) must be informed in writing about their right to withdraw the patient from the study at any time without specification of reasons. The legal representative(s) have to be informed that refusal to participate and a discontinuation of participation at any time will involve no penalty or loss of benefits to which the patient is otherwise entitled. The legal representative(s) have to be informed that they are covered by insurance and, therefore, need the consent of the Investigator if other medical treatment (e.g. to treat a concomitant illness) is required, except in an emergency situation. Written patient information should be given to each legal representative(s) before enrollment. The written patient information must not be changed without prior agreement with Fresenius Kabi. Furthermore, it is the responsibility of the Investigator to obtain a signed ICF from each legal representative prior to inclusion of a patient in the study.

The legal representative(s) should have enough time (ample time) and opportunity to enquire about details of the study and to decide whether or not to allow participation in the study.

If possible, patient assent must also be obtained (according to local law).

The dated and signed ICFs should be filed by the Investigator for mandatory review by study CRA or for possible audits and inspections where this is permitted or required. The Investigator will confirm the receipt of ICF from each legal representative in the CRF.

17.6 Patient Insurance

In accordance with current ICH E6 – Good Clinical Practice, and national requirements, Fresenius Kabi has taken out a personal liability insurance (HDI-Gerling America Insurance Company, 161 North Clark Street – 48th Floor, Chicago, IL 60601; policy no. CTD5460500S) in the amount of USD 5.000.000 for each patient participating in the trial.

17.7 Patient Privacy

Fresenius Kabi confirms and upholds the principle of the patients' right to protection against invasion of privacy. Throughout the study, all data which will be passed on to Fresenius Kabi will only be identified by patient numbers and patients' date of birth. The data will be blinded correspondingly in all data analyses.

In compliance with the ICH GCP guidelines concerning the acceptance of clinical studies, source data verification will be done in detail by the on-site monitor at each visit or during a study audit by the auditor. The source data verification will be performed according to local data protection law.

17.8 Initiation of the Study

The Investigator may not enroll any patient prior to completion of a formal study initiation visit with the CRA.

The following documents will be provided in original by the Investigator to Fresenius Kabi prior to study start:

- Signed protocol
- Investigators' agreement on the clinical study
- Financial disclosure according to 21 CRF Part 54
- Curriculum vitae of the Coordinating Investigator and his co-investigator(s).
- List of laboratory normal values of local laboratory including methods and certificates

18.Agreements

18.1 Confidentiality Agreement

This study protocol is provided to the Coordinating Investigator, potential investigator, or consultant, and the IRB for review. The information contained in this protocol is confidential

and, except for the extent necessary to obtain Informed Consent, may not be disclosed unless such disclosure is required by law. People to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Similarly, the Investigators and their staff will not pass any other study-related information, documents or medication to third parties. All study materials and documents provided by Fresenius Kabi including this protocol, are property of Fresenius Kabi.

18.2 Publication of Results

Publication of study results is intended. The publication of study results will be ruled by the agreement between the Investigator/Institution and Fresenius Kabi.

18.3 Payment

Financial obligations of Fresenius Kabi are outlined in a separate agreement between the Investigator/Institution and Fresenius Kabi.

18.4 Potential Conflicts of Interest

A financial disclosure form according to 21 CFR Part 54 will have to be signed by each Investigator participating in the study.

18.5 Incentives to Patients

Not applicable.

18.6 Archiving

At the end of the study the Investigator will receive an electronic copy of the eCRF in PDF/A format on CD/DVD. The Investigator must ensure that data remains readable throughout the requirement archiving period.

All records and documents pertaining to the conduct of the study (particularly eCRFs, ICFs, drug accountability sheets, original data including the patient files) must be retained. According to the CFR Chapter I, §312.62(c) the Investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until the investigation is discontinued and FDA is notified. Retrospective identification of all patients must be possible at any time. The Investigator shall discard any records only after consultation with Fresenius Kabi.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this section.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in this paragraph. Any alteration to the content of the clinical trial master file shall be traceable.

19.References

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20.Appendixes to this Clinical Study Protocol

APPENDIX 1: Smoflipid Prescribing Information

APPENDIX 2: Intralipid 20% Prescribing Information

APPENDIX 3: Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute, Publish Date: June 14, 2010.