Clinical Study Protocol

Title:	**A Prospective, Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare Safety and Efficacy of Smoflipid 20% to Intralipid 20% in Hospitalized Neonates and Infants Requiring 28 Days of Parenteral Nutrition**
Authority Identification no.:	PIND 102137
ClinicalTrials.gov Identifier	NCT02579265
FK Study Identifier:	SMOF-018-CP3
Indication:	A source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Investigational drug:	Smoflipid 20% (lipid injectable emulsion)
Control drug:	Intralipid® 20% (a 20% intravenous fat emulsion)
Protocol status:	Final 3.0
Date:	05 OCT 2020
Sponsor:	Fresenius Kabi Deutschland GmbH [redacted]

In case of emergency during out-of-office-hours please contact (sponsor's medical expert according to ICH Guideline E6 – Good Clinical Practice):

[redacted]

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The trial 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), CFR - Code of Federal Regulations Title 21 and the respective national laws and regulations.

The CSP and all subsequent amendments to the CSP are agreed upon between FK 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 and in the ICH-GCP Guideline, CFR - Code of Federal Regulations Title 21, Part 312 and applicable national laws and regulations. Changes to this protocol require the written agreement of both, investigator and Fresenius Kabi.

Coordinating Investigator

Biostatistics

Contract Research Organisation (CRO)

Responsibilities (Signature page)

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Coordinating Investigator

Biostatistics

Contract Research Organisation (CRO)

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Clinical Project Manager

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Head of Clinical Operations & Medical Affairs PN & Keto-Analogues

[redacted]

Medical Safety Officer

[redacted]

Clinical Project Manager

[redacted]

I, the signatory, confirm that this amendment to the Clinical Study Protocol contains all changes to information and regulations necessary for the conduct of this particular study. I sign the amendment as an agreement of the details of the clinical study and the means of data recording. I commit myself to comply with all instructions and regulations as laid down in this amendment to the Clinical Study Protocol, in the current version of the Declaration of Helsinki and applicable national laws and regulations (Code of Federal Regulations (CFR) Title 21, Part 312). Changes to this amendment require the written agreement of both, investigator and Fresenius Kabi.

Clinical Project Manager Fresenius Kabi

1 Study Outline

Title:	A Prospective, Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Safety and Efficacy of Smoflipid 20% to Intralipid 20% in Hospitalized Neonates and Infants Requiring 28 Days of Parenteral Nutrition.
Authority Identification no.:	PIND 102137
ClinicalTrials.gov Identifier	NCT02579265
FK Study Identifier:	SMOF-018-CP3
Indication:	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.
Objectives:	The primary objective of the study is to show the superiority in safety of Smoflipid over Intralipid® as measured by the number of study patients in each treatment group with conjugated bilirubin > 2 mg/dL during the first 28 days of study treatment, confirmed by a second sample collected 7 days after the first sample. The secondary objectives are to • compare efficacy of Smoflipid 20% to Intralipid 20% in neonates and infants reflected by specific nutritional parameters • evaluate overall safety of Smoflipid 20% in neonates
Study drugs:	Investigational drug: Smoflipid 20% Control drug: Intralipid 20%
Dosage:	The targeted maximal lipid dose is 3.0 g/kg/day. In patients that are already receiving parenteral nutrition (PN) before starting study treatment, the lipid dose will either stay at 3.0 g/kg/day or increased by 1 g/kg/day steps to a maximum of 3.0 g/kg/day. In patients that have not yet started PN prior to study

participation, lipid dose will be increased stepwise using the following regimen:

Study Day	Patients < 1500 g	Patients ≥ 1500 g
Day 1	1.0 g/kg/day	2.0 g/kg/day
Day 2	2.0 g/kg/day	3.0 g/kg/day
Day 3+	3.0 g/kg/day	3.0 g/kg/day

Investigational or control drug will be infused over 20 - 24 hours, as per hospital policy, at a weight based infusion rate. If the blood draw is from the PN/lipid infusion line, then lipid (study drug) should be held for 4 hours prior to the time of blood sampling. During study treatment, serum triglycerides (TGs) will be monitored to adjust lipid dose keeping TG levels < 250 mg/dL.

Blood samples for TG monitoring will be collected as follows:

Patients < 1500 g: At 1 g, 2 g and first dose of 3 g/kg/day
Patients ≥ 1500 g: At first dose of 3 g/kg/day

Once the target dose has been reached TGs will be assessed on a weekly basis.

Should TGs exceed 250 mg/dL, lipids will be paused until analysis of another blood sample on the following morning. If TGs are below 250 mg/dL lipids are restarted. If not this procedure has to be repeated the next morning.

Dosage of other PN components:

In addition to the study drug other macronutrients will be administered at a targeted dose as follows:

- Amino acids: 2 to 4 g/kg/day
- Dextrose: 8 to 18 mg/kg/min
- Trace elements, electrolytes, vitamins will be considered according to hospital practice and applicable guidelines.
- Use and dose of heparin and carnitine have to be documented in the concomitant mediation section in the CRF.

Route of Administration: The lipid emulsions will be infused into a central or peripheral vein

Treatment: Treatment group 1: Smoflipid 20% (investigational drug)

Treatment group 2: Intralipid 20% (control drug)

Intravenous lipid dose management

Conjugated bilirubin levels in plasma will be assessed on a weekly basis during the initial treatment phase (visits Day 1 – Day 29) and then bi-weekly in the treatment extension phase (visits Day 36 - Day 85). If in the treatment extension phase conjugated bilirubin levels increase beyond 1.5 mg/dL, then conjugated bilirubin will be assessed weekly.

- Lipid minimization:

If at any point conjugated bilirubin exceeds 1.5 mg/dL (> 1.5 mg/dL), 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 conjugated bilirubin levels decrease again below 1.5 mg/dL.

- Early discontinuation:

Should conjugated bilirubin exceed 2 mg/dL (> 2 mg/dL), a confirmatory analysis must be performed after 7 days. The patient's dose will remain at 1 g/kg/day until analysis of the confirmatory blood sample. If the confirmatory analysis reveals that conjugated bilirubin increased further by at least 1 mg/dL, then the patient has to be removed from the study immediately and may be treated with an alternative lipid emulsion at the investigator's discretion. If not, the patient continues to receive study medication.

- Weaning of lipids and PN:

As soon as the patient receives 80 mL/kg/day oral/enteral feeding and achieved tolerance (i.e. at least 3 days) the dose of study drug must be reduced to 1 g/kg/d.
As soon as patient receives 100 mL/kg/day oral/enteral feeding and achieved tolerance (i.e. at least 3 days) study drug must be stopped completely.

Duration of Treatment: The expected administration of lipid emulsions for each study patient should be 28 days. If PN is still indicated after 28 days, patients may receive the study drug for up to 84 days.

Patients: Hospitalized neonates and infants, expected to require PN for 28 days

Inclusion Criteria:	1. Neonates and infants, expected to require PN for 28 days 2. Postmenstrual age ≥ 24 weeks 3. Birth weight ≥ 750g 4. Gastroschisis, duodenal, jejunal or ileal atresia, volvulus, spontaneous intestinal perforation or necrotizing enterocolitis (Bell's stage 2B or higher) 5. At least 80% of nutritional needs at Baseline are met with PN 6. Signed and dated informed consent obtained from at least one parent or legal guardian
Exclusion Criteria:	1. Conjugated bilirubin > 0.6 mg/dL 2. Any known pre-, intra- or posthepatic complication that will increase conjugated bilirubin levels > 0.6, mg/dL during study participation 3. Suspected liver disease or liver damage based on either AST, ALT, or GGT exceeding 2.5x upper limit of normal range 4. Active bloodstream infection demonstrated by positive blood culture at screening 5. Cystic fibrosis 6. Meconium ileus 7. Serum TGs > 250 mg/dL 8. Cyanotic congenital heart defect 9. Severe renal failure as evidenced by creatinine > 2.0 mg/dL 10. History of shock requiring vasopressors 11. Anasarca 12. Extracorporeal Membrane Oxygenation (ECMO) 13. Known inborn errors of metabolism 14. Known congenital viral infection 15. Unlikely to survive longer than 28 days 16. Known hypersensitivity to fish-, egg-, soya- or peanut protein or to any of the active substances or excipients
Primary Endpoint:	The primary endpoint is the number of patients in each treatment group with conjugated bilirubin levels > 2 mg/dL during the first 28 days of study treatment period, confirmed by a second sample collected 7 days after the first sample.

Secondary Endpoints:

Efficacy:

- Body weight (change from Baseline)
- Body length (change from Baseline)
- Head circumference (change from Baseline)
- Time to full enteral or oral feeds
- Fatty acids in plasma and red blood cell membranes (change from Baseline)
- Holman index

Safety:

- Length of stay in hospital
- Ratio of number of independent bloodstream infections/number of days on study medication
- Ratio of the number of patients with 1 or more bloodstream infections / number of patients on study medication
- Number of patients who complete PN treatment without lipid minimization
- Number of patients who need to be withdrawn from the study due to elevated conjugated bilirubin levels
- Area under the curve of conjugated bilirubin for time period in which levels are > 1.5 mg/dL
- Cumulative number of days patients are administered a lipid dose without lipid minimization
- Time to conjugated bilirubin > 2mg/dL (confirmed by a second sample collected 7 days after the first)
- Conjugated bilirubin
- Total bilirubin
- Serum TGs
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl transferase (GGT)
- Alkaline phosphatase (ALP)
- Blood glucose
- Blood urea nitrogen (BUN)
- Creatinine
- C-reactive protein (CRP)
- Sterols including phytosterols
- α-tocopherol
- Collection of adverse event (AE) data
- Incidence of bronchopulmonary dysplasia (BPD)
- Incidence of retinopathy of prematurity (ROP)
- Incidence of intraventricular hemorrhage (IVH)

- Incidence of periventricular leukomalacia (PVL)
- Incidence of necrotizing enterocolitis (NEC)
- Incidence of late-onset sepsis in premature and low birth weight neonates

Statistics:

The primary outcome measure is the number of patients in each treatment group with conjugated bilirubin levels > 2 mg/dL during the first 28 days of study treatment, confirmed by a second sample collected 7 days after the first sample.

Due to the lack of reliable data on the effect size of Smoflipid compared to Intralipid a two-stage adaptive group sequential design according to Bauer and Köhne (Bauer, et al. 1994) will be performed.
An interim analysis will be performed once 50 patients in each group have completed the study per protocol (at least 14 days of study treatment).
A nominal significance level of 0.0102 will be applied to stage 1. The significance level of stage 2 will be based on error probabilities observed at interim-stage. Datasets from stage 1 and 2 will be analyzed separately.
Statistical analysis of the primary endpoint will be based on the risk ratio for developing cholestasis during 28 days of Smoflipid administration compared to Intralipid.
Non-inferiority will be a gatekeeper for superiority using a non-inferiority margin of 1.2. If non-inferiority of Smoflipid can be demonstrated, superiority will be tested subsequently. This procedure corresponds to a simple closed test procedure and requires no multiplicity adjustment.
If a second stage needs to be performed, the sample size calculation will be based on the treatment effect observed at stage 1. The overall one-sided significance level and minimum power are set to 2.5% and 80%, respectively.
If this sample size re-estimation results in a sample size that exceeds the maximum study size of up to 200 patients per group, the study will be stopped prematurely after the interim analysis for futility and be analysed descriptively and in an exploratory way.

Evaluations/Follow-up:

All data will be collected according to the study schedule. The number of blood samples collected will be minimized in this vulnerable target population.

After obtaining a signed/dated informed consent form (ICF) and prior to administration of the first dose of study drug, baseline

assessments will be completed including: review of inclusion/exclusion criteria, collection of demographic data including race and ethnicity, the patient's medical history and concomitant medications, blood sample for safety lab and analysis of sterols, fatty acids and α-tocopherol.

Adverse events will be documented at any time point of the study and followed up until resolved.
During treatment the following data will be recorded daily: Study drug administered, dextrose administered, amino acids administered, EN administered, body weight, AEs and concomitant medication.
Body length and head circumference will be measured and recorded once weekly.
Conjugated bilirubin, ALT, AST and GGT will be measured weekly up to day 29 and then biweekly until day 85 or discharge, respectively. If after day 29 conjugated bilirubin increases beyond 1.5 mg/dL, it has to be assessed weekly again.
Serum triglycerides will be measured and recorded once weekly. At TG > 250 mg/dL, TGs will be measured the following day.
In case of suspected systemic infections blood cultures will be drawn.
An End-of-Treatment Visit has to be performed on the following day after receipt of the last dose of study medication. AEs, concomitant medications, physical examination findings, vital signs, body weight, body length, head circumference, conjugated bilirubin, safety laboratory analyses, sterols, α-tocopherol and fatty acids in the blood will be assessed.
At the Follow-up Visit, 7 days after the End-of-Treatment Visit, all information regarding AEs and concomitant medications since the last study medication dose will be documented, and physical examination findings, vital signs, body weight, body length, head circumference and length-of-stay in the hospital will be recorded.
If conjugated bilirubin level was > 1.5 mg/dL at the End-of-Treatment-Visit, then conjugated bilirubin needs to be assessed again at the Follow-up Visit.

Investigators:

Coordinating Investigator:

[redacted]

Participating sites:

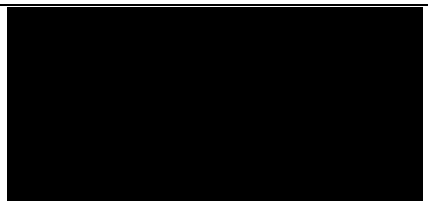
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



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2 Study Schedule

Daily procedures and assessments during treatment (starting on day 1): Study drug administration, study drug administered, dextrose administered, amino acids administered, EN and oral food administered, Body Weight, Adverse Events, Concomitant Medication

Initital Treatment Phase							Treatment Extension Phase								Follow-up Visit
Assessment / Records	**Screening**	**Day 1 Baseline**	**Day 8**	**Day 15**	**Day 22**	**Day 29 / End of Treatment[a]**	**Day 36**	**Day 43**	**Day 50**	**Day 57**	**Day 64**	**Day 71**	**Day 78**	**Day 85 / End of Treatment[a]**	**7d after End of Treatment**
Time Window (d)	Day 1 -3d	0	±1	±1	±1	+1	±2	±2	±2	±2	±2	±2	±2	+1	±1
Parent Informed Consent	X														
In- / Exclusion Criteria	X	X													
Randomization		X													
Demographics incl. race and ethnicity	X														
Medical History	X														
Prior Medication	X														
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Length		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Head Circumference		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Time to Full Enteral or Oral Feeds						X								X	
Length of Stay															X
Blood Sampling for Conjugated Bilirubin[b]	X		X	X	X	X		X		X		X		X	(X)[c]
Blood Sampling for Biochemistry, Hematology and Coagulation[d]	X		X	X	X	X		X		X		X		X	
Blood Sample for special analyses[e]		X				X				X				X	

[a]: End of treatment visit to be performed on the following day after receiving the last dose of study medication
[b]: If conjugated bilirubin exceeds 1.5 mg /dL it has to be assessed weekly, also after d29
[c]: If conjugated bilirubin is > 1.5 mg/dL at the end of treatment visit a blood sample for the assessment of conjugated bilirubin has to be drawn at the Follow-up Visit
[d]: Additional blood samples for assessment of TGs and blood glucose need to be drawn during ramp up of lipid dose. Should TGs exceed 250 mg/dL at any time, lipids will be withheld until analysis of TGs in another blood sample the following morning.
[e]: Special analyses: Fatty acids, sterols, α-Tocopherol

3 Contents

3.1 List of Tables

3.2 List of Figures

4 Table of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BPD	Bronchopulmonary Dysplasia
BUN	Blood Urea Nitrogen
CA	Competent/Regulatory Authority
CBC	Complete Blood Count
CI	Confidence Interval
CRA	Clinical Research Associate (Monitor)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EFAs	Essential Fatty Acids
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma -Glutamyl Transferase
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IVH	Intraventricular hemorrhage
IFALD	Intestinal Failure-Associated Liver Disease
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
IVLE	Intravenous Lipid Emulsion
MCT	Medium-Chain Triglycerides
MedDRA	Medical Dictionary for Regulatory Activities
NEC	Necrotizing Enterocolitis
PN	Parenteral Nutrition
PNALD	Parenteral Nutrition Associated Liver Disease
PP	Per Protocol
PVL	Periventricular Leukomalacia
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SUSAR	Suspected Unexpected Serious Adverse Reaction
TG	Triglyceride
US	United States

5 Introduction

5.1 Background

Parenteral nutrition (PN) is a life-saving procedure enabling the physician to provide adequate nutritional substrates to a patient whenever the patient's nutritional needs cannot be met with oral or enteral nutrition.
Total PN provides amino acids, dextrose, lipids, vitamins, electrolytes and water.
Within PN regimens, intravenous lipid emulsions (IVLEs) have 2 main functions: 1) to supply calorie-dense energy and 2) to provide essential fatty acids (Hamilton, et al. 2006, Krohn, et al. 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 1962.

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 conjugated bilirubin levels are considered to be a surrogate marker for evolving PN-associated cholestasis which is understood as the most common complication of the PN-associated liver disease (PNALD) (Colomb, et al. 2000, Javid, et al. 2011, Koseesirikul, et al. 2012, Pichler, et al. 2012). Clinically it is difficult to separate PNALD from intestinal failure-associated liver disease (IFALD), as intestinal failure by itself can contribute to liver disease with a similar increase in surrogate markers and IFALD requires PN as a treatment option. Parenteral nutrition-associated liver disease is considered to be multifactorial, and all quantitative as well as qualitative components of PN may promote cholestasis (Wales, et al. 2014). In recent years, investigators focused on the role of the soybean oil-based lipid emulsions 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 in α-tocopherol (Burrin, et al. 2014, Clayton, et al. 1998, Ng, et al. 2015, Wales, et al. 2014).

Smoflipid 20% has been developed to optimize the fatty acid profile of the lipid emulsion used in PN, reducing the amount of ω6 fatty acid linoleic acid given to the patient by replacing it in part with ω9 and ω3 fatty acids. Smoflipid is a fixed physical mixture of 4 different oils being used in clinical practice in many countries worldwide, combining soybean oil, medium-chain triglycerides (MCTs) from coconut oil, olive oil, and fish oil. Smoflipid contains 200 mg/L α-tocopherol, which protects unsaturated fatty acids against lipid peroxidation. Furthermore, Smoflipid contains only approximately 30% of total phytosterols compared to Intralipid.

Three company-sponsored studies have compared Smoflipid to Intralipid in the pediatric population, including 2 studies in preterm neonates and 1 study in infants and children 1 to 11 years of age (Goulet, et al. 2010, Rayyan, et al. 2012, Tomsits, et al. 2010). The data from these studies showed a beneficial effect on liver parameters, although liver function was not the primary endpoint in these studies.
In 2 studies, significantly greater decreases from baseline values were seen in total and direct bilirubin in the Smoflipid versus Intralipid group (Goulet, et al. 2010, Rayyan, et al. 2012). In the third study, lower gamma-glutamyl transferase (GGT) levels were noted in the Smoflipid

group versus the Intralipid group (Tomsits, et al. 2010). However, in 2 of these studies, PN was only administrated for up to 2 weeks. Consequently, long-term data for Smoflipid in the pediatric population is limited.

Smoflipid was first approved in Sweden in 2004 and is currently approved in 62 countries worldwide.

5.2 Rationale and Purpose of the Study

Fresenius Kabi, the manufacturer of Smoflipid, has applied for approval of Smoflipid in the United States (US). In order to meet the request of the Food and Drug Administration (FDA), a post-marketing study will be performed in hospitalized neonates and infants to show safety superiority of Smoflipid compared with Intralipid, a currently approved lipid emulsion in the US.

The present protocol describes a randomized, controlled, double-blind study in which either Smoflipid or Intralipid will be administered as part of a well-defined PN regimen to hospitalized preterm and term neonates and infants requiring at least 28 days of PN. The purpose of this study is to demonstrate the superiority in safety of Smoflipid (investigational drug) compared with Intralipid (reference drug) by evaluating the effect of these products on conjugated serum bilirubin levels. In addition, the study will explore if Smoflipid safely provides sufficient energy and essential fatty acids (EFAs) to ensure appropriate growth and development in these pediatric patients.

Sterols (including phytosterols) and α-tocopherol in the blood of the study patients will be evaluated to assess whether a correlation exists between the sterol and/or α-tocopherol levels and the incidence of cholestasis (Burrin, et al. 2014, Clayton, et al. 1998, Ng, et al. 2015), to address specific concerns communicated by the FDA given published experimental data (Carter, et al. 2007, El Kasmi, et al. 2013).

Per the request of the FDA, length of stay in hospital, the number of independent bloodstream infections and mortality (as part of serious adverse event [SAE] analyses) will be evaluated as well.

5.3 Benefit/Risk Assessment

Study patients will receive the study drugs as part of their nutritional support for at least 28 days during their hospitalization. It is standard clinical practice to incorporate lipid emulsions into the PN protocol in patients in whom enteral or oral nutrition is not sufficient or not feasible. The alternative treatment, (i.e., supply of calories by large amounts of dextrose, or dextrose exclusively) is associated with metabolic complications and liver damage and, therefore, is not appropriate (Koletzko, et al. 2005).
In neonates, and specifically in preterm neonates, an inadequate supply of EFAs and/or their derived long-chain polyunsaturated fatty acids during the critical periods of rapid brain growth and retinal development may lead to long-term impairment of neurodevelopment and visual

function (Clandinin, et al. 1980, Koletzko 1992, Lapillonne 2014). Essential fatty acids and polyunsaturated fatty acids cannot be synthesized from other metabolites and need to be provided to the neonates as part of their nutritional regimen. Therefore, the administration of IVLEs has to be initiated within days of birth in neonates who cannot be fed enterally (Driscoll, et al. 2008).

Both study drugs are approved in more than 60 countries. In addition, the comparator drug Intralipid is approved for use in the US. Like any other injectable lipid preparation, uncommon side effects of Smoflipid may include hypertriglyceridemia, nausea, chills, thrombocytopenia, cholestasis, and hepatic impairment after long-term treatment. However, since its introduction in 2006, no particular safety issue regarding the use of Smoflipid has been identified. In contrast, in the phase 1 study performed by Fresenius Kabi, the increase in serum triglyceride (TG) concentrations during infusion of Smoflipid was less pronounced, and elimination of TGs after the end of infusion was faster than during infusion of the standard soybean emulsion Lipovenös® 20%. This difference was probably due to the MCT portion in Smoflipid. It is expected that the fatty acid profile of Smoflipid will have a beneficial effect on the hepatic health patients compared to Intralipid (Driscoll, et al. 2008, Rangel, et al. 2012, Vanek, et al. 2012). The purpose of the present study is to confirm this beneficial effect.

6 Objectives

The primary objective of the study is to show the superiority in safety of Smoflipid over Intralipid as measured by the number of study patients in each treatment group with conjugated bilirubin > 2 mg/dL during the first 28 days of study treatment, confirmed by a second sample collected 7 days after the first sample.

The secondary objectives are to compare the 2 treatment arms with regards to nutritional efficacy, and to evaluate the overall safety of Smoflipid.

6.1 Study Hypothesis

The study hypothesis is that the number of study patients who develop cholestasis, defined as a conjugated bilirubin level > 2 mg/dL, during the first 28 days of study treatment and confirmed by a second sample collected 7 days after the first sample, will be significantly lower in the Smoflipid group than in the comparator group.

6.2 Study Variables

6.2.1 Primary Variable

The primary study variable is the number of patients in each treatment group with conjugated bilirubin levels > 2 mg/dL during the first 28 days of study treatment, confirmed by a second sample collected 7 days after the first sample.

6.2.2 Secondary Variable(s)

Secondary variables include:

Efficacy:

- Body weight (change from Baseline)
- Body length (change from Baseline)
- Head circumference (change from Baseline)
- Time to full enteral or oral feeds
- Fatty acids in plasma and red blood cell membranes (change from Baseline)
- Holman index

Safety:

- Length of stay in hospital
- Ratio of number of independent bloodstream infections / number of days on study medication
- Ratio of the number of patients with 1 or more bloodstream infections / number of patients on study medication
- Number of patients who complete PN treatment without lipid minimization
- Number of patients who need to be withdrawn from the study due to elevated conjugated bilirubin levels
- Area under the curve of conjugated bilirubin for time period in which levels are > 1.5 mg/dL
- Cumulative number of days patients are administered a lipid dose without lipid minimization
- Time to conjugated bilirubin > 2 mg/dL (confirmed by a second sample collected 7 days after the first)
- Conjugated bilirubin
- Total bilirubin
- Serum TGs
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl transferase (GGT)
- Alkaline phosphatase (ALP)
- Blood glucose
- Blood urea nitrogen (BUN)
- Creatinine
- C-reactive protein (CRP)
- Sterols including phytosterols
- α-tocopherol
- Collection of AE data
- Incidence of bronchopulmonary dysplasia (BPD)
- Incidence of retinopathy of prematurity (ROP)
- Incidence of intraventricular hemorrhage (IVH)

- Incidence of periventricular leukomalacia (PVL)
- Incidence of necrotizing enterocolitis (NEC)
- Incidence of late-onset sepsis in premature and low birth weight neonates

7 Study Design

7.1 Description of the Study Design

This is a prospective, randomized, controlled, double-blind, parallel-group, phase 3 multicenter study to compare safety and efficacy of Smoflipid to Intralipid in hospitalized preterm and term neonates/infants requiring 28 days of parenteral nutrition.

Treatment group 1: Smoflipid (investigational drug)

Treatment group 2: Intralipid (control drug)

The study drugs, Smoflipid and Intralipid, are lipid emulsions for infusion and will be provided in 100-mL bags. Detailed information on dose of study drug, packaging, and labelling is provided in Section 11.

The study population will be hospitalized preterm and term neonates/infants who are expected to require PN for at least 28 days. Randomization will be stratified depending on the underlying disease to ensure that those diseases are evenly distributed in both treatment groups.

Randomization group 1: No necrotizing enterocolitis (NEC)

Randomization group 2: NEC

Criteria for stratification into randomization group 2:

At least one of the following clinical signs present:
• Bilious gastric aspirate or emesis
• Abdominal distension
• Occult or gross blood in stool (no fissure)

And

At least one of the following radiographic findings present:
• Pneumatosis intestinalis
• Hepato-biliary gas
• Pneumoperitoneum

Patients who do not meet criteria for randomization group 2 will be stratified to randomization group 1.

At the Screening Visit, the signed and dated patient informed consent will be collected from the parent or guardian, demographics including race and ethnicity, medical history, prior medication, physical examination, vital signs, body weight, body length, and head circumference will be measured and documented and a blood sample will be collected to assess the eligibility of the patient (refer to Section 10.3).

Within 72 hours of the Screening Visit, the Day 1 Visit must take place, during which the eligibility of the patient must be confirmed, taking into consideration the result of the blood sample analysis. Upon confirmation of eligibility, an additional blood sample will be collected for determination of sterol, and α-tocopherol and fatty acids before the patient's random allocation to a treatment group and first infusion of study drug. Patients will receive PN, including study drug, and have their body weight assessed.

During treatment the following data must be documented daily: study drug administered, dextrose administered, amino acids administered, EN administered, body weight, AEs and concomitant medication.

During the first 28 days of treatment (initial treatment phase) physical examination findings, vital signs, body length, head circumference, conjugated bilirubin and results of biochemistry, hematology and coagulation analyses must be recorded weekly. If, at the end of the initial 28 days of treatment, PN is still indicated, patients may continue to receive the study drug until Day 84 (study extension phase).

On Day 29 the following criteria will be assessed: AEs, concomitant medications, physical examination findings, vital signs, body weight, body length, head circumference, conjugated bilirubin, results of biochemistry, hematology and coagulation analyses, α-tocopherol, sterols and fatty acids.

In the study extension phase physical examination findings, vital signs, body height, and head circumference must be recorded weekly. A blood sample for conjugated bilirubin, biochemistry, hematology and coagulation analyses will be collected every other week. However, should conjugated bilirubin exceed 1.5 mg/dL, it must be assessed weekly until conjugated bilirubin is again ≤ 1.5 mg/dL. On Day 57 and Day 85, an additional blood sample will be collected for the determination of sterols, α-tocopherol and fatty acids.

Whenever a patient receives his/her last dose of study medication, an End-of-Treatment Visit will be performed the following day. The assessments for the End-of-Treatment Visit are the same as for the Day 29 Visit. If administration of IV lipids is required after the End-of-Treatment Visit, the standard lipid emulsion used in the daily routine at the respective participating site will be used.

A Follow-Up Visit must be performed 7 days after the End of Treatment Visit. At the Follow-Up Visit, all information regarding AEs and concomitant medications since the last study medication dose will be documented, and physical examination findings, vital signs, body

weight, body length, and head circumference must be recorded. In addition, length-of-stay in the hospital will be recorded.

If at the End of Treatment visit the conjugated bilirubin level was > 1.5 mg/dL, then conjugated bilirubin must be assessed at the follow up visit and followed up until conjugated bilirubin is ≤ 1.5 mg/dL.

Study start is scheduled for Q3 2015 (first patient in), and study finish is anticipated to be Q4 2017 (last patient out).

To ensure safety of patients during their participation in the study, medical monitoring must be performed on all safety-relevant information collected during the trial: medical history, prior and concomitant medications, AEs, and laboratory results. A medical expert will be available for safety related questions 24 hours per day throughout the study.

An interim analysis will be performed once 50 patients in each group have completed the study per protocol (at least 14 days of study treatment) to calculate the final sample size (refer to Sections 8.2.2 and 8.2.68.2.6).

7.2 Rationale of Study Design, Including Choice of Control Group

Fresenius Kabi has been requested to perform a study demonstrating **superiority of Smoflipid compared to Intralipid in terms of a safety benefit** as reflected by changes in biochemical markers of liver health.

Long-term use of PN in neonates is sometimes associated with hepatic complications, including biochemical alterations (i.e., elevated bilirubin and transaminases) considered to be markers for early cholestasis (Colomb, et al. 2000, Javid, et al. 2011, Koseesirikul, et al. 2012, Pichler, et al. 2012). These biochemical alterations may worsen with prolonged PN and lipid administration and are more prevalent in neonates born at an early gestational age or in neonates with a surgical condition (Christensen, et al. 2007, Gura, et al. 2008, Javid, et al. 2011, Koseesirikul, et al. 2012).

The incidence of cholestasis in neonates receiving PN for 14 to 28 days ranges from 14% to 33%, depending on the underlying disease (Christensen, et al. 2007). Javid and colleagues reported a median time to cholestasis (defined as 2 consecutive bilirubin levels > 2 mg/dL obtained within 14 days) of 23 days in the groups of surgical neonates and 77% of the infants who developed cholestasis did so within 5 weeks of PN (Javid, et al. 2011). Consequently, a safety benefit of Smoflipid will only become visible, on average, after at least 3 weeks of PN.

The median time of exposure to PN in this patient group has been reported to be 28 days, with approximately 15% of patients still receiving PN after 3 months (8% after 6 months) (Javid, et al. 2011). As the number of patients on PN in a given population decreases over time, it may

be difficult to enroll enough patients who receive PN for more than 28 days to identify a statistically significant difference.

The major constraints for a superiority study comparing any IVLE to Intralipid are that 1) only a relatively small subgroup of patients will actually experience negative reactions to the standard soybean-oil based emulsion Intralipid, and
2) to date, no reliable markers have been identified permitting the detection of patients who may be at risk of having a negative experience with Intralipid prior to starting PN. Therefore, the present study is performed in a population which, in general, is highly sensitive to complications and drug-related side effects, including those for IVLEs (Christensen, et al. 2007). A study in this population could potentially demonstrate superiority in the safety of Smoflipid compared to Intralipid.

Superiority of Smoflipid over Intralipid will be assessed by comparing the number of patients in each treatment group developing conjugated bilirubin > 2 mg/dL within the first 28 days of study treatment, confirmed by analysis of a second serum sample taken 7 days after the first sample. The study will have an adaptive design as the effect size of Smoflipid is unknown. The data of the first 50 patients per arm that have completed the study per protocol (at least 14 days of study treatment) will be used to calculate the final sample size (refer to Sections 8.2.2 and 8.2.6).

Additionally, plasma sterol levels, including phytosterols, will be evaluated to assess whether a correlation exists between the sterol levels in the blood and the incidence of cholestasis, addressing specific concerns the FDA communicated based on experimental data (Carter, et al. 2007, El Kasmi, et al. 2013).

7.3 Randomization, Allocation of Patients

Eligible subjects will be stratified by their underlying disease:

Randomization group 1: No NEC

Randomization group 2: NEC

Criteria for adjudication to randomization group 2:

At least one of the following clinical signs present:
- Bilious gastric aspirate or emesis
- Abdominal distension
- Occult or gross blood in stool (no fissure)

And

At least one of the following radiographic findings present:
- Pneumatosis intestinalis

- Hepato-biliary gas
- Pneumoperitoneum

Patients that do not meet criteria for randomization group 2 will be stratified to randomization group 1.

Within each stratum, subjects will be randomized at Baseline in a 1:1 ratio to receive either Smoflipid or Intralipid.

Randomization will be implemented by the unblinded site pharmacist using TEMPO™ interactive web response system. Randomization allocation will be 1:1 to Smoflipid and Intralipid, respectively. 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 TEMPO™.

TEMPO™ 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.

Subjects 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 three 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 1802 will be number 1802-001. The unblinded site pharmacist will pick the study drug (either Smoflipid or Intralipid) as indicated by TEMPO™ for each randomized subject. The correctness of the picked study drug will be checked and confirmed by TEMPO™ 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.

7.4 Blinding and Decoding

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

Study drug will be delivered to the unblinded site pharmacist in cartons containing 10x 100mL bags with study drug type (Smoflipid or Intralipid) indicated on the carton. Both study drugs (investigational drug and comparator) are white emulsions and all bags will bear the same study specific label which precludes unblinding by visual inspection.

The bags will be labelled individually in accordance with the requirements of Good Clinical Practice (GCP)/Good Manufacturing Practice (GMP). The unblinded pharmacist will

implement the randomization of the patient as described in Section 7.3 and dispense individual blinded bags to the blinded site personnel to preserve the blind for investigator and study patient.

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 00001 to 25000 will be randomly assigned to Smoflipid or Intralipid to ensure that numbers are not indicative of study treatment.

Emergency subject unblinding will be managed in TEMPO™. In the event an investigator needs to unblind a study subject, authorized study personnel at the site will log into the appropriate TEMPO™ 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, TEMPO™ 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 specific treatment arm. Note that this information will also be captured in the study audit trail, so will be more secure than other forms of unblinding.

An interim analysis of the unblinded data of the first 50 patients per arm will be performed as soon as they have completed the study per protocol (at least 14 days of study treatment) in order to establish the final sample size. In accordance with the ICH Guideline E9 – Statistical Principals for Clinical Trials the execution of the interim analysis must be a completely confidential process. All staff involved in the conduct of the trial - except for those who are directly involved in the execution of the interim analysis - will remain blinded to the results of the analysis.

8 Data Management and Statistics

8.1 Data Management

This study will be monitored regularly by a Clinical Research Associate (CRA) from the CRO. The CRA will check for completion of the entries on the eCRF, compliance with the study protocol and GCP, and will compare the eCRF entries with the source data. 100% source data verification 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 reviewed by the CRA will be electronically signed 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 12.4.

8.2 Statistics

8.2.1 Study Outcome Measures

The primary outcome measure is the number of patients in each treatment group with conjugated bilirubin > 2 mg/dL during the first 28 days of study treatment, confirmed by analysis of a second sample collected 7 days after the first sample.

The secondary outcome measures are:

Efficacy:

- Body weight (change from Baseline)
- Body length (change from Baseline)
- Head circumference (change from Baseline)
- Time to full enteral or oral feeds
- Fatty acids in plasma and red blood cell membranes (change from Baseline)
- Holman index

Safety:

- Length of stay in hospital
- Ratio of number of independent bloodstream infections / number of days on study medication
- Ratio of number of patients with 1 or more bloodstream infections / number of patients who received study medication
- Number of patients who complete the PN treatment without lipid minimization
- Number of patients who need to be withdrawn from the study due to elevated conjugated bilirubin levels
-
- Area under the curve of conjugated bilirubin for time period in which levels are > 1.5 mg/dL
- Cumulative number of days patients are administered a lipid dose without lipid minimization
- Time to conjugated bilirubin > 2mg/dL (confirmed by a second sample collected 7 days after the first)
- Conjugated bilirubin
- Total bilirubin
- Serum TGs
- AST
- ALT
- GGT

- ALP
- Blood glucose
- BUN
- Creatinine
- CRP
- Sterols including phytosterols
- α-tocopherol
- Collection of AE data
- Incidence of Bronchopulmonary Dysplasia (BPD)
- Incidence of Retinopathy of Prematurity (ROP)
- Incidence of Intraventricular hemorrhage (IVH)
- Incidence of Periventricular Leukomalacia (PVL)
- Incidence of Necrotizing Enterocolitis (NEC)

8.2.2 Sample Size Estimation

Determination of sample size depends on the primary outcome measure.

There are no reliable data available on the effect size of Smoflipid compared to Intralipid 20% with respect to the primary endpoint. Depending on different assumptions a wide range of sample sizes is possible.

In the following table the sample size per group is displayed which is required for a 2-group Pearson Chi-square test with a one-sided significance level of 0.025 to have 80% power to detect the difference between groups depending on different risk probabilities p_1 (Intralipid) and p_2 (Smoflipid) for conjugated bilirubin levels > 2 mg/dL during the first 28 days of the study treatment period.

Table 1: Sample Size Calculation for Pearson Chi-Square Test for Two Proportions (alpha = 0.025 one-sided, power = 80%).

Intralipid p_1	Smoflipid p_2	Relative risk p_2 / p_1	N per Group	Performance
0.5	0.225 0.325	0.45 0.65	47 124	Best case
0.4	0.180 0.260	0.45 0.65	66 176	Average case
0.3	0.195	0.65	264	Worst case

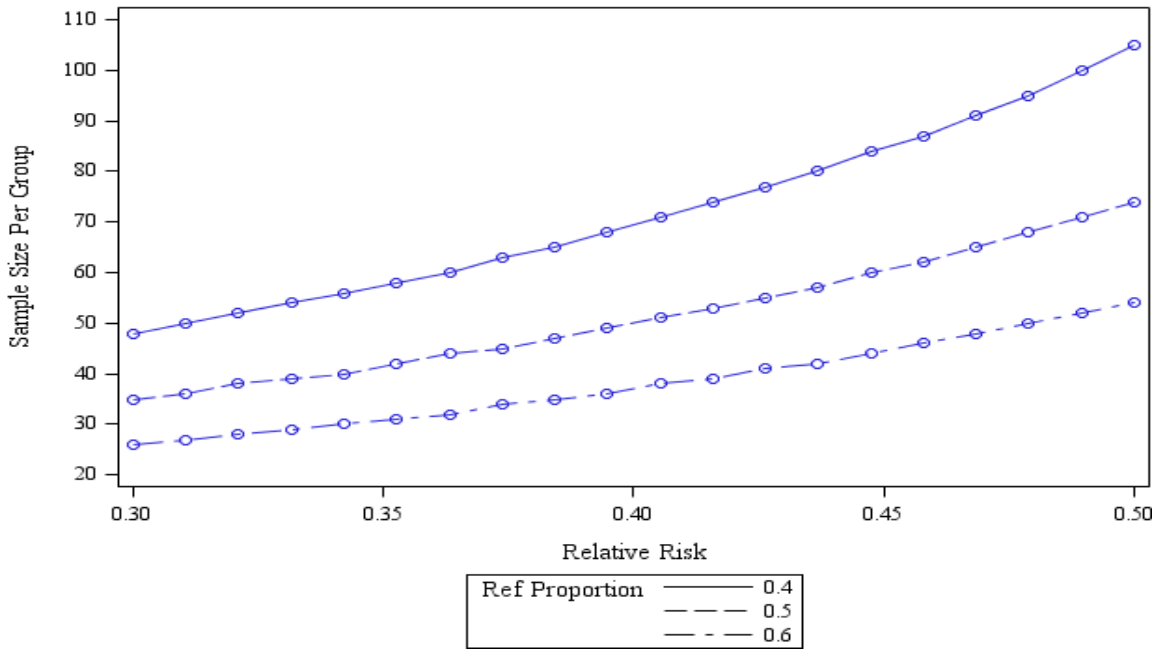
The demonstration of superiority of the safety of Smoflipid versus Intralipid is the primary objective of this study (see also Section 6). However, non-inferiority testing will be used as a gatekeeper for superiority. If superiority cannot be demonstrated with a reasonable sample size, based on the prognostic recruitment rate, the sample size may be adjusted in order to demonstrate non-inferiority instead of superiority in the final analysis. In this case non-

inferiority of Smoflipid compared with Intralipid can be shown if the upper limit of the 97.5% confidence interval (CI) would be $< \Delta = 1.2$ - the predefined limit of non-inferiority.

Based on the scenarios given above a 2-stage adaptive group sequential procedure will be performed with an interim analysis performed after 100 patients (50 patients per treatment arm) complete the study per protocol (see also Section 8.2.3 and Section 8.2.6). A maximum study size of up to 200 patients per group appears to be feasible for the scheduled recruitment period, based on recruitment estimates from the participating sites.

Depending on the probability for conjugated bilirubin levels > 2 mg/dL during the first 28 days of treatment with Intralipid and the relative risk (Smoflipid/Intralipid) there is a chance to terminate the study early after the first stage due to efficacy as visualized in the following figure. It displays the number of patients which is required for a 2-group Pearson Chi-square test with a one-sided significance level of $\alpha_1 = 0.01$ - the upper limit for the premature termination of the study at stage 1 (see Section 8.2.6) and power of 80% to detect the difference between groups.

Figure 1: Sample Sizes Needed for Pearson Chi-Square Test for Two Proportions to Achieve a Power = 80% (alpha = 0.01 one-sided).



Depending on the result of this interim analysis, the study will either be terminated prematurely based on the significance limits determined by Bauer and Köhne (Bauer, et al. 1994), or the second part of the trial will be planned with an adaptation of the sample size in an effort to demonstrate the superiority (or non-inferiority) of Smoflipid compared with Intralipid. If the interim analysis results in an adaption of the sample size that exceeds the maximum study size of up to 200 patients per group, the study will be stopped prematurely for futility after the interim analysis.

8.2.3 Hypothesis Testing

A detailed and comprehensive Statistical Analysis Plan (SAP) will be prepared and signed before the study is unblinded (i.e., before the interim analysis). Any changes to the statistical methods set out in this protocol need not be reported as a protocol amendment, but must be documented in the SAP and the Clinical Study Report.

The confirmatory analysis is based on the primary efficacy endpoint (number of patients in each treatment group with conjugated bilirubin > 2mg/dL during the first 28 days of treatment confirmed by analysis of a second sample collected 7 days after the first sample).

Two hypotheses will be tested stepwise:

- $H1_0$: Smoflipid is inferior to Intralipid
  $H1_A$: Smoflipid is equal or superior to Intralipid
- $H2_0$: Smoflipid is equal to Intralipid
  $H2_A$: Smoflipid is superior to Intralipid

$H2_0$ will be tested only if $H1_0$ can be rejected. In this case, there is no multiplicity argument because it corresponds to a simple closed test procedure.

The global significance level will be one-sided (0.025) for non-inferiority as a gatekeeper for superiority. Non-inferiority will be investigated using confidence intervals with a predefined margin of 1.2 for the risk ratio. Superiority will be based on statistical hypothesis testing (p-value)

The intention to treat (ITT) population will be the primary population for demonstration of superiority. The primary analysis of non-inferiority will be performed using the per protocol population.

An interim analysis will be performed after 100 patients in total (50 in each arm) have completed the study per protocol. Depending on the result of the interim analysis, the study will either be continued with an adapted sample size (if required and feasible) at a power of at least 80%, to achieve a statistically meaningful result or terminated prematurely on the basis of significance limits according to Bauer and Köhne (Bauer, et al. 1994) or – if the interim analysis results in an adaption of the sample size that exceeds the maximum study size of up to 200 patients per group – the study will be stopped prematurely after the interim analysis for futility and be analysed descriptively and in an exploratory way.

The demonstration of superiority of the safety of Smoflipid versus Intralipid is the primary objective of the present study. Only if it is determined that superiority cannot be demonstrated with a feasible sample size, based on the prognostic recruitment rate, the final analysis will attempt to demonstrate at least non-inferiority. If even non-inferiority cannot be demonstrated with a feasible sample size the study will be stopped prematurely after the interim analysis for futility and will be analysed descriptively and in an exploratory way. This adaptation – especially

the drop of confirmatory hypotheses – is considered appropriate because the respective statistical tests will suffer from a serious lack of power and cannot provide appropriate results for reliable decisions on the study hypotheses. This situation will be discussed with the FDA at that time prior to terminating the study prematurely to determine the feasibility of converting it to a non-inferiority study due to considerations of sample size. At present a maximum study size of 200 patients per group appears to be feasible for the scheduled recruitment period

The null-hypotheses will be analyzed stratified by the patients' underlying diseases (randomization group 1 or 2, see section 7.3) using the estimates of the common relative risk - controlling for stratum (non-inferiority hypothesis) - and the Cochran-Mantel-Haenszel statistics of general association for the combined strata (hypothesis of superiority).

The analysis of non-inferiority will be performed using the per-protocol population; superiority has to be shown on base of the intention-to-treat (ITT) population. Sensitivity analyses will be performed using the ITT population for demonstrating non-inferiority and the per protocol population for demonstrating superiority.

Exploratory subgroup analyses will be performed by race and ethnicity.

8.2.4 Blinded Review / Final Statistical Analysis Plan

The Sponsor will convene a Blinded Data Review after the data have been cleaned, but before the study is unblinded (i.e., interim analysis). The review will be performed within the framework of the requirements of ICH E9.

The terms of reference of the Blinded Data Review shall include, but not be limited to:

- the determination of whether protocol violations are 'major' or 'minor'
- the allocation of patients to analysis sets
- a review of missing data and outliers, their assessment and definition of handling
- a review of the distribution of the efficacy variables, considering any implications for the proposed methods for statistical analysis
- a review of whether additional covariates need to be included in the analyses
- the finalization of the SAP

The Blinded Data Review Report will include the definition of major and minor protocol deviations and the final allocation of patients to analysis sets.

The Blinded Data Review Report will be finalized before the blind will be broken. Formal records shall be kept of when the statistical analysis plan was finalized as well as when the blind was subsequently broken.

8.2.5 Definition of Populations

Safety population
The safety analysis set will consist of all randomised patients who received at least one dose of study medication.

Intention-to treat (ITT) population)
The primary confirmatory analysis of superiority will be performed using the ITT population. The ITT analysis set will consist of all randomised patients.

Per protocol (PP) population (main analysis) set
The primary analysis of non-inferiority will be performed using the PP population. The PP analysis set includes all patients who receive study drug for at least 14 days without major protocol violations. Major protocol deviations are those that may significantly impact the completeness, accuracy, and/or reliability of the study data. A patient may be excluded from the PP analysis set for, but not limited to, any of the following conditions:

- Patient does not meet critical inclusion/exclusion criteria
- Patient is removed from the study prior to day 28 for other reasons than elevated conjugated bilirubin levels
- Incorrect administration of study product

A blinded review will be performed before breaking of the blind in order to assess and define the handling of missing data, data issues as well as to classify major and minor protocol violations. The final allocation of patients to analysis sets will be performed during the blinded review as described in Section 8.2.4.

8.2.6 Interim and Final Analysis

A two-stage adaptive group-sequential procedure will be performed, using a global significance level of α=0.025. After 100 patients in total (50 in each arm) have completed the study per protocol an interim analysis will be performed. For the interim analysis, the following limits for a premature termination of the trial will be defined (Bauer, et al. 1994):

$\alpha_0 = 0.5$	lower limit for the premature termination of the trial with negative result
$\alpha_1 = 0.0102$	upper limit for the premature termination of the trial with rejection of the null-hypothesis

According to the one-sided formulation of the alternative hypotheses all p-values and confidence intervals in the following sections must be calculated one-sided.

At the interim analysis the primary efficacy criterion will be assessed as described in Section 8.2.3 at the significance level α_1. The null-hypothesis $H1_0$ can be rejected if the upper limit of the $(1-\alpha_1)\cdot 100\%$ CI is less than 1.2 (related to the NI hypothesis), $H2_0$ can be rejected if the corresponding p-value p_1 is less than α_1 (hypothesis of superiority). In this case the study may be terminated early due to efficacy.

If the upper bound of an $(1-\alpha^*)\cdot 100\%$ CI is less than 1.2 only for $\alpha^* \geq \alpha_0$ the null hypotheses will be considered accepted which allows early termination due to lack of efficacy.

If non-inferiority cannot be shown at the time of the interim analysis, but the upper-bound of the $(1- \alpha^*)\cdot 100\%$ CI is less than 1.2 for any α^* with $\alpha_1 < \alpha^* < \alpha_0$ (non-inferiority hypothesis) then the second part of the trial will be planned with an adaptation of the sample size. The results of the interim analysis at stage 1 influence the second stage as follows:

Let $p_1 = \min(\alpha^* |$ upper bound of $(1-\alpha^*)\cdot 100\%$-CI is $< 1.2)$ the actual level of significance for non-inferiority at stage 1. In order not to exceed the global significance level $\alpha = 0.025$, the corresponding level of significance in the second stage p_2 needs to satisfy $p_1 * p_2 \leq 0.0038$. Thus, the required number of patients can be calculated for the significance level $p_2 = 0.0038/p_1$ (i.e., non-inferiority of Smoflipid compared to Intralipid is shown if the upper limit of the $(1- p_2)\cdot 100\%$ CI is < 1.2 at the second stage).

To determine the sample size necessary to prove superiority of Smoflipid compared to Intralipid after non-inferiority is shown at the second stage of the study, the p-value p_1' of the actual difference between Smoflipid and Intralipid at the first stage will be calculated. It determines the level of significance $p_2' = 0.0038/p_1'$ at which $H2_0$ must be tested after $H1_0$ is rejected at the second stage in order not to exceed the global one-sided significance level $\alpha = 0.025$.

If $H1_0$ can be rejected at the significance level α_1 but $\alpha_1 < p_1' < \alpha_0$ with p_1' the p-value of the actual difference between Smoflipid and Intralipid at the first stage, then the second part of the trial will be planned with an adaptation of the sample size in order to enable rejection of the null hypothesis $H2_0$ (superiority). Similar to the explanation in the preceding section, the required number of patients can be calculated for the significance level $p_2' = 0.0038/p_1'$.

Additionally, the risk ratio between Smoflipid and Intralipid with respect to the primary outcome parameter observed in the first part of the trial will be taken as a basis for the relevant difference when adapting sample size for the second part of the study.

The conditional power for planning stage 2 should be at least 80%.

If the resulting sample size for the second part of the study with respect to the non-inferiority hypothesis is greater than the prognostic recruiting rate the study will be terminated after the first part of the study. Based on current estimates a maximum study size of 200 patients per group may be feasible for the scheduled recruitment period. In this case all data will be analysed descriptively and in an exploratory way. Confirmatory hypothesis testing will be dropped because the respective statistical tests will suffer from a serious lack of power and cannot provide appropriate results for reliable decisions on the study hypotheses.

To assure the stochastic independence of the two p-values, both trial parts must be analysed separately. This procedure ensures a global significance level of $\alpha = 2.5$ %.

In accordance with ICH E9, the execution of the interim analysis must be a completely confidential process. All staff involved in the conduct of the trial - except for those who are directly involved in the execution of the interim analysis - will remain blinded to the results of the analysis. Investigators will only be informed about the decision to discontinue the trial if

the trial will be terminated prematurely based of the result of the interim analysis. A second statistician, other than the trial statistician, and who is independent from the study will conduct the interim analysis. Further details will be provided in the interim analysis plan and/or Data Safety Monitoring Board (DSMB) charter.

After the interim analysis, the Statistical Report will be forwarded to an independent DSMB (refer to Section 13.5).

8.2.7 Analysis of Secondary Outcome Measures

Exploratory analysis of the secondary outcome measures for efficacy and safety as described in Section 8.2.1 will be performed comparing both treatment groups:

Summary tables will be presented. Between groups comparisons will be performed with adequate statistical tests (e.g. repeated measurement analyses examining the course of variables over time, the Kaplan-Meier method for time to event measures, Wilcoxon tests for continuous and Fisher's exact tests for binary outcome measures). The corresponding effect size measures and confidence intervals will be presented in addition.

If the study is stopped prematurely after the interim analysis because the required sample size to demonstrate superiority or non-inferiority for the primary outcome measure is too large to be feasible, the analyses of secondary outcome measures will be performed only with descriptive statistics and the statistical tests planned above will be dropped.
(In some cases, model-based analyses (such as competitive risk analysis) might be used to examine differences between treatment groups since they provide helpful parameters to describe treatment effects. Respective results will only be interpreted in an exploratory and descriptive manner. Details will be planned in the SAP for the final analyses.)

Adverse events (AEs) will be categorized by primary system organ class. The number, intensity, relation to study medication and action taken will be described by frequency tables. Serious adverse events will be discussed separately.

The analysis of the secondary efficacy outcome parameters will be performed using the ITT population (intention-to-treat) and the per protocol population (per protocol) in the sense of sensitivity analyses.

The analysis of the secondary safety outcome parameters will be performed using the safety population.

A comprehensive SAP covering the details of all methods used to analyze the various parameters will be prepared before unblinding. The SAP will be reviewed, and if needed, updated before unblinding.

8.3 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 and will not have any additional assessments.

9 Study Duration

The patients may receive the study drug up to Day 84. Every patient who has a conjugated bilirubin level > 1.5 mg/dL will be followed up until the conjugated bilirubin level returns to ≤ 1.5 mg/dL.

10 Patient Selection

10.1 Study Population

Long-term use of PN may be associated with hepatic complications, including biochemical alterations (i.e., elevated bilirubin and transaminases) considered to be markers reflecting the beginning of cholestasis (Colomb, et al. 2000, Javid, et al. 2011, Koseesirikul, et al. 2012, Pichler, et al. 2012). These biochemical alterations may worsen with prolonged lipid administration as part of PN and are more prevalent in neonates born at an early gestational age or in neonates with a surgical condition (Christensen, et al. 2007, Gura, et al. 2008, Javid, et al. 2011, Koseesirikul, et al. 2012).

Identifying these patients at the beginning of the PN regimen who may experience these hepatic complications is not possible (Christensen, et al. 2007). This study must therefore be performed in a population with a high likelihood of developing hepatic complications during prolonged PN to increase the chances to obtain a statistically significant result. According to literature, the incidence of cholestasis in surgical neonates who received PN for 14 to 28 days ranges from 14% for patients with diaphragmatic hernia to 33% for patients with jejunal atresia (Christensen, et al. 2007). Other indications related to a high incidence of PN-associated hepatic complications include surgical NEC (including spontaneous intestinal perforations; 33%), gastroschisis (18%), volvulus and spontaneous intestinal perforations (Christensen, et al. 2007, Javid, et al. 2011).
While the incidence of PNALD increases with the duration of PN, the number of patients requiring PN decreases rapidly with the duration of the PN (Javid, et al. 2011). The study treatment duration of 28 days was chosen as a compromise between the minimum duration to observe enough cases of PNALD and a maximum duration that still allows recruiting enough patients to obtain statistically significant results.

10.2 Inclusion Criteria

1. Neonates and infants, expected to require PN for 28 days

2. Postmenstrual age ≥ 24 weeks

3. Birth weight ≥ 750 g

4. Gastroschisis, duodenal, jejunal or ileal atresia, volvulus, spontaneous intestinal perforation, or NEC (Bell's stage 2B or higher)

5. At least 80% of nutritional needs at Baseline are met with PN

6. Signed and dated informed consent obtained from at least 1 parent or legal guardian

10.3 Exclusion Criteria

1. Conjugated bilirubin > 0.6 mg/dL

2. Any known pre-, intra- or posthepatic complication that will increase conjugated bilirubin levels > 0.6 mg/dL during study participation

3. Suspected liver disease or damage based on either AST, ALT, or GGT exceeding 2.5 × upper limit of normal range

4. Active bloodstream infection demonstrated by positive blood culture at screening

5. Cystic fibrosis

6. Meconium ileus

7. Serum TGs > 250 mg/dL

8. Cyanotic congenital heart defect

9. Severe renal failure as evidenced by creatinine > 2.0 mg/dL

10. History of shock requiring vasopressors

11. Anasarca

12. Extracorporeal Membrane Oxygenation (ECMO)

13. Known inborn errors of metabolism

14. Known congenital viral infection

15. Unlikely to survive longer than 28 days

16. Known hypersensitivity to fish-, egg-, soya- or peanut protein, or to any of the active substances or excipients

10.4 Withdrawal of Patients from the Study

Patients withdrawn from study after randomization but before receiving any study drug will be counted as "early drop-outs". These patients will be replaced and will not undergo additional assessments.

The patient's parent or guardian 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 guardian(s) refuses to have the patient continue with study participation, patient's parents or legal representatives should be asked to allow that the assessments for the Final Visit the day after receiving the last dose of study medication are completed. The reason(s) for study withdrawal must be documented.

Patients who are withdrawn from the study due to AEs or SAEs will be treated and followed according to established medical practice to evaluate the course of the AE and ensure reversibility or stabilization (also see Section 13).

The following are justifiable reasons for the Investigator to withdraw a patient from the study:

- Intolerable AEs/SAEs
- Deteriorating liver function (see below)
- Unacceptable risk/benefit ratio
- Major protocol deviation(s)

Major protocol deviations are those that may significantly impact the completeness, accuracy, and/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.

Fresenius Kabi reserves the right to discontinue the entire study for internal reasons at any time (see also Section 16.3).

Withdrawal Due to Deteriorating Liver Function

If conjugated bilirubin levels exceed 2 mg/dL, a confirmatory sample must be assessed after 7 days. If conjugated bilirubin levels have increased by at least 1 mg/dL, the Investigator must withdraw the patient from the study so the patient can receive an alternative lipid emulsion according to standard of care. If conjugated bilirubin levels increased less than 1 mg/dL, the patient will remain in the study and continue to receive study medication. Weekly conjugated bilirubin analyses must be performed until the patient's conjugated bilirubin level is again ≤ 1.5 mg/dL.

11 Study Drugs and Medication

11.1 Characterization of the Investigational Drug

Smoflipid is a lipid emulsion containing soybean oil, MCTs, 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.

1000 mL of emulsion for infusion contain:

Active ingredients:	
Soya-bean oil	60.0 g
Triglycerides, medium-chain	60.0 g
Olive oil, refined	50.0 g
Fish oil, rich in omega-3-acids	30.0 g
Excipients:	
Glycerol (anhydrous)	25.0 g
Purified egg phospholipids	12.0 g
all-*rac*-α-Tocopherol	163 to 225 mg
Water for Injection	ad 1000 mL
Sodium hydroxide for pH adjustment	pH approx. 8
Sodium oleate	0.3 g
Total energy	8.4 MJ/L (= 2000 kcal/L)
pH-value	6 to 9
Osmolality	approx. 380 mOsm/kg
Osmolarity	270 mOsm/L

Smoflipid is manufactured at the Fresenius Kabi facilities in Uppsala, Sweden. The Fresenius Kabi plant in Uppsala has been inspected and approved by the FDA for production of parenteral emulsions (e.g., Intralipid).

11.2 Characterization of the Control Drug

Intralipid is a long-chain triglyceride emulsion derived from purified soybean oil and egg yolk phospholipids. 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.

1000 mL of the emulsion contains:

Active ingredients:	
Soybean oil	200 g
Excipients:	
Glycerol (anhydrous)	22.5 g
Egg yolk phospholipids	12 g
Sodium hydroxide for pH adjustment	pH approx. 8
Water for injections	ad 1000 mL
Total energy	8.4 MJ/L (= 2000 kcal/L)
pH-value	6 to 8.9
Osmolality	approx. 350 mOsm/kg water
Osmolarity	260 mOsm/L

11.3 Preparation, Administration and Dosage of Investigational Medicinal Products

Both products will be delivered to the hospital pharmacists in 100 mL bags together with the appropriate documentation (e.g., Certificates of Analysis).

Storage conditions (e.g., temperature) of the final product should follow the instructions of the pharmacists. Independent from the pharmacy instructions, the final product is not allowed to be frozen or stored > 25°C.

The hospital pharmacist(s) will compound all PN components following the Investigator´s prescription and according to local regulations and procedures. Only those PN products and combinations are allowed during the study treatment period which have been agreed upon with Fresenius Kabi and for which compatibility tests have been performed.

The dosage of other macro- and micronutrients should reflect applicable guidelines such as those published by the American Society for Parenteral and Enteral Nutrition (ASPEN):

Amino acids:

Infants	Initiation	Advance by	Goal
preterm	1.5-3.0 g/kg/day	1.0 g/kg/day	3.0-4.0 g/kg/day
term	1.5-3.0 g/kg/day	1.0 g/kg/day	2.0-3.0 g/kg/day

Dextrose:

Infants	Initiation	Advance by	Goal
preterm	5.0-7.0 mg/kg/min	1.4-1.7 mg/kg/min	8.0-18.0 mg/kg/min
term	6.0-9.0 mg/kg/min	3.5 mg/kg/min	12.0-18.0 mg/kg/min

Trace elements, electrolytes and vitamins will be provided according to the Investigator's prescription, hospital practice approved by Fresenius Kabi and applicable guidelines.

Use and dose of heparin and carnitine must be documented.

Amino acid solution together with dextrose and micronutrients (trace elements, electrolytes, vitamins), heparin and carnitine may be mixed together in one container.

The study drug will be assigned according to the randomization scheme and administered separately. No total nutrient admixtures will be allowed using the study drug.

The type of venous access should follow clinical routine and is in the responsibility of the Investigator considering variables such as osmolarity.

In case of administration via a central vein, lipid will be connected to a Y-connector before entering the body. All required compatibility data will be provided by Fresenius Kabi.

The target lipid dose is 3 g/kg/day. In patients that are already receiving PN before starting study treatment, the lipid dose will either stay at 3.0 g/kg/days or increased in 1g/kg/days steps to a maximum of 3.0 g/kg/day. In patients that have not yet started PN prior to study participation, lipid dose will be increased stepwise using the following regimen:

Study Day	Patients < 1500 g	Patients ≥ 1500 g
Day 1	1.0 g/kg/day	2.0 g/kg/day
Day 2	2.0 g/kg/day	3.0 g/kg/day
Day 3+	3.0 g/kg/day	3.0 g/kg/day

The investigational or control drug will be infused over 20 - 24 hours, as per hospital policy, at a weight based infusion rate. The respective hospital policy will be filed in the investigator site file. If the blood draw is from the PN/lipid infusion line, then lipid (study drug) should be held for 4 hours prior to the time of blood sampling.

Blood samples for TGs and blood glucose monitoring during dose ramp-up will be taken as follows:

Neonates < 1500 g: At 1 g/kg/day, 2 g/kg/day and first dose of 3 g/kg/day
Neonates ≥ 1500 g: At first dose of 3 g/kg/day

Once the target dose has been reached, TGs must be checked weekly.

Should TGs exceed 250 mg/dL at any time, lipids will be withheld until analysis of another blood sample the following morning. If TGs are then ≤ 250 mg/dL, lipids will be restarted. If not, this procedure will be repeated the next morning.

Conjugated bilirubin values must be assessed weekly. If the conjugated bilirubin level exceeds 1.5 mg/dL, the lipid dose must be decreased to 1 g/kg/day. Dextrose will be increased accordingly to maintain adequate energy provision. Once the lipid dose is minimized to 1 g/kg/day, it will not be increased again.

If conjugated bilirubin exceeds 2 mg/dL the patient's dose will remain at 1 g/kg/day until analysis of the next weekly blood sample. If conjugated bilirubin has increased further by at least 1 mg/dL, the patient must be withdrawn from the study and the Investigator will use institutional standard of care for the provision of PN. If not, the patient will remain in the study and will continue to receive study medication. Weekly conjugated bilirubin analyses should be performed until the patient's conjugated bilirubin level is again ≤ 1.5 mg/dL.

As soon as the patient receives 80 mL/kg/day oral/enteral feeds and achieved sustained tolerance (i.e. at least 3 days), the dose of study drug will be reduced to 1 g/kg/day. Patients will be weaned off study drug upon receiving 100 mL/kg oral/enteral feeds and achieving sustained tolerance (i.e. at least 3 days).

The expected administration of study drug for each patient should be at least 28 days. If PN is still indicated at the end of 28 days, patients may receive the study drug for up to Day 84 (refer also to Section 12.2.4). If administration of parenteral lipids is required after termination of the 12 week study period, the standard lipid emulsion used at the respective participating site will be used.

11.4 Compliance

Study drug will be administered under the supervision of the (Sub-) Investigator and documented in the eCRF.

In the hospital pharmacy the CRA (refer also to Section 14.1) will perform checks of any used/unused study medication in the context of drug accountability.

Any interruption of the study drug infusion for longer than 4 hours has to be explained and documented in the eCRF. Any other deviations from planned infusions will be documented in the eCRF.

11.5 Supply, Packaging, Labelling and Storage

Fresenius Kabi will provide the Investigator with a sufficient amount of study medication together with the respective Certificates of Analysis and a temperature record documenting the temperature of the study medication during the transport to site.

The study mediation will be provided in 100 mL bags. The bags of both study drugs are labelled with the same study specific blinded clinical label. To ensure the traceability of each bag of the study drugs, each bag is labelled additionally with a uniquely numbered bag label according to a bag ID list provided to Fresenius Kabi manufacturing operations, as described in Section 7.4. All manufacturing and labelling operations are performed in accordance with the requirements of Good Manufacturing Practice (GMP)/Good Clinical Practice (GCP) and local regulations by authorized personnel. The information included on the clinical labels is attached to this protocol in Annex 1.

Study drugs will be delivered to the unblinded site pharmacist in cartons with non-blinded clinical labels (Smoflipid or Intralipid) containing 10 x 100mL bags. In addition to the study drugs, subject randomization tear-off labels will be delivered to the unblinded site pharmacist. The unblinded pharmacist will implement the randomization of the patient as described in Section 7.3. The pharmacist will affix an additional label with the subject (randomization) number onto the overpouch (secondary bag) of the study drug prior to dispensing the individual blinded bags to the blinded site personnel to preserve the blind for investigator and study patient relatives.
The investigator will receive blinded and randomized study drug. Directly prior to administration, the investigator will open the overpouch and transfer the label with the subject (randomization) number from the overpouch to the primary bag for the time of the duration of the infusion.
Throughout the study and until administration, the drugs will be stored in a securely locked area, only accessible to authorised personnel, at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
TEMPO™ will automatically record the use of study medication and order resupply when the trigger value has been reached.
Samples of the clinical supplies used in a clinical study must be retained by the organization that conducted the study and stored under conditions that will maintain the integrity, identity, strength, quality, and purity of the samples. Therefore, reference samples of each study drug will be kept by Fresenius Kabi. The retention period is at least 2 years after completion or formal discontinuation of the present clinical trial. Any reference samples must be retained and stored under conditions consistent with product labelling in a segregated area, locked, and with limited access.

11.6 Return of Study Materials and Study Drugs

Unused study documentation forms and any unused study drug will be returned to Fresenius Kabi (or a designated provider) for destruction at the end of the study or earlier. Alternatively, after written notice from Fresenius Kabi, unused forms and study medication may be destroyed at the investigational site. Destruction will be documented. Any used bags can be destroyed after the drug accountability check by the pharmacist, Investigator, or study nurse.

11.7 Drug Accountability (Delivery, Receipt, Storage, Use, Return)

Receipt of study medication (investigational/control medication), as well as return of any

unused medication will be documented by the Investigator in TEMPO™. The study medication is property of Fresenius Kabi and must not be provided to third parties. It will be stored separately and safely and will be used exclusively for this study as described in this protocol. Any use of study medication is documented on each patient's eCRF. At the end of the study, the Investigator will have to explain any discrepancies between delivery, use, and return of study drug (drug accountability).

11.8 Concomitant Medication

From the time of receipt of the signed/dated informed consent form and throughout the trial period, any concomitant medication will be allowed as clinically needed to treat concomitant diseases with the exception of:

- Beta-carotene, Lutein, Lycopene, Selenium, Vitamin A, Vitamin C and Vitamin E as sole additives
- Any IV lipid emulsion other than the study medication
- Enteral administration of fish oil

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

Concomitant nutrition, including enteral and oral feeding and also micronutrients, will be documented in the eCRFs during the study (type, dosage, route, caloric content).

Heparin and carnitine used in the PN will be documented on a specific eCRF page, as they are not related to a specific underlying disease but part of the PN regimen.

12 Study Schedule

12.1 Summary of Procedures

Please refer to the study schedule (Section 2) for a complete overview of all procedures to be performed at the individual study visit. All procedures must be documented in the eCRF.

12.2 Detailed Description of Investigations

12.2.1 Screening Visit

The Screening Visit has to take place no more than 3 days before the Day 1 visit.

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

Informed consent process

A signed/dated informed consent form must be obtained from the patient's parent(s) or

legal guardian(s) prior to the performance of any study related procedures or evaluations.

The parent(s) or guardian(s) of the patient will be informed of the nature of the study by the Principal Investigator or a designated Investigator of the study team to whom the Principal Investigator has delegated this task as documented on the study responsibility log. The parent(s) or guardian(s) will also receive a copy of the "parent information sheet".

The Investigator will inform the parent(s) or guardian(s) of the patient regarding the 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 guardian(s) of the neonate or infant will be given the opportunity to discuss the aspects of the study, ask questions about the study, and have those questions answered by the Investigator.

The parent(s) or guardian(s) of the neonate or infant will be allowed sufficient time to consider this information.
Two copies of the informed consent form will have to be signed and dated by the parent(s) or guardian(s) and Investigator; one copy will be provided to the parent(s) or guardian(s) of the neonate or infant, and the other copy will be kept in the investigator's site file and the date of consenting will be documented in the patient's medical file. The patient's medical file must also document that the parent(s) or guardian(s) provided consent prior to participation in the study.

Review of inclusion and exclusion criteria

The patients will be assessed for eligibility (Section 10.2 and Section 10.3). The patient will be enrolled in the study only 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 enrolled.

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

Additional procedures performed or assessed during the screening visit:

- Recording of demographic data:
  - age, defined as postmenstrual age in weeks
  - date of birth
  - sex

- race
- ethnicity

- Assignment of patient number and completion of the screening log

- Recording of physical examination findings and body weight
  - physical inspection
  - body weight

- Recording of vital signs
  - blood pressure (systolic and diastolic)
  - heart rate
  - body temperature

- Recording of the patient's medical history

- Recording of prior medications (e.g., medications prescribed / taken prior to obtaining signed and dated informed consent)

- Collection of blood sample for local laboratory analysis of the following parameters:
  - Biochemistry: total bilirubin, AST, ALT, GGT, ALP, TGs, creatinine, glucose, CRP
  - Hematology: CBC, leukocytes, platelets, erythrocytes, hemoglobin, hematocrit
  - Coagulation: INR

- Collection of a blood sample for central laboratory analysis of conjugated bilirubin

12.2.2 Baseline Visit/Day 1

During Baseline Visit, the patient receives the first dose of study medication. Thus, the day of this visit is defined as Day 1. All other Visits and Study Days are relative to the Baseline Visit; therefore, there is no time window defined for the Baseline Visit.

Prior to randomization and administration of the first dose of study drug, the Investigator must review the results of the analysis of the blood sample collected at the Screening Visit to ensure that none of the exclusion criteria is met.

If none of the exclusion criteria related to the laboratory analysis are met, the Investigator can proceed with the procedures for the Baseline/Day 1 Visit in the following sequence:

- Confirmation that all eligibility criteria are still fulfilled

- Collection of a blood sample for the specialized lab analyses (fatty acids, sterols and α-tocopherol) in babies that can tolerate the blood draw (1mL)

- Recording of physical examination findings and body measurements

- physical inspection
- body weight
- body length measured by a length board
- head circumference

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

- Randomization to study drug

- Administration of study drug in PN regimen

- Recording of oral, enteral, and parenteral nutrition

- Recording of AEs

- Recording of concomitant medication

12.2.3 Daily Assessments During Treatment Phase

During treatment, the patient receives study medication every day and the following patient data will have to be documented daily:

- Amount of study drug administered (dose in g/kg/day and volume in mL)

- Dose of dextrose administered (mg/kg/min)

- Dose of amino acids administered (g/kg/day)

- Amount of parenteral nutrition administered excluding study drug (volume and caloric content)

- Amount of enteral nutrition administered (volume and caloric content)

- Oral nutrition administered (volume and caloric content)

- Body weight

- Adverse events

- Concomitant medication

12.2.4 Treatment Visits

All treatment visits should occur in a time window of ±1 day relative to the scheduled day of

the visit.

The following procedures will be performed at each treatment visit:

- Recording of physical examination and body measurements
  - physical examination
  - body weight
  - body length measured by a length board
  - head circumference

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

Additional procedures performed only on visits on Days 8, 15, 22, 43, 57 and 71:

- Collection of a blood sample for local laboratory analysis of the following parameters:
  - Biochemistry: total bilirubin, AST, ALT, GGT, ALP, TGs, creatinine, glucose, CRP
  - Hematology: CBC, leukocytes, platelets, erythrocytes, hemoglobin, hematocrit
  - Coagulation: INR

- Collection of a blood sample for central laboratory analysis of conjugated bilirubin

Additional procedures only performed on visit on Day 57:

- Collection of a blood sample for the specialized lab analyses (fatty acids, sterols and α-tocopherol)

12.2.5 Day 29, Day 85, and End-of-Treatment Visit

The same procedures have to be performed on Day 29 (end of initial treatment phase), Day 85 (end of treatment extension phase), and the first day after receipt of the last dose of study medication (End-of-Treatment Visit), independent of the reason for which the study medication was stopped.

Conditions for continuing in the study after Day 29 / End-of-Treatment Visit:

Patients may continue in the study after the Day 29 / End-of-Treatment Visit if:

- PN is still indicated,
  and/or
- Conjugated bilirubin > 1.5 mg/dL

If the patient will continue to receive PN into the study extension phase (after Day 28) and later

weaned from study medication with a conjugated bilirubin value ≤ 1.5 mg/dL, then the End-of-Treatment Visit must be performed on the first day after receipt of the last dose of study medication.

If the patient has been weaned from study medication with a conjugated bilirubin value > 1.5 mg/dL, the patient needs to complete the End-of-Treatment Visit on the first day after receipt of the last dose of study medication, but will continue to be followed up until conjugated bilirubin levels are ≤ 1.5 mg/dL. Conjugated bilirubin levels must be assessed weekly until they are ≤ 1.5 mg/dL. As the patient will receive no study medication after the End-of-Study Visit, no additional evaluations will be performed.

If consent is withdrawn, the parent(s) or guardian(s) of the patient should be encouraged to allow the patient to complete scheduled evaluations, including the End-of-Treatment Visit evaluations and the Follow-Up Visit, and informed that the patient will be given appropriate care under medical supervision until any ongoing AEs resolve or until the patient's condition becomes stable.

No patient will receive study medication beyond Day 84 of the study.

The following procedures will be performed

- Recording of physical examination and body measurements
  - physical inspection
  - body weight
  - body length measured by a length board
  - head circumference

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

- Collection of a blood sample for local laboratory analysis of the following parameters:
  - Biochemistry: total bilirubin, AST, ALT, GGT, ALP, TGs, Cr, glucose, CRP
  - Hematology: CBC, leukocytes, platelets, erythrocytes, hemoglobin, hematocrit
  - Coagulation: INR

- Collection of a blood sample for central laboratory analysis of conjugated bilirubin

- Collection of a blood sample for the specialized lab analyses (fatty acids , sterols and α-tocopherol) (1mL)

- Time to full enteral or oral feeds (if study treatment ended)

- Recording of AEs

- Recording of concomitant medication

Note: Should the End-of-Treatment Visit be performed within the study extension phase and <2 weeks after the collection of the last blood samples for the specialized lab analyses, then this blood sample will not be collected again at the End-of-Treatment Visit

12.2.6 Additional Assessments

During the course of the study, blood samples will need to be collected in order to monitor TGs. This monitoring will occur whenever the lipid dose is changed:

- During initial increase in lipid dose
- With lipid pause or reduction due to increased plasma TG > 250 mg/dL

Investigators must collect blood samples for blood cultures in case of clinical symptoms of a bloodstream infection.

Bloodstream infections will be considered independent if at least one blood culture analysis between two positive blood cultures has given a negative result.

These additional assessments will be performed at the local laboratory of the individual site.

12.2.7 Follow-Up Visit

The Follow-Up Visit will be performed 7 days after the End-of-Treatment Visit to ensure the safety of the patient after study participation.

The following procedures have to be performed:

- Recording of adverse events
- Recording of concomitant medication
- Recording of physical examination and body measurements
  - physical examination
  - body weight
  - body length measured by a length board
  - head circumference
- Recording of vital signs
  - blood pressure
  - heart rate
  - body temperature
- Recording of Length of Stay in the hospital

- Recording of AEs
- Recording of concomitant medication

The Length of Stay in the hospital will be calculated using the worksheet provided in Annex 4 to this protocol.

All unresolved AE and SAEs will be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the adverse event is otherwise explained.

All patients that had conjugated bilirubin levels >1.5 mg/dL at the Follow up visit will have the conjugated bilirubin level assessed at the Follow-Up Visit, and then it should be assessed weekly until conjugated bilirubin is again ≤ 1.5 mg/dL.

12.3 Methods

12.3.1 Experimental and Analytical Methods

Assessment of Body Length
Body length of the patients will be assessed in lying position with the help of a length board.

Assessment of Body Weight
Scales used for measuring body weight of patients must be calibrated and revised according to applicable local requirements. The relevant documentation must be updated and available on request.

Calculation of Length-of-Stay
Length of stay in hospital will be calculated using the Worksheet from Annex 4 to the protocol.

12.3.2 Laboratory Variables

12.3.2.1 Standard Laboratory Values Including Conjugated Bilirubin

Determination of the standard laboratory values will be assessed using established validated techniques at the local laboratory of the site except for **plasma conjugated bilirubin** which **will be assessed using established validated techniques at the central laboratory**:

[redacted]

The following parameters will be assessed at the local laboratory:

Biochemistry: total bilirubin, AST, ALT, GGT, ALP, TGs, creatinine, glucose, CRP

Hematology: CBC (total white blood cells, total red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width and platelets)

Coagulation: INR

The valid normal ranges and a certification from the local laboratory will be obtained before start of the study.
The blood samples needed for the assessment of conjugated bilirubin at the central laboratory will be obtained at the same time as the blood sample for the local laboratory, to reduce the number of needle pricks. 1ml of full blood will be required for the analysis.
An exact description of the methodology for drawing, handling and shipping of the samples as well as the methodology used for the analysis of conjugated bilirubin at the central lab is outlined in the lab manual.

The investigators must review all laboratory results. Laboratory values outside the normal ranges must be assessed concerning their clinical significance by the respective investigator and the assessment must be documented on the lab report / in the patient's medical file. If the out of range value is considered clinically significant then it is an AE (see Section 13) and must be documented in the eCRF (see Section 12.4.1).

Assessments are preferably done at each visit. If the blood draw is from the PN/lipid infusion line, then lipid (study drug) should be held for 4 hours prior to the time of blood sampling.
Study investigators must draw additional blood samples to monitor TG levels during initial increase in lipid dose and if TG increases beyond 250 mg/dL. The Investigators must also draw blood samples for blood cultures if a patient shows clinical symptoms of a bloodstream infection.

12.3.2.2 Specialized Laboratory Analyses

Blood samples for analysis of fatty acids (in red blood cell membranes and plasma), sterols (including phytosterols) and α-tocopherol will be taken on Day 1 (Baseline) and Day 29 (End-of-Treatment Visit).
In case patients continue on study treatment beyond Day 29 additional samples should be taken on Day 57 and on Day 85 (End-of-Treatment Visit).
The blood samples needed for the specialized laboratory will be obtained at the same time as the blood sample for the local laboratory, whenever possible, to reduce the number of needle pricks. 1ml of full blood will be required for the analysis

Fatty acids to be assessed: linoleic acid, α-linolenic acid, Mead acid, eicosapentaenoic acid (EPA), arachidonic acid, docosahexaenoic acid (DHA).

The Holman index will be calculated to evaluate whether the minimum requirement for the essential fatty acid linoleic acid has been met (Holman 1960). The value of 0.2 will be considered as upper limit of the normal range (Holman, et al. 1979).

Sterols to be assessed: sitosterol, desmosterol, brassicasterol, lanosterol, ergosterol, campesterol, stigmasterol, sitostanol, lathosterol, squalene (a sterol precursor), and cholesterol.

Vitamin to be assessed: α-tocopherol

Those special assessments will be performed at the following specialized laboratory:

[redacted]

An exact description of the methodology for drawing, handling and shipping of the samples for the specialized laboratory analyses is outlined in the lab manual.

The sites will not receive any laboratory reports for those specialized analyses to maintain the blind, as the differences in the respective sterol, fatty acid and α-tocopherol content between study and control drug are expected to be reflected in the results of the blood sample analyses.

12.4 Documentation of Patient Data

All patient data generated during the study will be documented in the patient's medical records (source data). The definition of source data is: all information in original records and certified copies of original records of 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 "Authorisation of medical staff" provided by Fresenius Kabi) will transcribe the patient data from the source data into the eCRF.

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

12.4.1 The Electronic Case Report Form

All patient data generated during the study will be recorded in the electronic Case Report Forms (eCRFs) provided by 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. Only the investigator and authorized co-workers (as listed on the form "Authorisation of medical staff" provided by Fresenius Kabi and trained appropriately on the eCRF system) are allowed to fill-in the eCRFs or to make corrections, and will have access to the data or may change data, without the possibility of deleting the original entries. The documentation of this training will we kept in the investigator's site file.

After completion, each eCRF will be signed and dated by the investigator electronically. For all laboratory data, the units or any transformation of units must be clearly defined.

Transformation of data during data processing will be documented.

The eCRF will be validated to comply with FDA 21 CFR Part 11 requirements. Validation documentation will be filed in the Trial Master File

This study will be monitored regularly by a CRA from a CRO. The CRA will check for completion of the entries on the eCRFs, their compliance with the study protocol and with Good Clinical Practice, and will compare the eCRF entries with the source data. Source data verification will be performed for all patients and 100% of the data, including all informed consent forms.

Archiving has to be done according to requirements as described in Section 19.6 and the process for Data Management is described in Section 8.1.

13 Adverse Events and Serious Adverse Events

13.1 Definitions

13.1.1 Adverse Event

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose (21 CFR 312.32(a)).

A **treatment-emergent adverse event is** an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state

13.1.2 Serious Adverse Event

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening[1]
- 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[2]

[1]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.
[2]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 usually be considered serious (21 CFR 312.32(a)).

This definition permits either the sponsor or the investigator to decide whether an event is *serious*. The investigator's perspective may be informed by having actually observed the event, while the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. Because serious adverse events are critically important for the identification of significant safety problems, FDA believes taking into account both the investigator's and the sponsor's assessment is important.
Therefore, if either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

13.1.2.1 Suspected Adverse Reaction

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

13.1.2.2 Unexpected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.
The Smoflipid IB and the current version of the Product Information for Intralipid 20% (Annex 5) will serve as the main reference documents to assess expectedness. Referring to these documents, the expectedness of an Adverse Reaction is assessed by Fresenius Kabi exclusively.

13.1.2.3 Serious and Unexpected Suspected Adverse Reaction

Serious and unexpected suspected adverse reactions are all adverse reactions that are considered to be:

- Serious (by the investigator and/or Fresenius Kabi)
- Unexpected (by Fresenius Kabi)

If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)). The ***sponsor*** is responsible for determining whether there is a reasonable

possibility that the drug caused the adverse event, taking into consideration the investigator's assessment.

13.2 Assessment of Adverse Events

For each AE, the investigator has to perform an assessment on:

- Intensity (severity)
- Seriousness
- Clinical relevance
- Causality (to study drug and study procedures)
- Outcome
- Action taken

13.2.1 Intensity/Severity

For the intensity 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 (Annex 3). If these criteria are not reasonably applicable to an AE, the event's intensity 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: Adverse Event/Serious Adverse Event Intensity

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*	Life-threatening consequences; urgent intervention indicated.
5	Fatal**	Death related to the AE.

NOTE: *Life-threatening or **fatal AEs will also meet the identical seriousness criteria and thus will qualify as SAEs.

All AEs, including those related to laboratory values (see Section 12.3.2) and vital signs will be classified according to the CTCAE V4.03, if applicable.

Table 3: Assessment of Adverse Events Associated with Laboratory Variables and Vital Signs

CTCAE current version grading adverse events	**Rating of clinical relevance**	**Consequence**
grade 1	clinically relevant[1]	document as Adverse Event
	not clinically relevant	no further action
grade 2	clinically relevant[1]	document as Adverse Event
	not clinically relevant	Investigator must explain his rating that AE is not clinically relevant
grade 3	usually clinically relevant	document as Adverse Event
grade 4	usually clinically relevant	document as Serious Adverse Event
grade 5 ("death")	always clinically relevant	document as Serious Adverse Event

CTCAE V4.03 (Annex 3)
[1]An event is clinically relevant if it resulted in a clinical intervention.

For classification of other AEs (e.g., constipation, diarrhea) see CTCAE V4.03. Adverse Events that are not listed should be classified according to the Investigator's discretion as close as possible to CTCAE V4.03 (Annex 3).

In case the AE is reported as the result of an abnormal laboratory parameter or vital sign, the respective clinical manifestation should be described, if applicable. Indicating the laboratory parameter or vital sign only is unsufficient. All assessments will be supervised by the monitor, the data management (query), and the medical review.

13.2.2 Causality

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

"Related" means that a clinical event has a "reasonable causal relationship" to a medicinal product. A causal relationship between the study drug and the clinical event is at least a

reasonable possibility, i.e., the relationship cannot be ruled out. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A).

Clinical events which are not rated as "not related" are to be reported as related. A related event is equal to an adverse drug reaction. The following facts may indicate a "reasonable causal relationship":

- Situations where it cannot be excluded that the study drug has caused or contributed to the AE/SAE.
- A plausible temporal relationship between AE/SAE and administration of the investigational medicinal product.
- No alternative reason can be confirmed by laboratory or other investigations or testing.

In case of "no reasonable causal relationship" the alternative cause should be clearly stated, if available.

Not related with the use of the tested investigational medicinal product means that the criteria mentioned above are not met.

13.2.3 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.

13.2.4 Action Taken

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

1. None (= continuing according to protocol).
2. Dose reduced, possibly meaning:
    a) Reducing the dose of the study drug.
    b) Maintaining the dose level, despite required increase as per protocol.
    c) Reducing of the infusion rate.
3. Study drug discontinued and restarted.
4. Study drug discontinued permanently.
5. Other therapy, e.g.:
    - Drug therapy was initiated to counteract the AE. Action taken other than the above, e.g. reduced dose of concomitant medication, or initiated non-drug remedial therapy.

If considered necessary, the investigator may decide to withdraw patients from the study as a

consequence of AEs.

13.2.5 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 (= 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 deceases 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).

13.3 Reporting and Documentation Procedures

In this study, all AEs have to be documented and reported.

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

ALL SAEs must be entered into the eCRF and reported to the Sponsor within 24 hours of first knowledge of the event by study personnel.

If considered necessary, the investigator may decide to withdraw patients from the study as a consequence of SAEs or AEs (including Suspected Adverse Reactions). Similarly, the entire study may be prematurely terminated by Fresenius Kabi for medical or ethical reasons.

If a patient is withdrawn from the study due to an AE at the end of the study treatment period, the study 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.

Adverse events (AEs) will be coded by data management using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class and Preferred Term.

The list of undesirable effects observed during administration of Smoflipid or Intralipid is displayed in the current version of the IB for Smoflipid or the current Product Information for Intralipid 20% (Annex 5).
If any of these side-effects occur then the investigator should assess if infusion of study medication should be stopped or continued at a reduced dosage.

13.3.1 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 eCRF, in any case, no later than 24h after becoming aware of the SAE/SUSAR. 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.

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

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

Any:

- Pharmaceutical quality issue regarding study medication
- Report of overdose
- Report of use outside the scope of this clinical study protocol

must be documented and reported immediately but within 24 hours at the latest of awareness to the Safety Contact at Fresenius Kabi via e-mail (Section 13.3.3).

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 adverse events 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 (section 13.3.3 Safety Contact at Fresenius Kabi).

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.

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

13.3.3 Safety Contact at Fresenius Kabi

The Clinipace Safety Associate 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]

In case of urgent questions regarding any safety aspect of this trial, Safety in Clinical Trials at Fresenius Kabi OR Global Medical Affairs Officer at Clinipace can be reached as follows:

[redacted]

[redacted]

13.3.4 Reporting to Competent Authorities, Institutional Review Boards, and Investigators

Fresenius Kabi as the sponsor of this trial will inform the concerned competent authority on IND safety reports and IRBs about unanticipated problems involving risk to human subjects or others, including adverse events that should be considered unanticipated problems on an expedited basis (21 CFR 312.66).
Fresenius Kabi will also provide periodic safety reports and/or line listings to the IRBs as required. General and local requirements will be followed.
All investigators participating in the study will receive IND Safety Reports and information on unanticipated problems.

13.3.5 Period of Observation

The period of observation begins on the day the patient's legal representatives have signed the Informed Consent Form. The end of the observation period is defined as the time of the last follow-up visit.

All unresolved AEs should be followed-up by the Investigator until the outcome can be defined but at least until the last follow-up visit.

All patients, in whom study medication was stopped due to increased conjugated bilirubin levels, will be followed up until the conjugated bilirubin levels have decreased below 1.5 mg/dL.

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

When the patient has been discharged from the hospital, the Investigator should instruct the patient's personal physician (only if parent/guardian allows) to report any SAE/AE that this physician believes might reasonably be related to participation in this trial. The investigator should notify Fresenius Kabi immediately of any such SAE.

13.4 Unblinding of Treatment for Emergencies

In case of a medical emergency requiring identification of the treatment of the patient, the treatment blind may be broken. For unblinding procedure see Section 7.4.

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

If an Investigator, or patient, 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 Competent Authorities.
In case of unblinding, the blinding of Fresenius Kabi's (and the CRO's) clinical trial team must be maintained wherever possible, i.e., no information as to a broken treatment code must be communicated to any blinded member of the trial team. The unblinding must be notified immediately to the CRA responsible for the site.

13.5 Data Safety Monitoring Board

In this trial an independent DSMB will be involved. The DSMB is a multidisciplinary group consisting of clinical trial scientists and statisticians experienced in managing PN in preterm and term neonates 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.
In this study an unblinded interim analysis will be performed (Section 8.2.6) and the DSMB will make recommendations on further study conduct including the final sample size based on the safety and efficacy data from the Interim Analysis.

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.

14 Monitoring

Site monitoring is conducted by CRAs to ensure the human patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH E6 – Good Clinical Practice and, when appropriate, regulatory guidelines.

14.1 Function of the Clinical Research Associate

The Investigator will permit the CRA to monitor the study. The purposes of this monitoring are:

- To check that a valid signed informed consent form is on file for each study patient
- To check for pharmaceutical quality issues regarding study medication.
- To check for unreported overdose and report, if required.
- To assess the progress of the study.
- To review the compliance with the Clinical Study Protocol.
- To discuss any problems.
- To help the investigators dealing with the investigator's file.

- To check all signed Informed Consent forms for accuracy and completeness
- To check the completed CRFs for accuracy and completeness.
- To verify CRF's content against source documents
- To check if the staff has changed and if so whether the new employees have been accurately trained and informed about their tasks.
- To assess the status of drug storage, dispensing and retrieval.
- To review the documentation retention.
- To supervise, assist, initiate AE- and SAE-reporting, if applicable.
- To check for unreported safety issues (hidden AEs) and to assist with SAE reconciliation.

The Investigators and their staff will be expected to cooperate with the CRA, to be available during at least a portion of the monitoring visit to answer questions and to provide any missing information. The CRA will schedule such site visits in advance and not arrive unannounced.

Monitoring will be performed by:

[redacted]

14.2 Frequency of Monitoring

During the clinical part of the study, each study site will be visited by the monitor as soon as possible after first patient of each site has been screened and informed consent was signed, followed by visits approximately every 6 weeks, as appropriate.

15 Audits and Inspections

Auditing (quality assurance) and inspections may be performed to ensure compliance of the study with Good Clinical Practice (GCP) requirements. The auditor works on behalf of Fresenius Kabi but is independent from the operational departments within Fresenius Kabi. The investigator and Contract Research Organization permit the respective person direct access to source data/documents.

15.1 Audits

15.1.1 Auditing Procedures

At the study site the auditor will check the following:

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

15.1.2 Frequency of Audits

Auditing will be performed according to an audit plan.

Four on-site audits are planned for this trial, but audits may be performed at any time at any site during the study as considered necessary.

15.1.3 Documentation of Audits

After each auditing visit the auditor will compile an audit report including an audit certificate. A copy of the certificate may be passed on to the investigator on request.

15.2 Quality Control of Clinical Trial Documents

All key elements of a clinical study (e.g. Clinical Study Protocol, CRFs, Informed Consent, Clinical Study Report) will be checked internally, e.g. by an appropriate member of the clinical research department, at Fresenius Kabi.

16 Modifications During the Study

16.1 Protocol Amendments

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

Minor modifications, minor deviations or specifications of the study protocol can be described in a non-substantial amendment or a file note, as appropriate.
Substantial amendments must be submitted to the IRBs and the authorities. In case of substantial amendments that affect information submitted to both the CA and the IRBs, the sponsor should make arrangements to submit the notifications in parallel. For substantial amendments to information that only the CA assesses, the sponsor should not only submit the

amendment to the CA but also make arrangements to inform the IRBs about this application. Similarly, the sponsor should inform the CA of any substantial amendment to information for which only the IRB is responsible (e.g. facilities for the trial).

Examples for substantial amendments are:

- Change in trial design.
- Change in measures of efficacy.
- Change of inclusion and exclusion criteria.
- Change of safety reporting and evaluation.
- Changes that are likely to have an impact on the safety of the trial patient.
- Change of the interpretation of the scientific documents in support of the conduct of the trial.
- Changes that are otherwise significant.

16.2 Protocol Deviations

No deviation from the study protocol is allowed unless a formal amendment is made. 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, and/or reliability of the study data or that 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.

16.3 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 are:

- 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 completely filled in.
- The incidence and/or severity of AEs/SAEs in this or in parallel studies indicate a potential health hazard caused by treatment with the study medication/control medication.
- Fresenius Kabi is requested by CA to terminate the study.
- Fresenius Kabi decides to terminate the study due to internal reasons.

In case of prematurely termination of the study, the sponsor shall notify the CA and IRBs within 15 days and give reasons for termination, which should clearly be explained. Additionally, the investigator will be notified by the sponsor and will receive instruction, if necessary, as to what

final examinations are required.

17 Final Clinical Study Report

Fresenius Kabi is responsible for compilation of the final clinical study report (CSR). The report will be written according to the ICH E3 guideline. The final report will be submitted to the Coordinating Investigator and all Principal Investigators for approval and signature. A copy of the final CSR will be sent to each Principal Investigator for his/her file.

18 Administrative Requirements

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

18.1 Authority Identification Number

Fresenius Kabi has obtained an NCT identification number for the clinical study from the ClinicalTrials.gov database, via internet, by filling in an application form. This number identifies a trial unambiguously.

18.2 Institutional Review Board

Fresenius Kabi will submit the study protocol including the Informed Consent 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 CA and the IRBs and the sponsor should make arrangements to submit the notifications in parallel. For substantial amendments to information that only the CA assesses, the sponsor should not only submit the amendment to the CA but also make arrangements to inform the IRBs that they have made the application. Similarly, the sponsor should inform the CA of any substantial amendment to information for which only the IRB is responsible (e.g. facilities for the trial).

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

18.3 Submission to the Competent Authority

Fresenius Kabi is responsible for submission of study-related documents to the CA (Food and Drug Administration, Center for Drug Evaluation and Research, Division of Gastroenterology Products) before study start. Approval by the CA is a prerequisite for initiation of the study.

Fresenius Kabi will notify the CA of the end of the trial within 90 days.

18.4 Notification of Local Authority

Not applicable in the US.

18.5 Patient Information and Informed Consent

It is the responsibility of the investigator to give each legal representative(s) 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 must 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 enrolment. 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 Informed Consent Form (ICF) from all legal representative(s) prior to inclusion of the patient into the study.

The legal representative(s) should have enough time (ample time) and opportunity to enquire about details of the trial and to decide whether or not to allow participation in the trial.
The dated and signed Informed Consent forms should be filed by the investigator for mandatory review by study CRA or for possible future audits and inspections where this is permitted and/or required. The investigator will confirm the receipt of ICF from each legal representative by signing the appropriate page(s) of the eCRF.

18.6 Patient Insurance

In accordance with ICH E6 – Good Clinical Practice and national requirements, Fresenius Kabi has taken out a personal liability insurance [redacted] in the amount of US$ 5.000.000 for each patient participating in the trial.

18.7 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 as this is mandatory to know for the evaluation of the study. The data will be blinded correspondingly in all data analyses.

In compliance with ICH E6 – Good Clinical Practice 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.

18.8 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 PI and his co-investigator(s).
- List of normal laboratory values of local laboratory incl. methods and certificates.

19 Agreements

19.1 Confidentiality Agreement

This study protocol is provided to the Principal 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 Investigator 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.

19.2 Publication of Results

Fresenius Kabi is free to use all study results for registration, for world-wide scientific product information, and for publication.

The Investigator may publish a publication relating to the study in scientific or medical journals and may present an abstract or presentation relating to the study at medical and scientific conferences and meetings; provided, however, that Fresenius Kabi shall determine authorship of the multicenter publication for the study and the Investigator shall withhold its proposed publication, presentation, or abstract relating to the study until publication of the multicenter publication. In the event the multicenter publication does not occur within 365 days after the

completion of the study at all sites, the Investigator may publish its own abstract under the terms and conditions defined in the individual clinical trial agreement, between the investigator, the institution and Fresenius Kabi.

19.3 Payment

Financial obligations of Fresenius Kabi are outlined in the clinical trial agreement between the institution (investigator) and Fresenius Kabi.

19.4 Potential Conflicts of Interest

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

19.5 Incentives to Patients

Not applicable.

19.6 Archiving

Electronic CRF: At the end of the study, the investigator will receive a CD with the eCRFs of his study patients for archiving.

All records and documents pertaining to the conduct of the study (including eCRFs, patient informed consent forms, drug accountability sheets, original data including the patient files) must be retained by the investigator until Fresenius Kabi notifies the investigator(s)/institution(s) in writing that the trial related records are no longer needed (if not otherwise specified in national requirements and respective contracts with sites). It is the responsibility of the investigator to ensure that the data saved on electronic media remains readable thought the archiving period. Retrospective identification of all patients must be possible at any time.

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21 Annexes

ANNEX 1: Study Drug Label Information

ANNEX 2: Signature pages for Principal Investigators

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

ANNEX 4: Length of Stay calculation Worksheet

ANNEX 5: Product Information for INTRALIPID 20% (a 20% intravenous fat emulsion), revised May 2015.