

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207648Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Application Number(s)	207648
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Reviewer Name(s)	Karyn L. Berry, MD, MPH
Review Completion Date	December 11, 2015
Established Name	Smoflipid (lipid injectable emulsion, USP), 20%
(Proposed) Trade Name	Smoflipid (lipid injectable emulsion), for intravenous use
Therapeutic Class	Lipid emulsion for parenteral nutrition
Applicant	Fresenius Kabi
Formulation(s)	Intravenous
Proposed Dosing	Adults: 1.0 to 2.0 g/kg/day. It is

Regimen

recommended not to exceed a dose of 2.5 g/kg/day.

(b) (4)

Indication(s)

(b) (4)

Proposed Intended Population(s)

Adult

(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that Smoflipid 20% intravenous lipid emulsion be approved for the following indication:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

1.2 Risk Benefit Assessment

This 505(b)(1) NDA proposes a new lipid injectable emulsion product, Smoflipid. It contains fatty acids derived from four different oils: soybean oil (6%), medium chain triglycerides (6%), olive oil (5%), and fish oil (3%). With a different fatty acid composition, Smoflipid 20% provides [REDACTED] (b) (4) the essential fatty acids linoleic acid (omega-6) content: 35 mg/mL (range 28-50 mg/mL) and alpha linolenic acid (omega-3) content: 4.5 mg/mL (range 3-7 mg/mL) [REDACTED] (b) (4)

[REDACTED] Adequate essential fatty acids are crucial for neurocognitive and growth development in the pre-term neonate.

For this review, Smoflipid was evaluated in five randomized, active control clinical trials (two of which were open label) in adult patients and three randomized, active control clinical trials in pediatric patients who required parenteral nutrition (PN) for various lengths of time. In these trials, the Applicant stated that parameters that were analyzed as safety variables in the study reports were presented in this application to support the claim of efficacy. These trials were not powered to show statistically significant changes in safety or efficacy parameters. Descriptive statistics were used to analyze the data.

A total of 229 adult patients and 87 pediatric patients received Smoflipid 20% in the clinical trials conducted and submitted by the Applicant. Of the pediatric patients who received Smoflipid 20%, 15 were infants and children between the ages of 6 months

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and 81 months who received the study drug for 28 days and 72 were premature neonates who received the study drug for 7 to 14 days (mean of approximately 8 days).

The safety and efficacy parameters evaluated included indicators of growth (body weight/height and head circumference), triglyceride levels, albumin, fatty acid profiles, occurrence of adverse events, changes in laboratory parameters and vital sign monitoring.

In the applicant's "pivotal" adult clinical trial, FE-SM-03-DE, the efficacy of Smoflipid 20% was evaluated for 5 days in 249 patients [Smoflipid 126 patients; active comparator 123 patients. Additional adult trials were study FE-SM-04-CH in which 32 patients [Smoflipid 16 patients; active comparator 16 patients]) were treated for 10 to 14 days and study 05-SMOF-006 in which 73 patients [Smoflipid 34 patients; active comparator 39 patients]) were treated for 4 weeks. Study 03-3CB7-001 (53 patients [Smoflipid 26 patients; active comparator 27 patients]) and 03-3CB8-001 (52 patients [Smofkabiven 27 patients; active comparator 25 patients]) were open labeled trials that evaluated adult patients for 5 to 7 days.

The results of FE-SM-03-DE demonstrated that the Smoflipid 20% and soybean-oil comparator groups were comparable in terms of mean and median triglyceride concentrations over the course of treatment. In a subset of 33 patients fatty acids were evaluated. Fatty acid profiles were consistent with the composition of the lipid emulsion. Smoflipid 20% was associated with lower mean concentrations of the essential fatty acid linoleic acid compared with soybean oil based comparators and an increase in omega 3 fatty acids when compared with soybean oil based products. There was limited data reported on the triene:tetraene ratio. In study 05-SMOF-006, which at 4-weeks was the longest duration adult trial, the mean and median albumin values remained stable in both treatment groups during the course of the study.

In pediatric patients, Smoflipid was evaluated for 4 -weeks in children and infants in trial 00-SMOF-002 (Smoflipid 15 patients; active comparator 13 patients) and for 7 to 14 days in preterm neonates in study 00-SMOF-004 (60 patients [Smoflipid 30 patients; active comparator 30 patients]) and study 03-SMOF-005 (84 patients [Smoflipid 42 patients; active comparator 42 patients]).

In the pediatric patient studies, efficacy was based on nutritional endpoints, particularly body weight gain. In the pediatric trials, oral/enteral feedings were allowed. Patients could receive up to 20% of calories as fat via this route in studies 00-SMOR-004 and 03-SMOF-005 and up to 50% in 00-SMOF-002.

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Smoflipid appears to be a safe and effective source of calories and essential fatty acids in adult patients who require parenteral nutrition,

There are concerns though related to the adequate supply of essential fatty acids in this product. Although, the Applicant has provided only limited data on essential fatty acids (triene/tetraene ratio) in adults, EFAD in adults who are receiving fat free PN generally takes longer to develop (e.g. 4 weeks) and can be corrected without concern for the

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potential long term neurologic and growth consequences that can occur in pediatric patients. Based on guidelines from ASPEN and the amount of essential fatty acids in Smoflipid, this may be adequate for adult patients. However, there is concern that the provision of EFA may not be adequate for premature neonates and during the course of this review the Applicant has not been able to lessen our concerns.

(b) (4)

In addition to evaluation for adequate amount of essential fatty acids, which is both an efficacy and a safety concern for Smoflipid 20%, there is also a safety concern related to the presence of phytosterols in this product.

Phytosterols have been implicated as one of several potential causative factors of parenteral nutrition associated liver disease (PNALD). PNALD is believed to occur in stages starting with parenteral nutrition associated cholestasis (PNAC) as the predominant presentation in infants. As PNAC progresses to PNALD, the process can lead to a high incidence of morbidity and mortality (Rangel et al. 2012).

To further assess the risks of PNALD/phytosterols additional clinical trials are needed pediatric populations.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended for this submission.

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1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4)
pediatric studies (to include all age groups 0 to 16 years of age) are however required under the Pediatric Research Equity Act (PREA). Of particular concern is the adequacy of the supply of essential fatty acids in premature neonates, and to a lesser extent, in other pediatric age groups and the development of parenteral associated liver disease (PNALD).

The following trials are recommended PREA and FDAAA PMRs:

PREA studies which include all age groups 0 to 16 years of age (inclusive)

####-1 A prospective, randomized, controlled, double-blind, parallel-group study to compare the safety and efficacy of Smoflipid 20% (lipid injectable emulsion, USP) to standard of care soybean oil based lipid emulsion in hospitalized neonates including low birth weight and very low birth weight neonates. The study must enroll an adequate number of patients who receive parenteral nutrition for at least 28 days. Continue treatment for all patients who remain on PN for up to 84 days and follow-up 8 days after receiving the last dose of study treatment. The efficacy evaluation should include anthropomorphic measures and the risk of developing essential fatty acid deficiency (EFAD). Full essential fatty acid profiles should be evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. Secondary endpoints should include incidence of major neonatal morbidities, including BPD (bronchopulmonary dysplasia), ROP (retinopathy of prematurity), IVH (intraventricular hemorrhage), PVL (periventricular leukomalacia), NEC (necrotizing enterocolitis), and late-onset sepsis in premature and low birth weight neonates. The study's safety assessments should include evaluation of the risk of developing parenteral nutritional associated liver disease (PNALD) and parenteral nutrition associated cholestasis (PNAC). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR XXXX-5.

Final Protocol Submission: 03/2016

Study Completion: 03/2018

Final Report Submission: 03/2019

####-2 Randomized controlled trial to evaluate the safety and efficacy of Smoflipid 20% (lipid injectable emulsion, USP) administered for at least 90 days in pediatric patients, compared to standard of care soybean oil based lipid emulsion administered for the

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same duration. Continue treatment for all patients who remain on PN for up to 1 year. The study should enroll an adequate number of patients 3 months of age and older. The study's efficacy assessments should include anthropomorphic measures and evaluation of the risk of developing essential fatty acid deficiency (EFAD). Full essential fatty acid profiles should be evaluated according to standards set by major national reference laboratories. Genetic polymorphisms in the fatty acid desaturase genes (FADS) FADS1 and FADS2 should be determined in at least a subset of patients. The cut-off values for EFAD (e.g., suspected, mild and severe) should be established prior to the study. The study's safety assessments should include evaluation of the risk of developing parenteral nutritional associated liver disease (PNALD) and parenteral nutrition associated cholestasis (PNAC). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR XXXX-5.

Final Protocol Submission: 11/2016

Study Completion: 05/2020

Final Report Submission: 05/2021

Safety FDAAA PMRs:

PMRs #3, #4, #5, and #7 are to evaluate the safety signal related to PNALD and phytosterols. PMR #6 is to evaluate the safety(e.g. clinical outcomes) of increased omega 3 fatty acids and decreased omega 6 fatty acids found in Smoflipid compared to the fatty acid content of (b) (4) soybean oil lipid emulsion .

####-3 Test the three registration stability batches for the individual component phytosterol content in Smoflipid 20% (lipid injectable emulsion, USP) using the validated analytical methods.

Final Report Submission: 02/2016

####-4 Test for the individual component phytosterol content in all batches of Smoflipid 20% (lipid injectable emulsion, USP), manufactured over a three year period, using the validated analytical method. Based on these test results, establish limits for each of the individual component phytosterols in Smoflipid 20% (lipid injectable emulsion, USP) in the product specification.

Final Report Submission: 11/2017

####-5 Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

Final Report Submission: 02/2018

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####-6 Randomized clinical trial in hospitalized adult patients receiving either Smoflipid (lipid injectable emulsion) or other standard-of-care IV lipid emulsions to evaluate clinical safety outcomes of sepsis and mortality. The trial will also evaluate the requirement for ventilator support and length of stay in ICU and hospital.

Final Protocol Submission: 06/2021

Study Completion: 06/2024

Final Report Submission: 06/2025

####-7 Randomized controlled trial in pediatric patients, including neonates, comparing a phytosterols depleted formulation of Smoflipid (lipid injectable emulsion) and another standard-of-care lipid emulsion ((b) (4) soybean oil product) to evaluate the incidence of liver injury, including either parenteral nutrition-associated liver disease (PNALD) or intestinal failure-associated liver disease (IFALD). An adequate number of patients should receive treatment with parenteral nutrition for at least 90 days. This trial should be initiated after the results from PMRs XXXX-1, XXXX-2, and XXXX-3 are available. The phytosterol content of the phytosterol-depleted formulation of Smoflipid (lipid injectable emulsion) should be documented using validated analytical assay methods developed under PMR XXXX-3. Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR XXXX-5.

Final Protocol Submission: 01/2022

Study Completion: 07/2024

Final Report Submission: 07/2025

2 Introduction and Regulatory Background

This application was submitted as a 505(b)(1). Per a 505(b)(1), the Applicant owns or has right of reference for all of the data necessary for approval. The Applicant is relying on submitted clinical studies and on the general knowledge that lipids contribute a set amount of energy.

The Applicant's proposed established name, Smoflipid™ (lipid injectable emulsion, USP), 20% follows the applicable US Pharmacopeia (USP) standards.

During the course of the review, the Agency determined that none of the active ingredients in Smoflipid are considered new molecular entities (NME). The lipid content of Smoflipid is 0.20 g/mL and is comprised of a mixture of soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil. The major components of the fatty acids in Smoflipid are oleic acid (23% to 35%), linoleic acid (14% to 25%), caprylic acid (13% to

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24%), palmitic acid (7% to 12%), capric acid (5% to 15%), stearic acid (1.5% to 4%), alpha-linolenic acid (1.5% to 3.5%), [EPA] (1% to 3.5%), and [DHA] (1% to 3.5%). There is at least one active moiety in each of the active ingredients of Smoflipid that has been previously approved: EPA and DHA (in fish oil, approved in NDA 21654 Lovaza and NDA 202057 Vascepa); oleic acid, palmitic acid, linoleic acid, and linolenic acid (in soybean oil and olive oil, approved in NDA 204508 Clinolipid); and caprylic acid and capric acid (in MCT, approved in NDAs which have been subsequently withdrawn). Therefore, since each of these active moieties in Smoflipid has been previously approved by the Agency in an application submitted under section 505 of the Act or has been previously marketed as a drug in the US, Smoflipid did not meet the definition of a NME. Refer to the CMC review for further details.

Also, during the review, Smoflipid 20% was determined to be a prescription fixed-dose combination drug product because it contains multiple fatty acids due to combination of four oils: soybean, fish, olive and medium chain triglycerides. Per 21 CFR 300.50, (a) "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." On October 27, 2015, the Applicant submitted justification summarizing the contribution of each of the active pharmaceutical ingredients to the claimed effects in accordance with 21 CFR 300.50. The Applicant has stated that the combination of oils in Smoflipid provides a greater effectiveness as a source of calories and essential fatty acids.

Historical Background

Lipid emulsions are a necessary component of parenteral nutrition (PN), and have two main functions: 1) supply of energy, and 2) supply of essential fatty acids. Lipid emulsion products are used in conjunction with amino acids, electrolytes, trace elements and dextrose to provide total parenteral nutrition (TPN). (Mascioli 1996; Waitzberg 2006). The most widely used parenteral lipid emulsion contains long chain triglycerides (LCTs) from soybean oil, i.e. Intralipid. Soybean oil contains the two essential fatty acids (EFA) linoleic acid (LA) and alpha-linolenic acid (ALA).

Intralipid was the first intravenous lipid emulsion (IVLE) product to gain marketing approval in the US; a 10% solution in 1975, a 20% solution in 1981. and a 30% solution in 1993. Intralipid 10%, is now rarely used because adverse events are more likely after administration of a 10% fat emulsion formulation than a 20% formulation because the higher concentration of free phospholipid in the 10% formulation interferes with lipoprotein lipase activity (Mirtallo 2010). Intralipid is approved for use in adults and pediatric patients.

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Intralipid 20% contains high amounts of the essential long-chain fatty acids (LCFAs) LA (C18:2 ω 6, (b) (4)) and ALA (C18:3 ω 3, (b) (4)); both LA and ALA are polyunsaturated fatty acids (PUFAs). They cannot be synthesized de novo; therefore, they are classified as essential fatty acids (EFAs). They are necessary for a variety of physiological functions, including structural components of cell membranes and tissues, secondary messengers and mediators, as well as providing sources of energy in the form of triglycerides (Kalish 2012; Kremmyda 2011).

Another (b) (4) soybean oil IV lipid emulsions approved for use in the US is Nutrilipid. Clinolipid ((b) (4) olive oil and 20 % soybean oil) was approved for use in adults in 2013. Other IVLE products that were initially approved in the US, but have subsequently been withdrawn are the Liposyn lipid emulsion products: NDA 18203 Liposyn 10% ((b) (4) safflower oil), NDA 18614 20% ((b) (4) safflower oil), NDA 18997 Liposyn II ((b) (4) safflower oil and (b) (4) soybean oil), NDA 18991 Liposyn II 20% ((b) (4) safflower oil and (b) (4) soybean oil), NDA 18969 Liposyn III 10%, NDA 18970 Liposyn III 20% and NDA 20181 Liposyn III 30% ((b) (4) soybean oil). Liposyn ((b) (4) safflower only) was withdrawn in April 1996. Concern about decreased amounts of ALA (omega 3 FA deficiency) that predisposed a patient to neurological adverse events (visual problems and sensory neuropathy) was reported in a case study (Vanek 2012). The sponsor submitted a request to withdraw both Liposyn II and Liposyn III in December 2014. Per the sponsor, this request was not due to reasons of safety or efficacy.

Over the last 40 years other intravenous lipid products with different compositions have been approved in other jurisdictions but not in the US. Historically, in the US, IVLEs have been approved based on their ability to provide calories and essential fatty acids.

Early parenteral nutrition (PN) in clinical practice (1950s and 60s) started with amino acid and dextrose infusions. It was soon found though that providing most of the needed calories as dextrose resulted in fatty infiltration of the liver and essential fatty acid deficiency. These adverse effects were prevented by providing a substantial portion of the calories with lipids.

Over the following years alternatives to the (b) (4) soybean oil based fat emulsions have been developed. They were categorized in an American Society for Parenteral and Enteral Nutrition (ASPEN) position paper as follows (Vanek 2012):

- Generation 1 (1961): long-chain neutral triglyceride (TG) ((b) (4) soybean oil (SO))
 - 85 % omega-3, omega-6, omega-9 (nonessential)
- Generation 2 (1984): SO: medium chain triglycerides (MCT)=50:50
 - To reduce omega-6 content
- Generation 3 (1990's): olive oil (OO):SO=80:20

- o Further decrease of omega-6 content
- Generation 4 (recent): IV lipids containing fish-oil (FO)
 - o Increase content of omega-3

Lipids in the form of triglycerides can be converted into energy, carbon dioxide, and water in the mitochondria via the β -oxidation process and citric acid cycle. They also provide the structural components of cell membranes, contribute to membrane fluidity, are the precursors of biological mediators, and are regulators of gene expression.

Triglycerides (TG) are the major components of all dietary fats. These fatty acids (FAs) can be of varying chain length, depending on the number of carbon atoms contained in each molecule. Long chain FAs have 14–24 carbons, medium-chain FAs have 6–12 carbons, and short-chain FAs have 2–4 carbons in each molecule. Most TG derived from the diet are of the long-chain type and are designated as long-chain triglycerides (LCT). FA can be further characterized by the absence (saturated) or presence (unsaturated) of double bonds between the carbon atoms.

Humans generally do not need to synthesize FAs, because of the relatively high amounts derived from the diet. Saturated and most monosaturated FAs can be synthesized from glucose and amino acids if necessary. However, humans and other mammals do not have the desaturase enzyme responsible for the addition of a double bond before the ninth carbon from the methyl end. The enzymes responsible for these processes are called the Δ -9 and Δ -15 desaturase enzymes. These enzymes can metabolize oleic acid (OA; 18:1 ω -9) to form LA (18:2 ω -6) and ALA (18:3 ω -3). Because humans cannot produce LA and ALA, they are termed essential fatty acids. These two EFA are abundant in vegetable oils because these two enzymes are present in plants.

Based on studies by Holman et al, in 1979, it was established that a triene: tetraene ratio (mead acid [MA]: arachidonic acid [AA]), the standard used to diagnose EFAD, greater than 0.2 is considered the upper limit of normal (Hamilton 2006)

Richardson and Sgoutas reported biochemical EFAD within 3 weeks in 4 under-nourished patients receiving fat-free PN and noted that a deficiency developed more rapidly in the severely vs less severely malnourished patients. In a prospective study of surgical patients ranging from newborns to adults, O'Neill et al gave fat-free PN and observed the development EFAD within 2 weeks in the infants and 4 weeks in the adults. (Richardson 1975) (O'Neil 1977)

Since the Holman index was developed several decades ago, there have been clinical analytical method advancements that have led to discussion about the appropriate ranges for the triene/tetraene ratio (Lagerstedt 2001). The Mayo Medical Laboratories have established reference ranges for the triene/tetraene ratio that are very different

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from the classic Holman index. Further discussions are needed to determine the most appropriate measurements and reference values to diagnose EFAD.

Table 1: Mayo Laboratories Reference Values-Triene/Tetraene Ratio used to Diagnose EFAD

Age Range	Triene/Tetraene Ratio
1-31 days	0.017-0.083
32 days - 17 years	0.013-0.050
≥ 18 years	0.010-0.038

<http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82042>

Accessed on 10/26/2015

2.1 Product Information

The Applicant's rationale for the development of Smoflipid is that it contains a wider range of lipids than soybean oil only based lipid emulsions. Because Smoflipid contains MCTs, olive oil and fish oil, in addition to soybean oil, the Applicant purports (b) (4)

Smoflipid 20%, an example of a Generation 4 product, is an intravenous lipid emulsion (IVLE) for use in PN. It contains fatty acids derived from four active ingredients (four different oils): soybean oil (6%), medium chain triglycerides (6%), olive oil (5%), and fish oil (3%). The oils are mixed with small quantities of purified egg phospholipids and sodium oleate (b) (4) together with glycerol (b) (4)

(b) (4) sodium hydroxide to adjust the pH and Water for Injection (b) (4) and α -Tocopherol (Vitamin E (b) (4)

(b) (4) presented as 163-225 mg/1000 mL (a physiologically active dose), Egg phospholipids, sodium oleate, glycerol, sodium hydroxide and α -tocopherol are considered as excipients and are non active ingredients.

Soybean oil

The soybean oil content of Smoflipid 20% is 60 g/L. Soybean oil provides energy from long chain triglycerides (LCTs). The oil contains a high concentration of PUFAs, mainly in the form of the EFAs linoleic acid ($\omega 6$ fatty acid) and α -linolenic acid ($\omega 3$ fatty acid).

Medium chain triglycerides (MCT)

The MCT content of SMOFlipid 20% is 60 g/L. Medium chain triglycerides (MCT) are composed of saturated medium chain fatty acids (MCFA) with eight and ten carbon

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atoms, caprylic acid (C8:0) and capric acid (C10:0). MCTs have been suggested as an alternative energy source. Medium-chain fatty acids are cleared from the bloodstream and converted into energy more rapidly than LCFAs (Bach 1982; Deckelbaum 1990); they are not stored in tissue and do not accumulate in the liver (Zurier 1967; Ulrich 1996). The optimum concentration of MCTs in a lipid emulsion is considered to be $\leq 50\%$ (Cotter 1987). A possible disadvantage with MCT is related to the rapid hydrolysis, which causes high plasma concentration of medium chain free fatty acids. This may lead to side effects such as metabolic acidosis and neurological effects. In order to avoid the potential adverse effects of MCT and to provide the essential fatty acids present in LCT, MCT are always given together with LCT in humans. In animal studies, hepatic metabolism of MCFAs administered at high doses as the sole source of energy has been associated with ketogenesis which may result in acidosis.

(b) (4) Olive

SMOFlipid 20% contains 50 g/L olive oil, which includes LCTs rich in MUFAs. Olive oil is rich in monounsaturated fatty acids and will decrease the proportion of polyunsaturated fatty acids present in LCT. The main fatty acids are oleic acid (C18:1), palmitic acid (C16:0), and linoleic acid (C18:2). The number of double bonds in the different fatty acids can vary from zero (saturated) to three (unsaturated).

(b) (4) fish oil

The fish oil content in SMOFlipid 20% is 30 g/L. Fish oil is rich in omega-3-fatty acids, which are defined as the following unsaturated fatty acids: α -linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), eicosapentaenoic acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), docosapentaenoic acid (C22:5 n-3, clupanodoic acid) and docosahexaenoic acid (C22:6 n-3; DHA). The n-3 LCPUFAs DHA and EPA are crucial for neurodevelopment.

Reviewer's comments: Recent literature has purported benefits other than a source of energy and nutrition (e.g. less pro-inflammatory response), with the above alternative fatty acids in IVFEs. Data supporting real clinical benefits linked to these purported effects of alternative fatty acids are limited. For this submission, the Applicant proposes to demonstrate that Smoflipid is a source of calories and nutrition. The Applicant has not provided data to support the use of these other oils for any other purported benefits.

Proposed indication:

(b) (4)

Proposed trade name: Smoflipid (lipid injectable emulsion), for intravenous use

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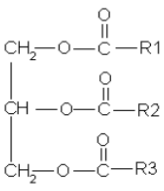
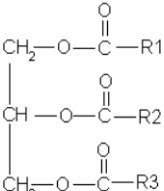
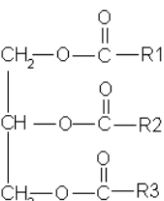
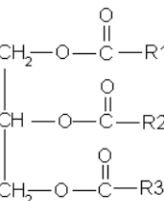
Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Pharmacological class: Solutions for parenteral nutrition, fat emulsions

Manufacturer: Fresenius Kabi AB, Sweden

Molecular and Structural formulas: See Figure 1

Figure 1: API Molecular Structure(s)

API	Structural formula	Molecular formula
Soybean oil	 CH₂-O-C(=O)-R₁ CH-O-C(=O)-R₂ CH₂-O-C(=O)-R₃ R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C16:0, C18:1, C18:2, C18:3
Medium chain triglycerides (MCT)	 CH₂-O-C(=O)-R₁ CH-O-C(=O)-R₂ CH₂-O-C(=O)-R₃ R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C8:0, C10:0
Olive oil	 CH₂-O-C(=O)-R₁ CH-O-C(=O)-R₂ CH₂-O-C(=O)-R₃ R = Fatty acid chains	Triacylglycerol with fatty acid chains mainly C16:0, C18:1, C18:2
Fish oil	 CH₂-O-C(=O)-R₁ CH-O-C(=O)-R₂ CH₂-O-C(=O)-R₃	Triacylglycerol with fatty acid chains mainly C20:5, C22:6

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	R = Fatty acid chains	
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Applicant's table 2.2 Introduction

Proposed aged groups: Adults (b) (4)

Proposed Dosing and Administration: Smoflipid is intended for intravenous infusion into a peripheral or central vein. The daily dose of SMOFlipid should be based on individual requirements and the patient's lipid tolerance.

Adults: The SMOFlipid dose is 1.0 to 2.0 g/kg/day. It is recommended not to exceed a dose of 2.5 g/kg/day.



Smoflipid is packaged in a single chamber (b) (4) bag. The sponsor proposes to manufacture the product in three sizes, 100, 250 and 500 ml. The following table lists the component composition used in the manufacture of the drug product.

Table 2: Component Composition per Unit Dose for Product Code

Strength	20%		
Packaging Configuration (Bag size)	100 mL	250 mL	500 mL
SMOFlipid	Content (per 1000 mL)	Function	Quality of ingredient
Active ingredients			
Soybean oil	60 g	Active substance	USP
Triglycerides, medium-chain	60 g	Active substance	NF
Olive oil (b) (4)	50 g	Active substance	NF
Fish oil, rich in omega-3 acids	30 g	Active substance	USP Dietary

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			supplements
Other ingredients			
all-rac- α -Tocopherol (Vitamin E)	163-225 mg	(b) (4)	USP
Purified egg phospholipids	12 g		NF
Glycerol (b) (4)	25 g		USP
Sodium oleate	(b) (4)		In-house specification
Sodium hydroxide	to pH (b) (4)		NF
Water for injections	to 1000 ml		USP
(b) (4)	(b) (4)		NF

Use in Other Jurisdictions

The Applicant reports that Smoflipid is approved in the EU and many non-EU countries for the treatment of adult and pediatric patients (neonates, infants and children). The product was first approved in Sweden in 2004. Approval for use in pediatric patients was obtained in Europe in September 2009.

The following table contains label information from other jurisdictions. Some labels limit the population to adults and/or in the indication in addition to a supply of energy and essential fatty acids, they also state a supply of omega-3 fatty acids. The dosing regimens in the comparator labels differ from the proposed US dose for adults (b) (4)

Table 3: Comparison of Smoflipid Labels

Comparison of Smoflipid Labels			
	Sweden	Australia	Canada
Indication	Supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is	Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated	Indicated for supply of energy and essential fatty acids and omega-3 fatty acids to adult patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated.

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	impossible, insufficient or contraindicated.	Proposed US Indication: (b) (4)	
Pivotal Studies	Two studies in home parenteral nutrition patients in need of long-term nutrition	Adults - FE-SM-03-DE Children-00-SMOF-002 Preterm neonates-00-SMOF-004, 03-SMOF-005	FE-SM-03-DE FE-SM-04-CH 03-3CB7-001 03-3CB8-001 05-SMOF-006
Population/duration	One study in adults and one study in pediatric patients (both long term) Adult study not described Pediatric study 00-SMOF-002	Same trials submitted in US application	Same trials submitted in US application
Dosing	Adults- 1.0 – 2.0 g fat/kg (b.w) / day Children- not to exceed a daily dose of 3 g fat/kg b.w./d Neonate/Infants- initial dose should be 0.5 – 1.0 g fat/kg b.w./day followed by a successive increase by 0.5 – 1.0 g fat/kg b.w./day up to 3.0 g fat/kg b.w./day. not to exceed a daily dose of 3 g fat/kg b.w./d,	Adults- 1.0 – 2.0 g fat/kg (b.w) / day Children- not to exceed a daily dose of 2g fat / kg b.w/ day; dose up to a maximum of 3g fat / kg b.w / day can be considered. Neonates/Infants- initial dose should be 0.5 – 1.0 g fat / kg b.w / day followed by a successive increase by 0.5 – 1.0 g fat / kg b.w / day up to 3.0 g fat / kg b.w / day. not to exceed a daily dose of 3g fat / kg b.w / day	Adults - 1.0 – 2.0 g lipid/kg body weight (b.w.)/day Children – Not approved for use Neonates/Infants – Not approved for use
		Proposed US dosing: Adults- 1.0 to 2.0 g/kg/day. Not to exceed a dose of 2.5 g/kg/day. (b) (4)	

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Endpoints	Efficacy (secondary objective) in the pediatric study was measured by weight gain, height, body mass index, pre-albumin, retinol binding protein and fatty acid profile	Adults- serum triglycerides, fatty acid profile Children- Efficacy was a secondary objective and was assessed by fatty acid profile in plasma lipoproteins and RBC phospholipids and by body weight, height and body mass index Preterm neonates- primary efficacy measure in both studies was change in	Efficacy- Serum triglyceride concentration and fatty acid profile Safety- assessed by adverse event profile, laboratory safety parameters and vital signs
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Table 4: Concentration of various free fatty acids in Smoflipid 20%

Fatty acid	Oil	Limits in SMOFlipid 20%, mg/mL
Caprylic acid	MCT oil	(b) (4)
Capric acid	MCT oil	
Oleic acid	Soybean oil Olive oil	
Linoleic acid	Soybean oil Olive oil	
Alpha-Linolenic	Soybean oil Fish oil	
Eicosapentenoic acid	Fish oil	
Docosahexaenoic acid	Fish oil	

Range of linoleic acid and α -Linolenic acid composition based on clinical description found in the respective package inserts.

Table 5: Content of linoleic and α -Linolenic acid

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Fatty acid	Smoflipid 20%	Clinolipid 20%	Intralipid 20%
linoleic acid (n-6)	35 mg/mL (range 28-50 mg/mL)	35.8 mg/ml (range 27.6-44 mg/mL)	(b) (4)
α-Linolenic acid (n-3)	4.5 mg/mL (range 3-7 mg/mL)	4.7 mg/mL (range 1.0-8.4 mg/mL)	(b) (4)

Essential fatty acids

For adults, A.S.P.E.N. recommends that a minimum of 1% to 2% of the daily calorie requirements should come from LA and 0.5% from ALA to prevent EFAD (ASPEN 2002). The daily requirement for EFAs is 7 to 10 grams, corresponding to 170 to 240 mL of Smoflipid 20% (Stuan et al 2009). Smoflipid 20% has an EFA content of approximately (b) (4)%. Per the Applicant, a daily energy intake of (b) (4)% of energy from lipids, Smoflipid 20% provides LA and ALA at a level of (b) (4)% and (b) (4)% of energy requirements, respectively.

(b) (4)

Reviewer's comments: Based on A.S.P.E.N. recommended daily requirements it appears that Smoflipid provides adequate amounts of EFA (LA and ALA) for adults.

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Lipid products for parenteral infusion that are available are: 1) (b) (4) soybean oils and 2) combination of (b) (4) soybean oil and (b) (4) olive oil.

The (b) (4) soybean oil products are available in different strengths, with (b) (4) formulations the most widely used. Of the licensed (b) (4) soybean based products Intralipid and Nutrilipid are currently available and marketed. All of these products are indicated for use in adults and pediatric patients.

Clinolipid, which contains (b) (4) soybean oil and (b) (4) olive oil, was approved for use in adults as a source of calories and essential fatty acids in October 2013.

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Table 6: Available intravenous lipid emulsions

Brand Name	Type	Status
Intralipid (NDAs 17643, 18449, 20248, 19942) Intralipid 20%- NDA 18-449 – Approved January 1981	Long chain triglycerides/soybean oil 10%, 20%, 20% (Pharmacy bulk package), 30% (Pharmacy bulk package)	Active
Nutrilipid Approved May 1993	Long chain triglycerides/soybean oil 10% and 20%	Active
Clinolipid (NDA 204508) Approved October 2013	(b) (4) olive oil; (b) (4) soybean oil	Active
Kabiven/Perikabiven (NDA 200656) Approved August 2014	Long chain triglycerides/soybean oil with electrolytes/amino acids/glucose	Active

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients are soybean oil, medium chained triglycerides, olive oil and fish oil.

2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues related to IV lipid emulsions are:

1) the provision of adequate amounts of essential fatty acids (EFA) to prevent and/or treat essential fatty acid deficiency (EFAD) especially in pre-term neonates 2) the development of parenteral nutrition associated liver disease (PNALD) which is thought to be related to the presence of phytosterols in IV lipid emulsion products and/or the amount of omega 6 fatty acids in (b) (4) soybean oil IV lipid emulsions and 3) the presence of elemental impurities in large volume parenteral (LVP) products.

Essential Fatty Acids

Lipid emulsions used for parenteral administration to humans during nutritional support are water-based emulsions made primarily from soybean oil, coconut or palm oil, olive oil and egg yolk phospholipids. These lipid emulsions serve as an important source of

energy and essential fatty acids. (b) (4) soybean oil lipid emulsions provide polyunsaturated fatty acids that are rich in the essential fatty acids linoleic acid (LA) and alpha linolenic acid (ALA). LA and ALA cannot be synthesized by humans and are therefore essential components of the diet. The requirements for LA are approximately ten times higher than those for ALA; and LA can therefore be considered the more important of the two. The concern related to newer IV lipid emulsions that contain decreased amounts of soybean oil is their ability to provide adequate amounts of the essential fatty acids, LA and ALA.

The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio of >0.2 (elevated Mead acid and reduced arachidonic acid level [ratio of Mead acid/arachidonic acid]). EFAD in the adult leads to recognizable symptoms of which dermatological are the most prominent. EFAD is reversible in adults with administration of essential fatty acids, but in the infant, EFAD is far more serious and associated with possible permanent sequela related to neurological development.

PNALD and Phytosterols

Another major complications encountered in patients that are dependent upon parenteral nutrition for survival is the development of parenteral nutrition-associated liver dysfunction (PNALD). PNALD has been associated with the use of greater than 1 g/kg/day of soybean oil-based lipid emulsion (Xu 2012). Parenteral nutrition lipid emulsions made from various plant oils contain steroidal compounds, called phytosterols. Phytosterols are sterol alcohols that occur naturally in plants as a component of the cell membrane. Phytosterols are considered impurities and not active ingredients. Phytosterols have been associated with impaired biliary secretion.

Soybean oil contains high concentrations of phytosterols. During parenteral administration of lipid emulsions, phytosterols can reach levels in the blood that are many fold higher than during enteral administration. The elevated phytosterol levels have been implicated with the development of PNALD.

The FDA has required pharmaceutical manufacturers to monitor the levels of various phytosterols in drug products containing oils from plant origin. The Applicant has developed and validated gas chromatography-mass spectrometry (GC-MS) analytical method. The Applicant has conducted a study of the occurrence of individual sterols in Smoflipid. See the CMC review for additional details regarding compounds detected and identified.

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Elemental impurities

The presence of heavy metals in PN can have significant adverse effects on organs and tissues, such as nephropathy (b) (4) and neurotoxicity and hepatotoxicity (b) (4). Over the years, there have been numerous reports in the literature regarding the presence of heavy metals in PN products. The Agency has required manufacturers to control for a set group of elemental impurities. See Section 4.1, the CMC review for further details related to elemental impurities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

April 9, 2014 (Type B meeting – pre-NDA)

The sponsor was informed that they would need to include testing for elemental impurities in their drug product specification. This should include testing for (b) (4) any other metals that are present during the manufacturing process and have the potential to contaminate the product. In addition, the sponsor was also informed that their submission should include a validated method for quantitating the following individual phytosterols in their product (b) (4).

The Division recommended that nutritional efficacy in adults be assessed by at least the following parameter: body weight, arm circumference, skin-fold thickness, total protein, albumin, lipid metabolism and assessment for fatty acid deficiency. These data should be available from trials that exceed short term (< 2 weeks) exposure and should include a control arm. Pediatric trials should be conducted to assess a signal of a serious risk of essential fatty acid deficiency (short term and long term), sepsis, mortality and length of ICU/hospital stay and risk of liver injury in pediatric patients including neonates. The sponsor confirmed that the requested endpoints would also be included in the planned study.

December 10, 2013 (Type C Meeting – Written Responses)

The sponsor requested to include the Chinese study as supportive data, since it was not conducted by the sponsor. The Division stated that this may be acceptable, but additional clarification regarding the data they plan to submit is needed.

July 24, 2013 (Type C Meeting)

The Division discussed with the sponsor the planned public workshop that will discuss IV lipid emulsion study design, endpoints and patient populations. Comments were provided on their proposed protocol synopsis. The Division also commented to the sponsor, that the available studies that they plan to submit are 28 days maximum

duration. No long term exposure data (i.e. year long) is available. The sponsor was informed that this may impact the indication statement and dosage and administration section limiting the duration of recommended treatment to short term. In addition, the sponsor was informed that additional important efficacy and safety data could become subject to a required post-marketing trial and/or post marketing commitment.

The sponsor understood that the language of the disclaimer statement in the indication statement is likely to be linked to the targeted outcomes of the PMRs and/or PMCs.

The Division agreed that the sponsor could file the NDA with the data from the previously conducted studies and perform the proposed study to show safety superiority for liver function in neonates as a post approval requirement.

May 8, 2012 (Type B Meeting)

Based on comments received from the Division at the December 6th meeting, the sponsor proposes to modify the indication for their product as only as source of calories and essential fatty acids. The Division responded that because of the substantial literature on fish oil purporting that implies benefits of the fish oil in IV lipids, the sponsor must submit data to support the benefit of the inclusion of fish oil in their product, beyond being a source of calories and fatty acids. This could be established by submission of adequate and well controlled trials published in the literature or by conducting an adequate clinical trial. The Division stated that an AC may be necessary to discuss clinical development and a path for regulatory approval for IV lipid emulsion products that contain fish oil.

December 6, 2011 (Type B- Pre-IND Meeting)

Purpose of meeting was to obtain advice on proposed clinical and non-clinical development plan. The Agency commented that since the Applicant's product contained fish oil, the Applicant would need to provide data to support the benefit of inclusion of the fish oil in their product, i.e. clinical outcomes associated with beneficial immunomodulatory and anti-inflammatory effects. Applicant informed that they would need to design a trial that shows superiority of Smoflipid to Intralipid. Applicant informed that if they failed to demonstrate superiority of Smoflipid, the Division may be willing to re-assess their product as only a source of calories and essential fatty acids. Based on previous meeting discussions, the sponsor agreed to conduct a non-inferiority Phase 3 study comparing Smoflipid to Intralipid 20% with an emphasis on including meaningful clinical endpoints. The Division stated that a non-inferiority trial was not acceptable.

June 22, 2009 (Type C Meeting)

The sponsor discussed a survey of efficacy and safety parameters used in clinical studies with PN products that they conducted and submitted to the Division on

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September 17, 2008. The Division commented that clinical endpoints to compare new PN IV lipid formulations with currently approved products should include clinical outcome measures, such as infection rate, mortality and length of hospital stay.

July 2, 2008 (Type C Meeting)

Purpose of meeting was to obtain guidance from Agency on the general acceptability of information for an NDA. Clinical discussion centered around data standards, i.e. primary and secondary endpoints, safety endpoints and clinical outcome parameter that would be needed to support these types of studies.

2.6 Other Relevant Background Information

Multiple clinical Information requests (IR) were submitted to obtain additional safety and efficacy data and analyses for adult and pediatric patients.

June 18, 2015 (IR submitted to Applicant)

Information requested from Applicant to provide additional data (patient line list) for adult and pediatric trials related to pre-study and trial daily IV lipid dose in grams/kg/day for each patient

April 2, 2015 (IR submitted to Applicant)

Information requested from Applicant to provide additional data (patient line list) for adult and pediatric trials related to EFAD monitoring (e.g. Hollman index) anthropometric measurements (pre and post), amount of fat calories provided by enteral oral route.

March 17, 2015 (Mid-cycle communication teleconference)

The purpose of the meeting was to provide an update on the ongoing review. Items discussed included the following: 1) Applicant's coordination with the Office of Scientific Investigations for site inspections, 2) Applicant's coordination with their drug substance and drug product manufacturing and testing facilities on their current status; the Applicant was reminded that a satisfactory evaluation of all facilities is required for NDA approval, 3) timeline for submission of CMC IR and 4) discussion of clinical IR related to monitoring for EFAD, anthropometric measurements and enteral/oral feedings.

January 20, 2015 (Type C Guidance meeting) IND 102137

The purpose of this meeting was to discuss the pediatric protocol (initial Pediatric Study Plan), a trial to evaluate the superiority of Smoflipid compared to Intralipid in the prevention of PNALD in neonates.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant submitted the application in electronic modular format. The application was generally well organized and navigable. No Refusal-To-File-issues were raised at the filing meeting.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all trials were conducted in accordance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements of the countries in which they were conducted.

A request for an audit by the Office of Scientific Investigations (OSI) was submitted for this application. The Office of Scientific Investigations (OSI) inspected five (5) clinical investigator sites (two adult trial sites and three pediatric trial sites). All clinical sites had the classification of No Action Indicated (NAI). OSI reported that the studies appeared to have been conducted adequately, and the data generated by the studies appeared acceptable in support of the respective indication. For further details regarding this application's site investigations, see the review in DARRTS by Dr. Susan Leibenhaut dated June 15, 2015.

3.3 Financial Disclosures

Per the Applicant, the submitted studies were conducted during the years 1996 to 2008. The involved investigators are no longer in contact with the Applicant and their contact information was not available. However, the Applicant confirms that none of the investigators had any material financial connection with the company and that none of the listed investigators were employed by the company. Additionally none of the listed investigators were the recipients of significant payments of other sorts. See Section 9.4

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewer, Dr. Tarun Mehta, stated that the Applicant provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. An

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“acceptable” recommendation was issued by the Office of Compliance for this application.

Smoflipid 20% has added two new active ingredients (MCT and Fish oil) to the currently approved products. This product was determined not to be a New Molecular Entity (NME) because the active moieties (fatty acids) were parts of previously approved products including those that have been withdrawn from the market.

To comply with the Agency’s requirement for heavy metal controls on large volume parenteral (LVP) products, nine heavy metals (b) (4) were controlled with acceptance criteria that in general have been found adequate per Dr. Mehta.

Dr. Mehta reports that phytosterols have also been controlled with acceptable levels. Per, Dr. Mehta’s review, the Applicant has conducted a study of the occurrence of individual sterols in SMOFlipid for three different batches. The compounds detected and identified were (b) (4). The phytosterols, quantitatively determined in SMOFlipid are (b) (4). Additionally, (b) (4) was quantitatively determined as well as the (b) (4).

Table 7: Calculated amounts of sterols in Smoflipid 20% as found in Dr. Mehta’s review

(b) (4)



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4.2 Clinical Microbiology

The microbiology reviewer, Erika Pfeiler, Ph.D., recommended approval of this application. In her review she notes the following: the container closure integrity studies are adequate to ensure the microbiological quality of the drug product; the manufacturing process described is adequate to ensure the microbiological quality of the drug product; process validation studies are adequate to ensure the microbiological quality of the drug product; specifications and analytical methods are adequate to ensure the microbiological quality of the drug product and stability information provided in the application is adequate to ensure the microbiological quality of the drug product. See her full review dated May 14, 2015.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Babatunde Emmanuel Akinshola stated that the Applicant provided adequate nonclinical pharmacology and toxicology information to support this NDA application. Dr. Akinshola stated in his review that in the nonclinical studies, Smoflipid or its constituent fatty acids were generally well-tolerated in a rodent (rats) and a non-rodent (dogs) species at the maximum doses administered, with slight or moderate, but reversible adverse effects. There were no significant nonclinical safety concerns for Smoflipid 20 %. Refer to Dr. Akinshola's review dated June 30, 2015.

4.4 Clinical Pharmacology

The Applicant submitted two clinical pharmacology studies in support of this NDA; however, both studies were considered to be exploratory. The constituents of Smoflipid20% used in these two studies were different from the current proposed product. These studies were conducted with 10 to 12 healthy subjects each given single short term (4 to 6 hours) infusion and dated from 19 years ago. Per the Dr. Elizabeth Shang's clinical pharmacology review, the information generated from these studies has very limited value and will not be included in the labeling. Refer to Dr. Shang's full review dated June 10, 2015 for a full review of the two submitted clinical pharmacology studies.

4.4.1 Mechanism of Action

Lipids in the form of triglycerides can be converted into energy, carbon dioxide, and water in the mitochondria via the β -oxidation process and citric acid cycle. They also provide the structural components of cell membranes, contribute to membrane fluidity, are the precursors of biological mediators, and are regulators of gene expression.

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4.4.2 Pharmacodynamics

The Applicant states that the pharmacodynamics of Smoflipid 20% are the provision of energy and essential fatty acids. The PD properties of SMOFlipid 20% have not been systematically examined in clinical studies because the properties of the individual fatty acids have been previously described

4.4.3 Pharmacokinetics

Pharmacokinetic studies were not conducted in infants and children.

4.5 Center for Devices and Radiological Health (CDRH)

The CDRH reviewer, Mr. William M. Burdick, found no outstanding engineering-related issues for this application. See his full review dated February 25, 2015.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The table below summarizes the primary studies used in the review of this NDA to evaluate the efficacy and safety of Smoflipid.

Table 8: Table of clinical trials

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Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
Adult Trials					
FE-SM-03-DE (09/1997- 07/1998)	Phase 3, double-blind, randomized, active-controlled, parallel-group, multicenter	<u>SMOFlipid 20%</u> central IV infusion of 1.5 g/kg/d <u>Lipovenös 20%</u> central IV infusion of 1.5 g/kg/d	249/249 SMOF 20%: 126 Lipovenös 20%: 123	Male and female adult patients (aged 18 years or older) following major abdominal, thoracic, or urological surgery	Continuous infusion over approximately 24 hours per day for 5 days after surgery
FE-SM-04-CH (01/1998- 08/1998)	Phase 3, double-blind, randomized, active-controlled, parallel-group, single-center study	<u>SMOF 20%</u> central IV infusion up to a maximum of 2 g/kg/d <u>Lipovenös 20%</u> central IV infusion up to a maximum of 2 g/kg/d	35/32 SMOF 20%: 16 Lipovenös 20%: 16	Male and female adult patients (aged 18 years or older) in need of TPN	Continuous infusion over 18 to 24 hours per day for 10 to 14 days
03-3CB7-001 (07/2004- 02/2005)	Phase 3, prospective, open-label, randomized, active-controlled, parallel-group, single-center study	<u>SmofKabiven</u> central IV infusion of 15-30 mL/kg/d, corresponding to 0.57-1.14 g/kg/d (SMOFlipid 20%) <u>Kabiven</u> central IV infusion of 15-30 mL/kg/d, corresponding to 0.6-1.2 g/kg/d (Intralipid 20%)	60/53 SmofKabiven: 26 Kabiven: 27	Male and female adult patients (aged 18 to 85 years) following major intestinal tract surgery requiring PN	Continuous infusion for approximately 24 hours per day for 5-7 days after surgery
03-3CB8-001 (07/2004- 10/2005)	Phase 3, prospective, open-label, randomized, active-controlled, parallel-group, multicenter study	SmofKabiven Peripheral peripheral IV infusion, MXDD: 40 mL/kg/d, corresponding to 1.13 g/kg/d (SMOFlipid 20%) Kabiven	52/52 SmofKabiven Peripheral: 27 Kabiven Peripheral: 25	Male and female patients (aged 18 to 85 years) requiring PN	Peripheral IV infusion for 14-24 hours per day for 5-7 days

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Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
		Peripheral peripheral IV infusion, MXDD: 40 mL/kg/d, corresponding to 1.42 g/kg/d (Intralipid 20%)			
05-SMOF-006 (10/2007- 10/2008)	Phase 3, double- blind, randomized, active-controlled, parallel-group, multicenter	SMOF lipid 20% central IV infusion of 1-2 g/kg/d Intralipid 20% central IV infusion of 1-2 g/kg/d	75/73 SMOF 20%: 34 Intralipid 20%: 39	Male and female adult patients (aged 18 to 85 years) in need of PN	Continuous infusion over 10-24 hours per day for 5-7 days per week for 4 weeks
**SMOF-001- CP3 (08/2008- 09/2009)	Phase 3, double- blind, randomized, active-controlled, parallel-group, multicenter	Smoflipid 20% - 1.2 g/kg/d Intralipid 20% - 1.2 g/kg/d	212/212 SMOF lipid:: 106 Intralipid: 106:	Male and female adult patients (aged 18 to 80 years) after moderate and major abdominal surgery	Central or peripheral infusion for 6 days
Pediatric Trials					
00-SMOF-002 (05/2003- 05/2005)	Phase 2b, double- blind, randomized, active-controlled, parallel-group, single-center	SMOF lipid 20% central IV infusion approximately 2 g/kg/d Intralipid 20% central IV infusion approximately 2 g /kg/d	28/28 SMOF 20%: 15 Intralipid 20%: 13	Male and female infants and children (aged 1 month to 11 years) with stable disease requiring PN	1 week run-in period with Intralipid 20%; 1 day washout; SMOF lipid 20% or Intralipid 20% as 12-14 hours continuous infusion per day for 4-5 days per week for 4 weeks
00-SMOF-004 (04/2003- 02/2006)	Phase 2b, double- blind, randomized, active-controlled, parallel-group, single-center	SMOF lipid 20% or Intralipid 20% IV via umbilical artery or peripheral infusion Dose (in g/kg/d): Day 1: 0.5 Day 2: 1.0 Day 3: 1.5	60/60 SMOF 20%: 30 Intralipid 20%: 30	Male and female premature neonates (gestational age <34 weeks; 0 to 7 days old) with birth weight of 1000 to 2500 g and requiring PN	Continuous infusion for 20-24 hours per day for 7 to 14 days

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Trial (Trial Time Period)	Trial Design	Dosing	Number of patients randomized/treated	Study population	Planned Duration
03-SMOF-005 (05/2004- 02/2006)	Phase 3, double- blind, randomized, active-controlled, parallel-group, 2- center	Days 4-14: 2.0 SMOFipid 20% or Intralipid 20% IV via peripheral indwelling cannula or central infusion Dose (in g/kg birth weight/d): Days 1-3: 1.0 Day 4: 2.0 Day 5: 3.0 Days 6-14: 3.5	84/84 SMOF 20%: 42 Intralipid 20%: 42	Male and female premature neonates (gestational age <34 weeks; 0 to 7 days old) c with birth weight of 500 to 2000 g and requiring PN	Continuous infusion for 18-24 hours per day for 7 to 14 days

** Data from Trial SMOF-001-CP3 was not included in the Integrated Summary of Safety (ISS) or Integrated Summary of Efficacy (ISE)

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5.2 Review Strategy

The clinical development program consisted of six studies which were performed in adult patients and three studies in pediatric patients. Four of the six adult studies were active-controlled, double-blind studies and the other two adult trials were open-label, randomized. All three of the pediatric studies were randomized, active-controlled, double-blind studies conducted.

Per prior discussions with the Division, Study SMOF-001-CP3, one of the adult active-controlled, double-blind studies was not included in the Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS). Per the Applicant, the data from this study wasn't available at the time the ISE and ISS were prepared. The Applicant has included this study as supportive only and it is not included in the efficacy or safety sections of this review. Therefore, for this application, five adult studies and three pediatric studies were the primary studies that were reviewed.

In two studies (one in adult patients and one in pediatric patients), SMOFlipid 20% was administered for 28 days. The clinical data presented in this submission do not include data from any clinical trials evaluating the efficacy or safety of treatment with SMOFlipid 20% for longer than 28 days. All of the studies were conducted in Europe, Israel and Australia.

The active comparators were Intralipid (approved for use in the US), Lipovenos (b) (4) soybean oil product, not approved for use in the US) and Kabiven, a PN product in a 3 chamber bag that contains Intralipid, glucose, amino acids and electrolytes (approved for use in the US in August 2004). In the two open labeled adult trials, SmofKabiven, a PN product (not approved for use in US) in a 3 chamber bag that contains Smoflipid, glucose, amino acids and electrolytes was the study drug.

In all clinical studies of Smoflipid 20%, patients received a complete PN regimen including glucose, amino acids, electrolytes, vitamins, and trace elements, in addition to the assigned lipid emulsion.

The Applicant has stated that based on discussions with the Division, they reviewed available data with respect to their efficacy value. The Applicant has chosen select variables to support the efficacy claim for Smoflipid. In some cases, parameters that were analyzed as safety variables (i.e. triglyceride levels) in the study reports are presented to support efficacy. Therefore, the review of efficacy is to a large extent also a clinical safety evaluation.

Safety and efficacy analysis also intersect in the assessment of the adequate delivery of

essential fatty acids. A lipid product that cannot supply an adequate amount of fatty acids may both lack efficacy and be considered unsafe in certain circumstances.

From an efficacy perspective an intravenous lipid emulsion for clinical use should be expected to supply adequate amounts of calories and adequate amounts of essential fatty acids to prevent the development of essential fatty acid deficiency. From a safety point of view an intravenous lipid product should be able to restore essential fatty acids stores when these are low or depleted and keep up with long-term requirements so that essential fatty acid deficiency does not arise while patients are on the product.

It is important that prescribers can be confident that the administration of a specific lipid emulsion can replenish essential fatty acid stores in patients who have preexisting EFAD using the usually tolerated or recommended infusion amounts, especially in premature infants who rely on EFA for their neurological and overall development.

The Applicant's claim of efficacy for the use of SMOFlipid 20% in adult patients is based on the results of 5 prospective, randomized, active-controlled studies:

- Study FE-SM-03-DE was conducted in 249 postoperative adult patients in need of total parenteral nutrition (TPN) for ≥ 5 days. The objective of the study was to evaluate efficacy, safety, and tolerance of SMOFlipid 20% compared to Lipovenös® 20% (soybean oil emulsion). Efficacy was assessed on the basis of effects on serum triglyceride concentrations, fatty acid profiles as well as fatty acids in plasma and cell membrane phospholipids (defined as primary and secondary efficacy variables in the clinical study report [CSR]), and albumin levels (defined as a safety variable in the CSR).
- Study FE-SM-04-CH was conducted in 35 adult patients in need of TPN for 10 to 14 days. The objective of the study was to evaluate safety and tolerance of SMOFlipid 20% compared to Lipovenös 20%. Efficacy was assessed on the basis of effects on serum triglyceride concentrations (defined as a safety variable in the CSR).
- Study 03-3CB7-001 was conducted in 60 postoperative adult patients in need of PN for ≥ 5 days. The objective of the study was to evaluate safety and tolerance of SmofKabiven compared to Kabiven®. Efficacy was assessed on the basis of effects on serum triglyceride concentrations (defined as a safety variable in the CSR).
- Study 03-3CB8-001 was conducted in 52 adult patients in need of PN for 5 to 7 days. The objective of the study was to compare safety and tolerance of SmofKabiven Peripheral with Kabiven® Peripheral. Efficacy was assessed on the

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basis of effects on serum triglyceride concentrations (defined as a safety variable in the CSR).

- 05-SMOF-006 was conducted in 75 adult patients in need of PN for at least 4 weeks. The primary objective of the study was to compare safety and tolerance of SMOFlipid 20% with Intralipid® 20%. Efficacy was assessed on the basis of effects on serum triglyceride levels, fatty acids in plasma lipoproteins and red blood cell (RBC) phospholipids, and albumin levels (all defined as safety variables in the CSR).

In the adult studies included in this submission, the Applicant states that only study FE-SM-03-DE was designed to examine changes in triglyceride levels as the primary efficacy endpoint; while the other clinical studies in adult patients evaluated triglyceride levels and other potential measurements of nutritional status or lipid metabolism as assessments of safety.

Study SMOF-001-CP3, entitled “A prospective, randomized, double-blind, parallel controlled, multicentre clinical trial to evaluate efficacy and safety of SMOFlipid 20% vs. Intralipid® 20% during PN of moderate or major abdominal surgery” was initiated in China in August 2008. Postoperative adult patients who required treatment with PN for at least 5 days were included in this study. This Phase 3 clinical study in adult patients was conducted in China to meet the local regulatory requirements for the approval of SMOFlipid 20% in China only. Per discussions with the Division, this study was not integrated into the safety or efficacy summary, but is instead reviewed separately.

(b) (4)



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(b) (4)

The investigative treatments were Smoflipid 20%, or SmofKabiven or SmofKabiven Peripheral, both 3CB systems where Smoflipid 20% was the lipid component of the bag and the other 2 chambers contained glucose and amino acids, respectively. In the Smoflipid 20% studies, the active comparators were commercially available pure soybean oil lipid emulsions: Lipovenös 20% in studies FE-SM-03-DE and FE-SM-04-CH in adult patients, and Intralipid 20% in study 05-SMOF-006 (adult patients) and studies 00-SMOF-002, 00-SMOF-004, and 03-SMOF-005 (pediatric patients). In the SmofKabiven studies, 03-3CB7-001 and 03-3CB8-001, the active comparators were Kabiven (in study 03-3CB7-001) and Kabiven Peripheral (in study 03-3CB8-001), where the lipid component was Intralipid 20%. Intralipid 20% is approved in the US. Lipovenos 20% is not approved for use in the US, (b) (4). Kabiven and Kabiven Peripheral (Perikabiven) are approved for use in the US.

Table 9: Composition and Characteristics of Smoflipid 20% and Control Lipid Emulsions

Component	SMOF lipid 20%	Lipovenös 20%	Intralipid 20%
Soybean oil, g/L	60	200	(b) (4)
MCTs, g/L	60	—	
Olive oil, g/L	50	—	
Fish oil, g/L	30	—	
Glycerol, g/L	25	25	
Egg phospholipids, g/L	(b) (4)		
α -tocopherol ^a , mg/L			
Energy content, kcal/L	2,000	2,000	2,000

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Energy content, MJ/L

(b) (4)

ω 6: ω 3 fatty acid ratio

MCT = medium-chain triglyceride.

^a SMOFlipid 20% includes 163–225 mg all-rac- α -tocopherol, considering the natural variation from the raw materials.

^b α -tocopherol in Lipovenös 20% and Intralipid 20% is a natural component of the soybean oil emulsion. (Antébi 2004; Pironi 2003).

Source: Section 3.2.P.2 for SMOFlipid 20% and Fresenius Kabi data on file for Lipovenös 20% and Intralipid 20%.

Applicant's table

Per the ASPEN guidelines, adult energy requirements range from 20–30 kcal/kg. In addition, the guidelines state that the standard distribution of non-protein calories should be 70–85% as carbohydrate and 15–30% as fat. The guidelines also state that this distribution may be adjusted based on tolerance and that “there is limited clinical benefit when fat content exceeds 30% of nonprotein calories.”

Based on these estimates, in adult patients it is recommended that the fat content of parenteral nutrition formulations not exceed 2.5 g/kg/day. The applicant has therefore based their proposed dosing on the ASPEN guidelines.

5.3 Discussion of Individual Studies/Clinical Trials

Adult Trials

FE-SM-03-DE

A Phase 3, double-blind, randomized, active-controlled, parallel-group, multicenter study conducted from September 1997 (first patient in [FPI]) to July 1998 (last patient out [LPO]). The target patient population was adult patients 18 years of age or older requiring at least 5 days of PN following major abdominal, thoracic, or urological surgery. The Applicant considered this study the pivotal trial for this submission.

The study was conducted in 18 centers in Belgium, France, and Germany. A total of 249 (126 Smoflipid 20% and 123 Lipovenös 20%) patients were randomized. Of these, 244 were included in the ITT population and 199 (99 Smoflipid 20% and 100 Lipovenös 20%) in the PP population used in the primary efficacy analysis. The 2 treatment groups were similar with respect to demographics, surgical procedures, and use of concomitant medications and blood substitutes.

Exclusion criteria included hyperlipidemia (fasting serum triglycerides >2.8 mmol/L, total cholesterol >7.8 mmol/L); diabetes mellitus; body mass index (BMI) >30 kg/m²; hepatic or renal insufficiency; acute or chronic cardiac insufficiency; severe hemorrhagic

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diathesis; any acute or life-threatening disease; and history of severe allergy against any of the ingredients of the lipid emulsions (allergy against egg, soybean or fish protein).

Screening for entry into the study was performed within 3 days before surgery. Final study assessments were scheduled for the day after the end of the treatment period (Day 6).

Smoflipid 20% was to be administered as a continuous IV infusion over each 24-hour period at a rate of 1.5 g lipids/kg/d, starting on the morning of Day 1 (the day after surgery) and continuing for 5 days. The active control, Lipovenös 20%, was to be administered at the same dose, infusion rate, and duration of treatment. Amino acids (approximately 1.5 g/kg/d) and glucose (3 to 4 g/kg/d) were to be administered concomitantly as additional PN. Depending on the metabolic condition of the patient, the doses of lipids and glucose could each be optionally reduced by up to 50% on the first postoperative day. Electrolytes, trace elements, and vitamins were administered as required. Enteral nutrition during the first 5 postoperative days was not to be allowed.

The following variables were used to support the claim of efficacy of Smoflipid 20%:

- Change in mean and median serum triglyceride concentration, and individual shifts from baseline to Day 6
- Change in proportions of free fatty acids in plasma and fatty acids in plasma phospholipids, leukocyte phospholipids, and platelet phospholipids

In the study report, the primary efficacy endpoint was the change from the pre-infusion serum triglyceride concentration, based on the area under the concentration-time curve (AUC) of the difference between baseline value and the values at each measurement point up to Day 6. The following secondary efficacy variables were analyzed in a per-protocol (PP) subgroup of 33 patients at 2 pre-specified centers: fatty acid profiles, eicosanoid synthesis in leukocytes and platelets, including leukotrienes (LTB), thromboxanes (TXB), and α -tocopherol concentration. Further secondary efficacy endpoints analyzed in patients at all centers included serum total cholesterol, serum phospholipids, clinical outcome including length of stay in hospital / intensive care unit (ICU), and other clinical outcome parameters.

For the primary efficacy analysis in the PP population, missing values for serum triglycerides on Days 0, 1, 3, or 6 (analyzed by a central laboratory), were to be imputed using the results from the safety (local) laboratory, and missing values on Days 2, 4, or 5 were to be imputed using the mean of values preceding and succeeding the missing value.

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The primary efficacy endpoint was also analyzed for the ITT population using a combined LOCF/imputation approach for missing values. The same analysis method was applied for the PP population. Descriptive statistics for serum triglyceride concentrations up to Day 6 were also presented for the PP and ITT populations.

For secondary parameters, descriptive statistics were presented by treatment group.

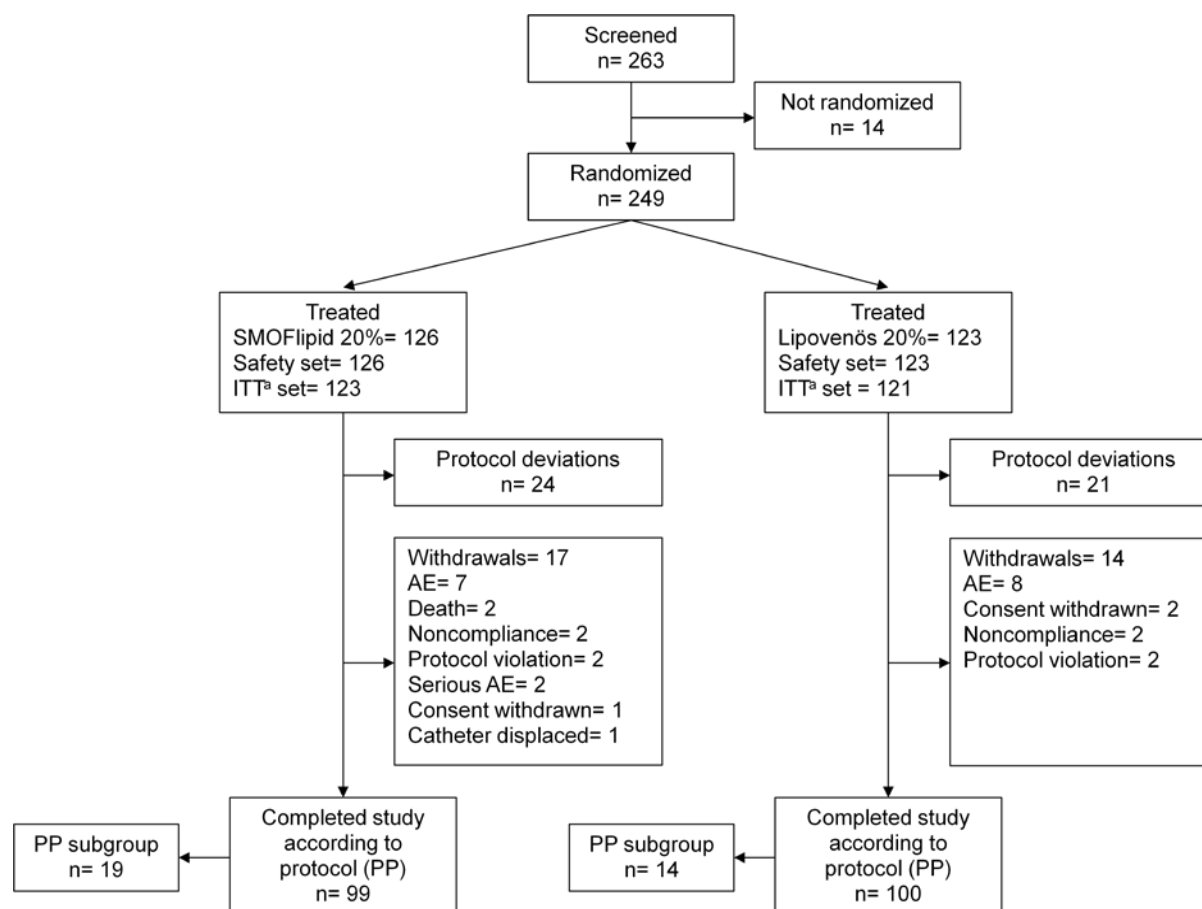
Results:

Demographics

Table 10: Demographics Study FE-SM-03-DE

Characteristic	Smoflipid 20% (N=99)	Lipovenös 20% (N=100)
Sex, n (%)		
Male	58 (58.6)	65 (65.0)
Female	41 (41.4)	35 (35.0)
Race, n (%)		
White	98 (99.0)	98 (98.0)
Other ^a	1 (1.0)	2 (2.0)
Age (years)		
Mean (SD)	60.5 (14.15)	60.2 (13.75)
Median (min-max)	61.0 (23.0-89.0)	62.0 (19.0-84.0)
Body weight (kg)		
Mean (SD)	70.5 (11.70)	71.6 (12.81)
Median (min-max)	70.0 (45.0-92.0)	72.0 (39.0-104.5)
Body height (cm)		
Mean (SD)	168.3 (7.88)	170.0 (9.43)
Median (min-max)	168.0 (150.0-188.0)	169.0 (136.0-188.0)
BMI (kg/m²)		
Mean (SD)	24.7 (3.21)	24.5 (3.45)
Median (min-max)	25.0 (17.0-30.0)	25.0 (17.0-32.0)

Figure 2: Flow of Patients in Study FE-SM-03-DE



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In the safety population, the mean lipid dose administered on Day 1, following the optional dose reduction of up to 50%, was 1.274 g/kg/d for the Smoflipid 20% group, and 1.306 g/kg/d for the Lipovenös 20% group. Mean lipid dose on Days 2 to 5 ranged from 1.484 g/kg/d to 1.494 g/kg/d for the Smoflipid 20% group, and from 1.476 g/kg/d to 1.497 g/kg/d for the Lipovenös 20% group.

The primary endpoint was the serum concentration of triglycerides measured by the AUC of the difference between the pre-infusion value on day 1 and the value at each measurement point, up to day 6. For the per-protocol population, the mean daily AUC (difference from baseline) for the serum concentration of triglycerides was 0.7340 mmol/l for the Smoflipid group and 0.7197 mmol/l for the Lipovenos group. The Applicant stated that the lower limit of the one sided 95% confidence interval for this difference between the treatment means was -0.0891, demonstrating that the treatments were equivalent. The Applicant reported similar results for the ITT population, the lower limit of the one sided 95% confidence interval for the difference between the treatment means was higher than -0.0474, demonstrating that the treatments were equivalent.

Cholesterol

For both treatment groups, a post-operative decrease in mean total cholesterol was observed, followed by an increase to the end of the study. The increase in the Smoflipid group was mildly greater than the comparator group. Mean values at day 6 were not higher than values obtained at baseline in either group.

Table 11: Total cholesterol (mmol/l)

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Total Cholesterol (mmol/l)						
Per-Protocol Population	N	Mean	SD	LCLM	UCLM	Median
SMOF Group						
day 0	97	4.822	1.3238	4.5548	5.0885	4.820
day 1	97	2.810	1.0863	2.5913	3.0291	2.630
day 2	95	2.962	0.9790	2.7623	3.1611	2.960
day 3	98	3.235	0.9370	3.0467	3.4225	3.165
day 4	99	3.552	0.8976	3.3731	3.7311	3.460
day 5	97	3.795	0.8350	3.6267	3.9632	3.810
day 6	97	4.026	0.9310	3.8380	4.2133	4.020
Lipovenos Group						
day 0	98	4.811	1.3425	4.5418	5.0801	4.795
day 1	98	2.977	0.9928	2.7777	3.1758	2.920
day 2	99	2.995	0.8482	2.8263	3.1646	2.890
day 3	99	3.261	0.8276	3.0960	3.4261	3.160
day 4	100	3.418	0.7891	3.2615	3.5747	3.415
day 5	97	3.667	0.8642	3.4930	3.8414	3.660
day 6	97	3.891	0.9729	3.6954	4.0875	3.750

Applicant's table

Clinical outcomes

Length of stay (LOS) hospital/ICU

For the PP population, the mean LOS in hospital was shorter for the Smoflipid group (15.688 days) than for the Lipovenos group (17.827 days). Median LOS in hospital was similar for the two treatment groups (14.500 days for the Smoflipid group and 14.000 days for the Lipovenos group). The mean LOS in ICU was similar for the two treatment groups.

For the I.T.T. population, there were no apparent differences between the treatment groups with respect to the mean LOS in hospital (17.633 and 18.322 days for the Smoflipid and Lipovenos groups, respectively) or the mean LOS in ICU (5.418 days for the Smoflipid group and 5.587 days for the Lipovenos group).

Clinical comments: The clinical outcome measures are presented as descriptive statistics. No statistical analysis plan was conducted.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

FE-SM-04-CH

Study FE-SM-04-CH was a single-center study conducted from January 1998 (FPI) to August 1998 (LPO). The objective of this study was to evaluate safety and tolerance of Smoflipid 20% vs. Lipovenös 20% in patients requiring PN. The target population comprised adult patients ≥ 18 years of age in need of TPN for 10 to 14 days. Exclusion criteria included treatment for hyperlipidemia (fasting serum triglycerides >3.5 mmol/L, total cholesterol >8 mmol/L); known diabetes mellitus requiring insulin; severe hemorrhagic diathesis; acute or life-threatening diseases with an anticipated life expectancy ≤ 3 days; end-stage disease (uncontrolled sepsis); and history of severe allergy against any of the ingredients of the lipid emulsion (e.g., allergy against egg, soybean, or fish protein).

Screening for entry into the study was done within 3 days before the start of study treatment. Final study assessments were scheduled after the last infusion (Days 11 to 15).

The investigative treatment was Smoflipid 20% and the active comparator was Lipovenos 20%.

Smoflipid 20% or Lipovenös 20% was to be administered as a continuous central IV infusion over 18 to 24 hours at a maximum infusion rate of 0.625 mL/kg/h, corresponding to a lipid dose of 0.125 g/kg/h, for 10 to 14 days. The maximum daily dose was 10 mL/kg corresponding to a lipid dose of 2 g/kg. Fluid substitution, electrolytes, vitamins, and trace elements could be administered according to the patient's requirements.

The following variables were used to support the claim of efficacy of Smoflipid 20%: Change in mean and median serum triglyceride concentration, and individual shifts, from baseline to final assessment.

There were no pre-specified efficacy endpoints in this study since the study objective was to evaluate the safety and tolerability of Smoflipid 20%. Triglyceride concentration was reported as a safety parameter in the study report.

The analysis was planned to be descriptive only; no inferential tests between the treatment groups were planned to be performed on safety parameters. The efficacy parameter, triglyceride concentrations, was evaluated for both the PP and ITT populations.

Results:

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

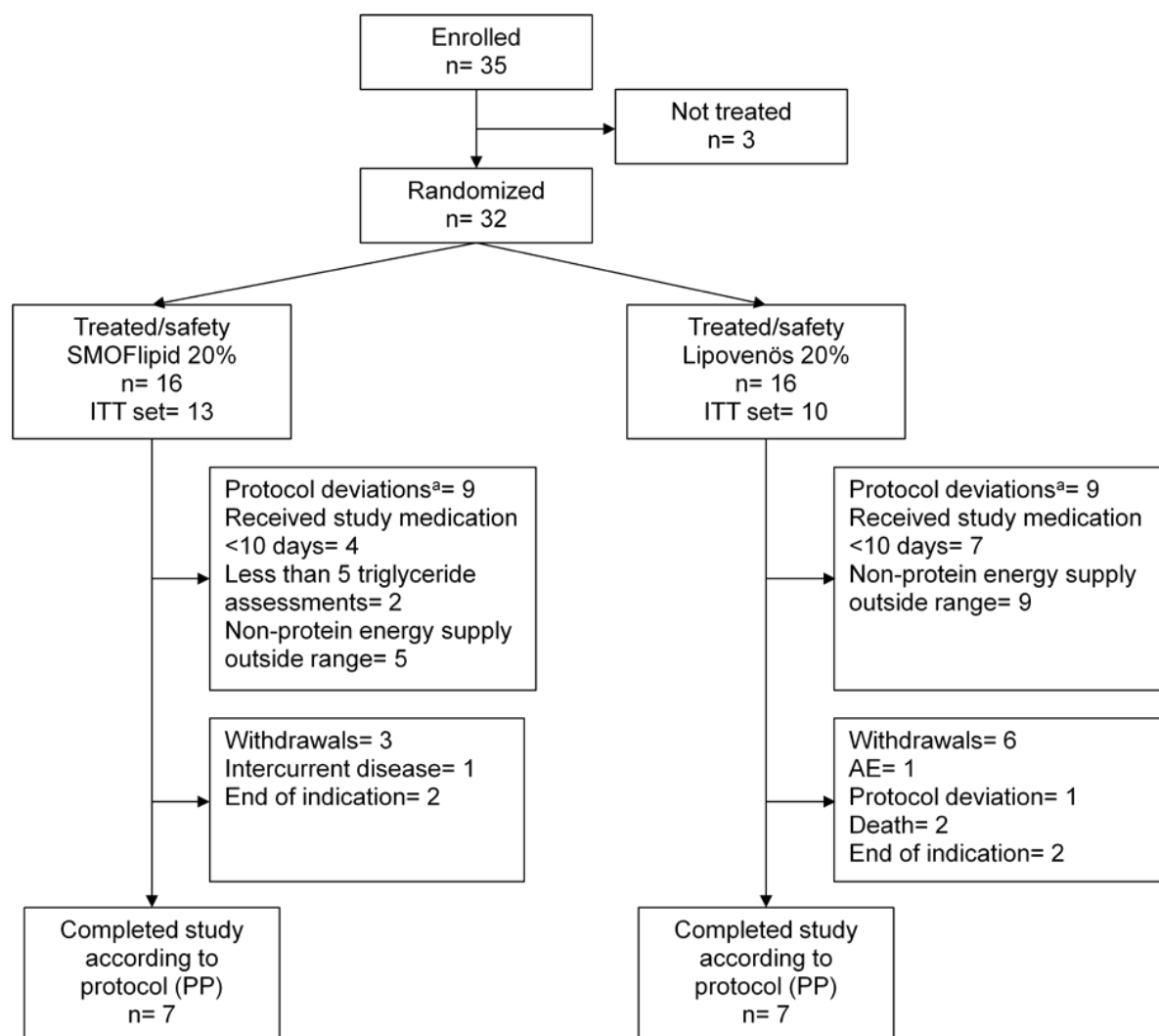
Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

The demographics were similar between both groups, except for sex. There were more males in the Smoflipid group (69.2%) than in the comparator group (40%) and more females in the comparator group (60%) versus the Smoflipid group (30.8%).

Table 12: Summary of Demographic Characteristics in Study FE-SM-04-CH at Baseline – Intent to Treat Population

Characteristic	Smoflipid 20% (N=13)	Lipovenös 20% (N=10)
Sex, n (%)		
Male	9 (69.2)	4 (40)
Female	4 (30.8)	6 (60)
Race, n (%)		
White	12 (92.3)	8 (80.0)
Other	1 (7.7)	2 (20)
Age (years)		
Mean (SD)	49.14 (20.03)	51.87 (23.13)
Median (min-max)	49.44 (22.21-74.95)	45.49 (25.26-86.27)
Body weight (kg)		
Mean (SD)	60.2 (10.23)	54.7 (14.8)
Median (min-max)	56 (47.3-82.6)	52.50 (30-86)
Body height (cm)		
Mean (SD)	170.85 (11)	162.70 (11.66)
Median (min-max)	173.00 (150-190)	165.00 (142-177)

Figure 3: Flow of Patients in Study FE-SM-04-CH



Triglycerides

The median triglyceride concentration during the course of the study were comparable between the two treatment groups. An elevation from pre-infusion (screening) to the first day of study infusion was seen in both groups (medians of 1.40 mmol/L (screening) and 1.80 mmol/L (day 1) in the Smoflipid group; medians of 1.30 mmol/L (screening) and 1.60 mmol/L (day 1) in the Lipovenos group). Further, during the course of the study the

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

median triglyceride concentration decreased again and was comparable between both treatment groups with final values of 1.55 mmol/L in the Smoflipid group and 1.30 mmol/L in the Lipovenos 20% group. These changes were not clinically meaningful.

03-3CB7-001

A Phase 3, prospective, open-label, randomized, active-controlled, parallel-group, single-center study conducted in Germany from July 2004 (FPI) to February 2005 (LPO). The target population comprised adult patients 18 to 85 years of age expected to require PN for 5 to 7 days following major intestinal tract surgery. Exclusion criteria included severely malnourished or overweight patients (BMI of <16 or >35 for men, or <15 or >34 for women); body weight exceeding 95 kg; septic shock; diabetes mellitus with known ketoacidosis within 7 days of onset of study treatment; renal insufficiency; acute liver dysfunction; known type IV hyperlipidemia; disturbances in lipid metabolism or hypertriglyceridemia; known congenital error of amino acid metabolism; unstable angina pectoris; chemotherapy or radiation therapy within 7 days before the start of study treatment; and contraindication of the study products including history of severe allergy against any of the ingredients of lipid emulsions (e.g., allergy to egg, soybean, or fish protein).

Screening for entry into the study was completed before surgery. Final study assessments were scheduled for completion within 24 hours of the last administration of study treatment (Period 7; equivalent to Day 7). During the follow-up phase, adverse events (AE) up to 1 day and serious adverse events (SAE) up to 7 to 10 days after the last study infusion were documented.

The investigative treatment was SmofKabiven (Smoflipid 20%) and the active comparator was Kabiven (Intralipid 20%).

SmofKabiven or Kabiven was to be administered as a continuous central IV infusion over 24 hours for 5 to 7 days. Study days were defined as 24-hour periods starting before the administration of study treatment in Period 1 (the first post-operative day). Initially, 15 mL/kg/d were to be administered during Period 1. During Periods 2 to 4, the dose was to be increased to 22.5 to 30.0 mL/kg/d (corresponding to lipid doses of 0.86 to 1.14 g/kg/d from Smoflipid 20% [the lipid component of SmofKabiven], or 0.9 to 1.2 g/kg/d from Intralipid 20% [the lipid component of Kabiven]), and to 15.0 to 30.0 mL/kg/d during Periods 5 to 7 (corresponding to lipid doses of 0.57 to 1.14 g/kg/d from Smoflipid 20%, or 0.6 to 1.2 g/kg/d from Intralipid 20%). The dose was reduced for subjects with a body weight between 86 and 95 kg. Limited amounts of oral or enteral nutrition were permitted in Periods 5, 6, and 7 at the investigator's discretion, and these were to be accounted for by a reduction of the infusion volumes in these periods. Individual deviations from the selected dosage could be taken at the investigator's discretion.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Vitamins, trace elements and electrolytes could be administered at the investigator's discretion.

The following variables were used to support the claim of efficacy of Smoflipid 20%: Change in mean and median serum triglyceride concentration, and individual shifts, from baseline to final assessment

There were no pre-specified efficacy variables in this study, since the study objective was to evaluate the safety and tolerability of Smoflipid 20%. Triglyceride concentration was reported as a safety parameter in the study report.

The analysis was planned to be descriptive only; no formal hypothesis testing was planned.

Results:

A total of 60 patients were enrolled and randomized (30 patients in each group). Of these, 7 patients did not receive any treatment and had to be excluded from the analysis. 53 patients were included in the ITT population (SmofKabiven: 26 patients, Kabiven: 27 patients).

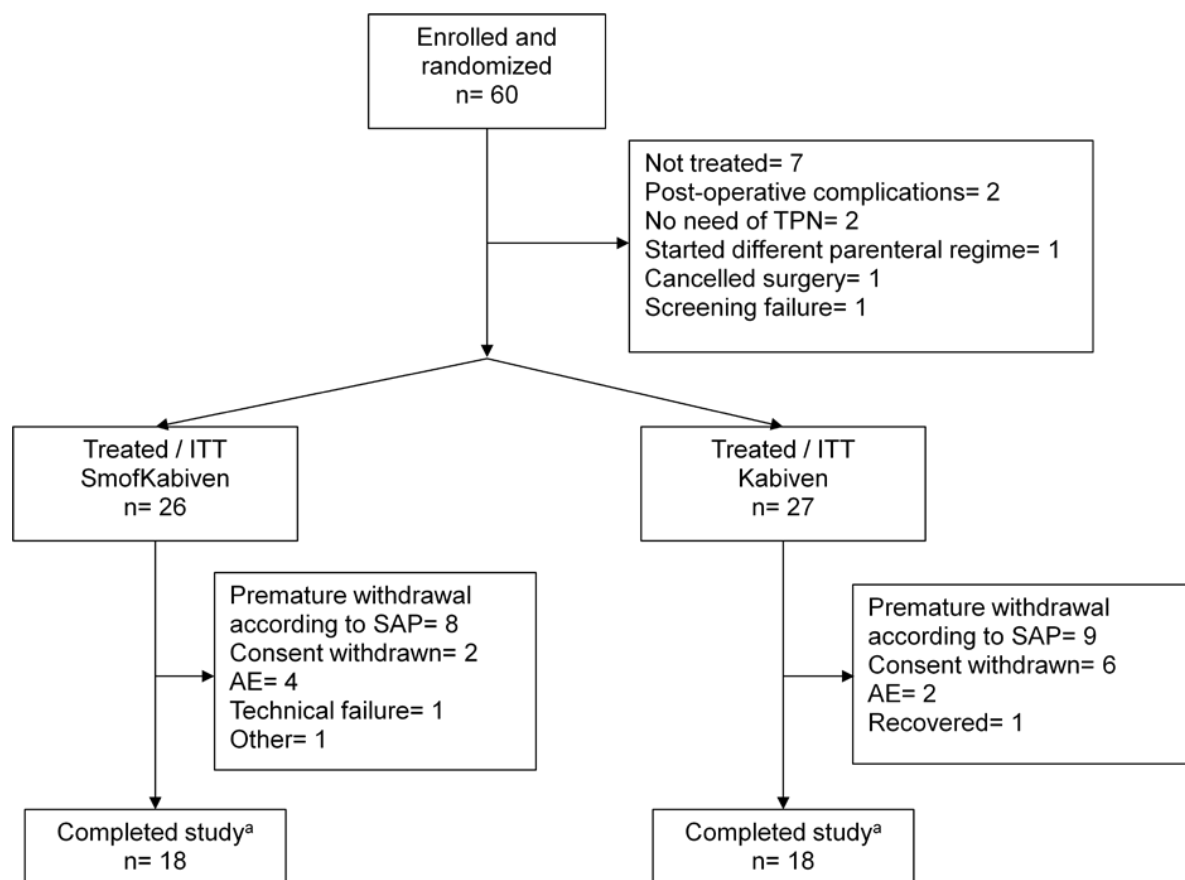
The baseline demographics were similar except for sex. Overall, there were more males in the study. The ratio of males to females was approximately 2:1. There were more males in the Kabiven group (77.8%) compared to the SmofKabiven group (57.7%) and there were more females in the SmofKabiven group (42.3%) compared to the Kabiven group (22.2%).

The main inclusion criterion was that patients had to undergo major intestinal tract surgery anticipated to require PN for ≥ 5 days. The majority of patients had colon cancer (3CB SMOF EL: 3/26 (11.5 %); Kabiven: 8/27 (29.6 %)) or gastric cancer NOS (3CB SMOF EL: 2/26 (7.7 %); Kabiven: 3/27 (11.1 %)). The most frequently performed surgeries were partial colectomy (3CB SMOF EL: 4/26 (15.4 %); Kabiven: 8/27 (29.6 %)) and cholecystectomy (3CB SMOF EL: 3/26 (11.5 %); Kabiven: 6/27 (22.2 %)). A resection of the rectum was conducted in 6/26 (23.1 %) 3CB SMOF EL and 1/27 (3.7 %) Kabiven patients.

Table 13: Summary of Demographic Characteristics in Study 03-3CB7-001 at Baseline – Intention-to-Treat Population

Characteristic	SmofKabiven (N=26)	Kabiven (N=27)
Sex, n (%)		
Male	15 (57.7)	21 (77.8)
Female	11 (42.3)	6 (22.2)
Age (years)		
Mean (SD)	57.7 (12.64)	63.0 (10.06)
Median (min-max)	62.5 (35-79)	63.0 (35-82)
Body weight (kg)		
Mean (SD)	72.4 (11.26)	74.4 (10.24)
Median (min-max)	73.0 (48-93)	77.0 (47-93)
Body height (cm)		
Mean (SD)	167.9 (7.62)	172.5 (7.51)
Median (min-max)	169.0 (153-183)	173.0 (152-188)
BMI (kg/m²)		
Mean (SD)	25.7 (3.62)	25.0 (3.09)
Median (min-max)	25.0 (20-31)	24.3 (20-32)

Figure 4: Flow of Patients in Study 03-3CB7-001



Triglyceride levels

The postoperative patients in the study population had low mean and median triglyceride values at baseline. While the median triglyceride concentrations at baseline were similar between the treatment groups, the mean values were higher in the SmofKabiven group than in the Kabiven group. Mean and median triglyceride concentrations showed similar changes from screening to final assessment (LOCF) in both treatment groups; decreasing from screening (presurgery) to Period 1 (baseline, post-surgery and pre-infusion), increasing rapidly from Period 1 to Period 4, and then increasing more gradually until final assessment. The mean and median increases were greater in the SmofKabiven group (mean change from baseline to final of 74.54 mg/dL) than in the Kabiven group (mean change from baseline to final of 66.75 mg/dL). Of note, this trial reported triglyceride values in mg/dl compared to first two trials which reported triglyceride values in mmol/L.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

03-3CB8-001

A Phase 3, prospective, open-label, multicenter, randomized, active-controlled, parallel-group, multicenter study conducted from July 2004 (FPI) to October 2005 (LPO). The target population comprised adult patients 18 to 85 years of age requiring PN for 5 to 7 days. Exclusion criteria included general contraindications of infusion therapy (acute pulmonary edema, hyperhydration or decompensated cardiac insufficiency); known hypersensitivity to egg, soy protein or any of the ingredients of the study treatments; severe blood coagulation disorders; shock necessitating acute resuscitation at the discretion of the investigator; diabetes mellitus with known ketoacidosis within 7 days of onset of study treatment; renal insufficiency; severe liver dysfunction; known type IV hyperlipidemia; disturbances in lipid metabolism or hypertriglyceridemia; known inborn error of amino acid metabolism; unstable angina pectoris; and chemotherapy within 7 days before the start of study treatment.

Screening was completed within 24 hours before the start of study treatment. Final study assessments were scheduled after administration of the last study treatment (Day 7). During the follow-up phase, AEs up to 1 day and SAEs up to 7 to 10 days after the last study infusion were documented.

The investigative treatment was SmofKabiven (Smoflipid 20%) and the active comparator was Kabiven (Intralipid 20%).

One bag of SmofKabiven Peripheral (1904 mL) or Kabiven Peripheral (1920 mL) was to be infused per day via a peripheral IV line over an infusion period of 14 to 24 hours for 5 to 7 days. SMOFlipid 20% was to be infused at a dose of 1 to 2 g lipids/kg/d. Up to 700 kcal/day of oral/enteral nutrition were acceptable at the discretion of the investigator.

The following variables were used to support the claim of efficacy of SMOFlipid 20%: Change in mean and median serum triglyceride concentration, and individual shifts, from baseline to follow-up (last observation carried forward [LOCF]).

There were no pre-specified efficacy variables in this study, since the study objective was to evaluate the safety and tolerability of SMOFlipid 20%. Triglyceride concentration was reported as a safety parameter in the study report.

The analysis was planned to be descriptive only. No formal hypothesis testing was planned.

Results:

Overall, the treatment groups were similar with regard to demographic baseline data.

Clinical Review

Karyn L. Berry, MD, MPH

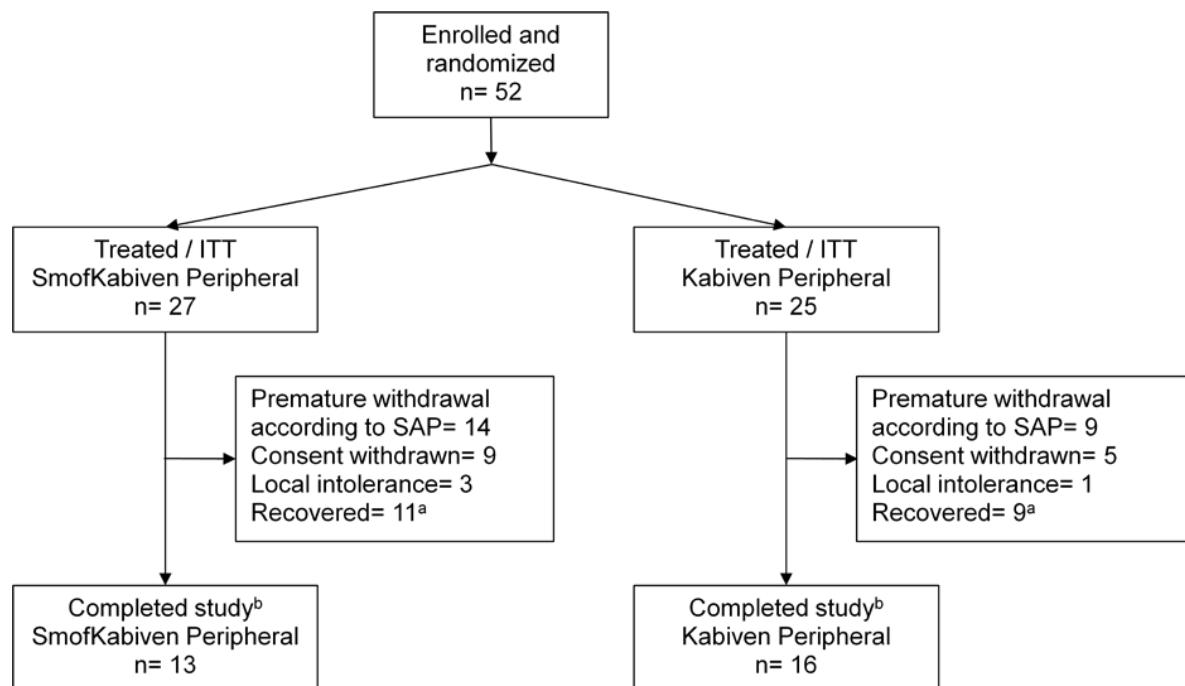
NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Table 14: Summary of Demographic Characteristics in Study 03-3CB8-001 at Baseline – Intention-to-Treat Population

Characteristic	SmofKabiven Peripheral (N=27)	Kabiven Peripheral (N=25)
Sex, n (%)		
Male	6 (22.2)	10 (40.0)
Female	21 (77.8)	15 (60.0)
Age (years)		
Mean (SD)	51.6 (21.1)	56.9 (17.6)
Median (min-max)	50.0 (20-82)	62.0 (20-84)
Body weight (kg)		
Mean (SD)	59.0 (14.3)	63.2 (15.0)
Median (min-max)	60.0 (39-90)	65.0 (35-99)
Body height (m)		
Mean (SD)	1.662 (0.116)	1.681 (0.104)
Median (min-max)	1.65 (1.45-1.90)	1.66 (1.53-1.92)
BMI (kg/m²)		
Mean (SD)	21.39 (4.88)	22.31 (4.67)
Median (min-max)	21.0 (13.8-31.2)	22.5 (12.7-30.8)

Figure 5: Flow of Patients in Study 03-3CB8-001



Study duration and infusion time (mean $\pm$ SD [median]) were longer in the Kabiven Peripheral group (6.9 $\pm$ 2.0 [7.0] days; 80.5 $\pm$ 37.9 [79.9] hours) than in the SmofKabiven Peripheral group (5.9 $\pm$ 1.9 [6.0] days; 66.2 $\pm$ 37.4 [76.8] hours).

Triglyceride levels

There were no significant differences in mean or median serum triglyceride concentrations between the treatment groups at baseline. In both treatment groups, mean and median triglyceride concentrations increased from baseline (Day 1 LOCF) to Day 4 (LOCF); mean values then decreased between Day 4 (LOCF) and the follow-up visit (LOCF) in both groups, while the median values remained stable through the follow-up visit (LOCF). Larger increases in the mean and median values (change in baseline to follow-up) were seen in the SmofKabiven Peripheral group (mean 13.5 mg/dL) than in the Kabiven Peripheral group (mean -2.0 mg/dL). No triglyceride levels outside the normal range in either treatment group were reported as AEs in this study. As in study 03-3CB7-001, triglyceride values are reported in mg/dL.

05-SMOF-006

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

A Phase 3, double-blind, randomized, active-controlled, parallel-group, multicenter study conducted from October 2007 (FPI) to October 2008 (LPO). The target patient population comprised adult patients 18 to 85 years of age who were unable to sustain an adequate oral/enteral food intake and in need of PN for at least 4 weeks. Exclusion criteria included known hypersensitivity to fish, egg, soy, or peanut protein or to any of the active substances or excipients; known type IV hyperlipidemia; disturbances in lipid metabolism or hypertriglyceridemia (fasting serum triglycerides at the time of inclusion >3 mmol/L); severe liver insufficiency; severe blood coagulation disorders; chronic stable renal insufficiency; general contraindications to infusion therapy such as acute pulmonary edema; hyperhydration; decompensated cardiac insufficiency; unstable conditions (e.g., severe post-traumatic conditions); unstable angina pectoris; acute shock; and chemotherapy within 4 weeks before start of the study or during the study.

Screening for entry into the study took place within 24 hours before the start of study treatment. Final study assessments were scheduled for 2 to 24 hours after the end of the treatment period (Day 29).

The investigative treatment was Smoflipid 20% and the active comparator was Intralipid 20%.

The study treatments Smoflipid 20% and Intralipid 20% were provided in 500 mL glass bottles. Additionally, Fresenius Kabi provided the pharmacy with suitable PN bags, (e.g., multilayer (b) (4) bags), if locally required. Therefore, 2-chamber bags and all-in-one bags were used in this study for PN administration. Smoflipid 20% was to be infused at a dose of 1 to 2 g lipids/kg/d corresponding to 5 to 10 mL/kg/d emulsion via central vein catheter for 10 to 24 hours/day, 5 to 7 days/week for a total of 4 weeks. Intralipid 20% was administered at the same dose, infusion rate, and duration. Additional oral or enteral nutrition could be given at the discretion of the investigator.

The following variables were used to support the claim of efficacy of Smoflipid 20%:

- Change in mean and median serum triglyceride concentration, and individual shifts from baseline to Week 4
- Change in proportions of fatty acids in plasma lipoproteins and RBC phospholipids
- Change in mean and median albumin concentration

There were no pre-specified efficacy variables in this study, since the study objective was to evaluate the safety and tolerability of Smoflipid 20%. Triglyceride concentration, fatty acid profiles, and albumin concentration were reported as safety parameters in the study report.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

The analysis was planned to be descriptive only.

Results:

Overall, except for sex, the treatment groups were comparable at baseline.

Table 15: Summary of Demographic Characteristics in Study 05-SMOF-006 at Baseline – Evaluable Population

Characteristic	SMOFlipid 20% (N=28)	Intralipid 20% (N=29)
Sex, n (%)		
Male	16 (57.1)	16 (55.2)
Female	12 (42.9)	13 (44.8)
Race, n (%)		
White	27 (96.4)	28 (96.6)
Black	1 (3.6)	0
Oriental/Asian	0	0
Other	0	1 (3.4)
Age (years)		
n	28	29
Mean (SD)	52.5 (13.91)	43.9 (12.61)
Median (min-max)	55.5 (23-73)	49.0 (21-61)
Body weight (kg)		
n	28	29
Mean (SD)	55.68 (11.84)	55.62 (14.71)
Median (min-max)	54.80 (38.0-90.0)	53.00 (35.0-85.0)

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Body height (cm)

n	27	29
Mean (SD)	164.30 (12.13)	165.88 (9.03)
Median (min-max)	163.00 (128.0-180.0)	166.00 (150.0-185.0)

BMI (kg/m²)

n	27	29
Mean (SD)	20.78 (4.55)	20.09 (4.70)
Median (min-max)	20.50 (14.7-35.5)	18.40 (14.3-34.0)

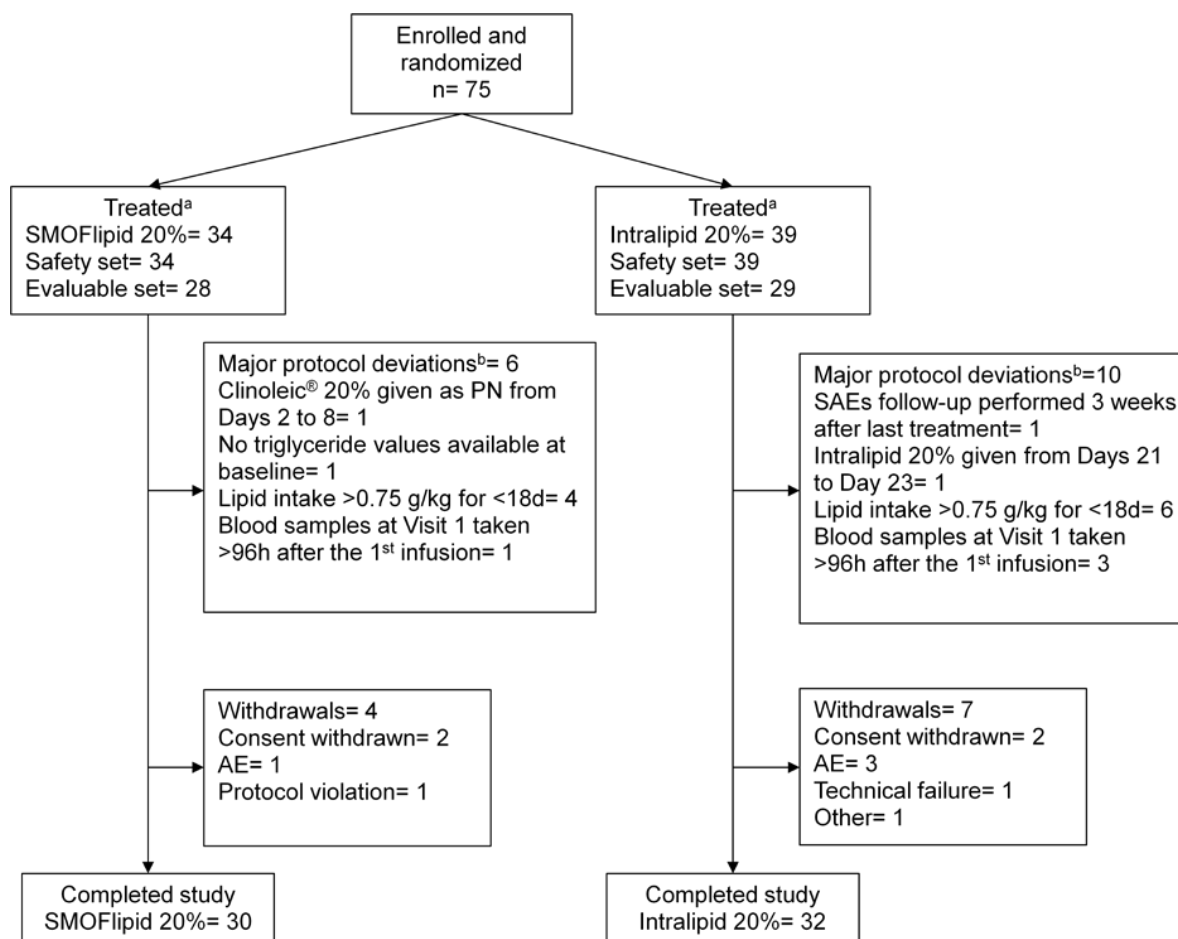
Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Figure 6: Flow of Patients in Study 05-SMOF-006



No efficacy parameters were evaluated in this study. Only safety assessments were evaluated. Data were summarized using descriptive statistics for continuous variables and using frequency percentage for discrete/categorical variables.

Both treatment groups had a similar exposure to study drug with a mean of 26.8 days (median of 29 days) in the Smoflipid group and mean of 25.6 days (median of 28 days) in the Intralipid group. Both treatment groups also were similar with regards to daily and total amount of glucose and amino acid intake per kg of body weight. Patients in the Smoflipid group received (arithmetic mean $\pm$ SD [median]) 3.0 ± 1.3 (3.3) g/kg bw/day glucose and 1.2 ± 0.6 (1.1) g/kg bw/day amino acids while patients the Intralipid® group

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

received 3.1 ± 1.6 (3.2) g/kg bw/day glucose and 1.2 ± 0.7 (1.1) g/kg bw/day amino acids.

Laboratory parameters

In both treatment groups, hematology, biochemistry and coagulation parameters as well as inflammatory markers IL-6 and sTNF-RII remained stable throughout the study. Serum vitamin E levels changed from (arithmetic mean $\pm$ SD [median]) 30.1 ± 15.9 (27.2) $\mu\text{mol/L}$ at baseline to 39.5 ± 13.6 (39.1) $\mu\text{mol/L}$ at Week 4/End of Study in the SMOFlipid group and from 28.9 ± 13.0 (26.6) $\mu\text{mol/L}$ at baseline to 29.7 ± 12.7 (26.0) $\mu\text{mol/L}$ at Week 4/End of Study in the Intralipid group. Table 15 looks at liver function test over time.

Table 16: Laboratory values over time

– Safety Set (n=73) (continued)

	SMOFlipid [®] (n=34)			Intralipid [®] (n=39)		
	Baseline	Week 4/ End of Study	Change	Baseline	Week 4/ End of Study	Change
Glucose (mmol/L)						
n	33	33	33	38	38	38
Mean	5.3	5.7	0.4	5.1	5.3	0.3
SD	1.1	1.5	0.8	0.6	0.7	0.6
Median	4.9	5.2	0.3	5.0	5.2	0.3
AP (U/L)						
n	34	34	34	38	38	38
Mean	185.2	165.1	-20.1	209.3	192.7	-16.6
SD	128.3	109.6	66.6	190.3	161.2	111.0
Median	151.5	129.0	-9.0	151.5	146.0	-4.0
AST (U/L)						
n	30	30	30	38	38	38
Mean	32.0	26.5	-5.5	40.5	41.0	0.6
SD	16.4	10.9	15.7	27.6	33.7	28.7
Median	27.0	26.0	-1.5	30.5	28.0	0.00
ALT/ (U/L)						
n	34	34	34	38	38	38
Mean	38.1	30.3	-7.8	45.1	48.7	3.6
SD	44.4	19.1	46.4	43.7	50.8	44.0
Median	26.0	25.0	-1.5	29.0	30.0	0.5
γ-GT (U/L)						
n	31	31	31	38	38	38
Mean	77.7	71.0	-6.7	110.6	101.4	-9.2
SD	72.8	70.4	36.8	116.3	151.6	131.8
Median	55.0	43.0	-3.0	82.0	56.0	-8.3

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Total protein (g/L)						
n	30	30	30	35	35	35
Mean	72.6	71.5	-1.1	74.1	73.2	-0.9
SD	9.3	9.7	6.3	8.9	9.1	8.1
Median	74.0	72.0	-2.0	76.0	76.0	-1.0
Albumin (g/L)						
n	32	32	32	38	38	38
Mean	36.8	36.5	-0.4	38.7	38.4	-0.4
SD	7.6	7.2	3.9	5.8	6.3	4.7
Median	37.0	37.0	-0.5	38.0	39.0	-1.0
AP = Alkaline Phosphatase, ALT = Alanine transaminase, AST = Aspartate transaminase, γ -GT = Gamma-glutamyl transferase, SD = standard deviation Only patients with both a baseline value and a value at End of Study were summarized here.						

In RBC phospholipids, the ratio of ω 6/ ω 3-fatty acids changed from (arithmetic mean $\pm$ SD [median]) 16.89 $\pm$ 12.50 (11.56) at baseline to 8.03 $\pm$ 4.47 (6.39) at Week 4/End of Study in the SMOFlipid group, and from 14.76 $\pm$ 9.45 (11.12) at baseline to 14.02 $\pm$ 6.73 (12.72) at Week 4/End of Study in the Intralipid group. In plasma lipoproteins, the ratio of ω 6/ ω 3-fatty acids changed from 29.70 $\pm$ 13.73 (27.95) at baseline to 12.35 $\pm$ 8.68 (11.21) at Week 4/End of Study in the SMOFlipid group, and from 31.39 $\pm$ 16.84 (28.69) at baseline to 30.84 $\pm$ 13.43 (29.32) at Week 4/End of Study in the Intralipid group. The observed changes in the ω 6/ ω 3-fatty acids reflects the difference in the composition of the lipid emulsions (the concentration of omega 3 fatty acids). The clinical significance of this difference has not been demonstrated.

SMOF-001-CP3

The following is a description of the conduct of this trial. The trial though was not included in the efficacy evaluation and is only discussed in this review as a supportive study for safety per previous discussions with the Applicant (see Section 5.2 Review Strategy).

A randomized, parallel-controlled, double-blind, multi-center clinical trial to evaluated the safety and efficacy of fat emulsion injection parenteral nutrition treatment used for patients receiving moderate or above abdominal surgery. The trial was conducted in China from August 21, 2008 to September 24, 2009.

A total of 212 adult patients were randomized, of which 106 patients received Smoflipid and 106 patients received Intralipid. The patients were to undergo moderate or above abdominal surgery requiring at least 5 days of parenteral nutrition support. Patients were between the ages of 18 to 80 years.

The primary efficacy endpoints were:

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1) comparison of changes in serum triglycerides between the two groups (Smoflipid 20% and Intralipid 20%) 4 and 6 days after surgery compared with the values 1 day after surgery and

2) Comparison of changes in serum prealbumin and transferrin for the 2 groups 4 and 6 days after surgery compared with the values 1 day after surgery.

The secondary efficacy endpoints were:

1) Comparison of changes in serum total cholesterol, total protein, albumin, body weight and BMI for the 2 groups 4 and 6 days after surgery compared with the values 1 day after surgery.

2) Comparison of changes in serum free fatty acids (linoleic acid, linolenic acid, arachidonic acid, EPA, DHA), LTB5 / LTB4 and TXB3 / TXB2 ratios, IL-1 IL-2, IL-6 and CD4 / CD8, as well as HLA-DR levels (selected center visits) for the 2 groups 4 and 6 days after surgery compared with the values 1 day after surgery.

Safety evaluation included:

1) Changes of the vital signs of the 2 groups of patients 1 and 6 days after surgery;

2) Changes in patients' blood, urine, liver and kidney functions, serum electrolytes, glucose, coagulation and other laboratory examinations for the 2 groups 1 day and 6 days after surgery;

3) All adverse events occurring during the trial among the 2 groups of patients.

Patients were randomized to receive either Smoflipid 20% 1.2 g/kg/d or Intralipid 20% 1.2 g/kg/d.

Results:

With respect to baseline demographics, the two treatment groups were similar.

Table 17: Demographics Study SMOF-001-CP3

Item	Statistic	Trial group	Control group
	Number of cases	106	106
Age (years)	Mean ± standard deviation	52.14±13.19	54.40±14.48

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	Number of cases	106	106
Ethnicity (Cases)	Han	105	106
	Mongolian	1	0
	Number of cases	106	106
Sex (Cases)	Male	57(53.77)	61(57.55)
	Female	49(46.23)	45(42.45)
	Number of cases	106	106
Height (cm)	Mean $\pm$ standard deviation	165.71 $\pm$ 7.16	166.70 $\pm$ 7.31
	Number of cases	106	106
Gross Weight (kg)	Mean $\pm$ standard deviation	60.84 $\pm$ 10.75	62.97 $\pm$ 11.44
	Number of cases	106	106
BMI (kg/m ²)	Mean $\pm$ standard deviation	22.58 $\pm$ 3.38	22.08 $\pm$ 3.20
	Number of cases	106	106

Primary efficacy evaluation:

Triglycerides

There were no significant difference in baseline triglyceride levels between the two treatment groups (Smoflipid – mean 1.3 mmol/L and Intralipid mean 1.22 mmol/L).

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there was a decrease in TG levels for both groups on postoperative day 1, which was thought to be related to the significant surgical trauma. The TG levels in both groups were higher on postop day 6 compared to postoperative day 1 (Smoflipid mean 1.24 mmol/L and Intralipid mean 1.03 mmol/L). Triglyceride levels at days 4 and 6 were within the normal range.

Pre-albumin

Postoperative day 1, postoperative day 4 and postoperative day 6 changes in serum pre-albumin showed no significant difference between the two treatment groups.

Day 1 (Smoflipid mean 176.11 mg/L; Intralipid mean 171.86 mg/L); Day 4 (Smoflipid mean 161.41 mg/L; Intralipid mean 150 mg/L) and Day 6 (Smoflipid mean 190.39 mg/L; Intralipid mean 185.18 mg/L).

Transferrin

Postoperative day 1, postoperative day 4 and postoperative day 6 changes in serum transferrin showed no significant difference between the two treatment groups.

Day 1 (Smoflipid mean 3.08 g/L; Intralipid mean 3.17 g/L); Day 4 (Smoflipid mean 3.01 g/L; Intralipid mean 2.92 g/L) and Day 6 (Smoflipid mean 2.95 g/L; Intralipid mean 2.86 g/L).

Fatty acids

Compared with the control drug, the trial drug significantly increased serum free fatty acid EPA ($\Delta 1.13 \pm 0.77$ and $\Delta -0.01 \pm 0.30$, $P < 0.01$) and DHA ($\Delta 0.19 \pm 0.70$ and $\Delta -0.29 \pm 0.48$, $P < 0.01$) concentrations; significantly reduce linoleic acid ($\Delta -1.70 \pm 3.03$ and $\Delta 1.90 \pm 2.30$, $P < 0.01$), linolenic acid ($\Delta 0.11 \pm 0.18$ and $\Delta 0.31 \pm 0.28$, $P < 0.01$) concentrations. These changes are reflective of the differences in the composition of the lipid emulsions (e.g the concentrations of the different FA in each of the lipid formulations). As previously noted, the Applicant has not demonstrated the clinical significance of these changes.

Other secondary endpoints

Except for the change in one of the surrogate endpoints, blood cholesterol, ($\Delta 0.24 \pm 1.72$ and $\Delta -0.14 \pm 0.68$) 6 days after surgery, other secondary surrogate endpoints - the total protein change after 6 days ($\Delta 2.69 \pm 6.55$ and $\Delta 1.53 \pm 6.29$), the change in albumin after 6 days ($\Delta -0.40 \pm 3.75$ and $\Delta -0.95 \pm 4.92$), change in HLA-DR 6 days after surgery ($\Delta 17.06 \pm 17.37$ and $\Delta 11.42 \pm 24.27$), the change in CD4/CD8 6 days after surgery ($\Delta 0.43 \pm 0.58$ and $\Delta 0.42 \pm 0.58$), the change in body weight 6 days after surgery ($\Delta -1.56 \pm 1.90$ and $\Delta -1.69 \pm 2.27$), and the change in body mass index (BMI) 6 days after surgery ($\Delta -0.56 \pm 0.67$ and $\Delta -0.61 \pm 0.82$) were similar.

Pediatric Trials

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

00-SMOF-002

A Phase 2b, double-blind, randomized, active-controlled, parallel-group, single-center study conducted from May 2003 (FPI) to May 2005 (LPO).

Twenty-eight (28) patients (15 Smof and 13 Intralipid) were randomized. 25 patients were treated per the protocol (13 Smof and 12 Intralipid). 13 patients (7 Smof and 6 Intralipid) were in Strata A (aged 6 month to < 2 years) and 15 patients (8 Smof and 7 Intralipid) were in Strata B (aged 2 years to 11 years).

The primary objective was to evaluate the safety of long-term treatment with Smoflipid 205 compared to Intralipid 20%. Safety criteria included: plasma triglycerides, liver enzymes, total cholesterol, adverse reactions and vital signs.

The secondary objective was to investigate the effect of the different composition of Smoflipid 20% and Intralipid 20% in the long term treatment of children. The efficacy criteria were body weight, height and BMI.

The target patient population was infants (1 month to ≤ 2 years of age) and children (2 to 11 years of age). Patients had a stable disease (e.g., short bowel syndrome, severe chronic diarrhea, or chronic intestinal pseudo-obstruction) resulting in a requirement for PN for at least 4 weeks. Patients could be treated in the hospital or a home setting. Exclusion criteria included hyperlipidemia (fasting serum triglycerides >4 mmol/L); metabolic disease; insulin treatment; hepatic disease; renal disease requiring dialysis; thrombocytopenia (platelet count $<50 \times 10^9/L$) or cancer; chemotherapy, radiation, anticoagulant, steroidal, or immunosuppressive therapy; and history of severe allergy against any of the ingredients of the lipid emulsion (e.g., allergy against egg, soybean, or fish protein).

Screening for entry into the study was performed up to 28 days before the start of study treatment. Before the start of study treatment, all patients received Intralipid 20% for a 1-week run-in period, followed by a 1-day washout during which no lipid emulsion was administered. The treatment period for this study was 28 days. All patients were to be followed up 3 months $\pm$ 2 weeks after the last treatment.

The investigative treatment was Smoflipid 20% and the active comparator was Intralipid 20%.

The study treatments, SMOFlipid 20% or Intralipid 20%, were administered as part of a PN regimen together with other nutrients (amino acids, glucose, vitamins, trace elements, and electrolytes; determined on an individual patient basis) in a 2-chamber bag. Parenteral nutrition was to be administered as a central IV infusion for 4 to 7

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periods per week over 4 consecutive weeks. Within the regimen, the lipid emulsion was to be administered for 4 to 5 periods per week at a lipid dose of approximately 2 g/kg/d. The recommended continuous period of lipid infusion was 12 to 14 hours. The recommended lipid infusion rate was 0.125 g/kg/h, and was not to exceed 0.15 g/kg/h. In this study, patients without major malabsorption syndrome could receive up to 50% of their total energy supply orally/enterally. If PN was required after 4 weeks, the hospital's usual lipid emulsion was to be used.

Before the start of study treatment, all patients received Intralipid 20% for a 1-week run-in period. There was a 1-day washout before the start of randomized study treatment, during which no lipid emulsion was administered.

In the study report, body weight, body height, and BMI were analyzed as primary efficacy endpoints. Retinol-binding protein, pre-albumin, and albumin were evaluated as secondary efficacy endpoints. The following laboratory variables were also analyzed: plasma leptin, fatty acid profiles in plasma and RBCs, phospholipids, plasma anti-oxidative capacity, plasma α -tocopherol, low-density lipoprotein thiobarbituric acid reactive substances (LDL-TBARS), apolipoprotein (Apo) A-1, and Apo B-100.

Triglyceride concentrations were analyzed as a safety parameter in the study report.

Efficacy data were analyzed for the ITT and PP populations, which included all patients who met the following predefined criteria:

- ITT: Received at least 1 dose of study treatment and underwent at least 1 post-baseline assessment
- PP (subset of the ITT population): completed at least 16 periods of lipid-containing PN treatment and had no major protocol deviations

Results:

Demographics

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The sponsor used

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Table 18: Trial 00-SMOF-002 Demographics

	arith. mean	SD	minimum	lower quartile	median	upper quartile	maximum	n
Age [months]	(b) (4)							
All patients, n=28								
SMOF 20%, n=15								
Intralipid 20%, n=13								
Height [cm]								
All patients, n=28								
SMOF 20%, n=15								
Intralipid 20%, n=13								
Weight [kg]								
All patients, n=28								
SMOF 20%, n=15								
Intralipid 20%, n=13								
BMI [kg/m ²]								
All patients, n=28								
SMOF 20%, n=15								
Intralipid 20%, n=13								

Sponsor's table CSR

(b) (4)							

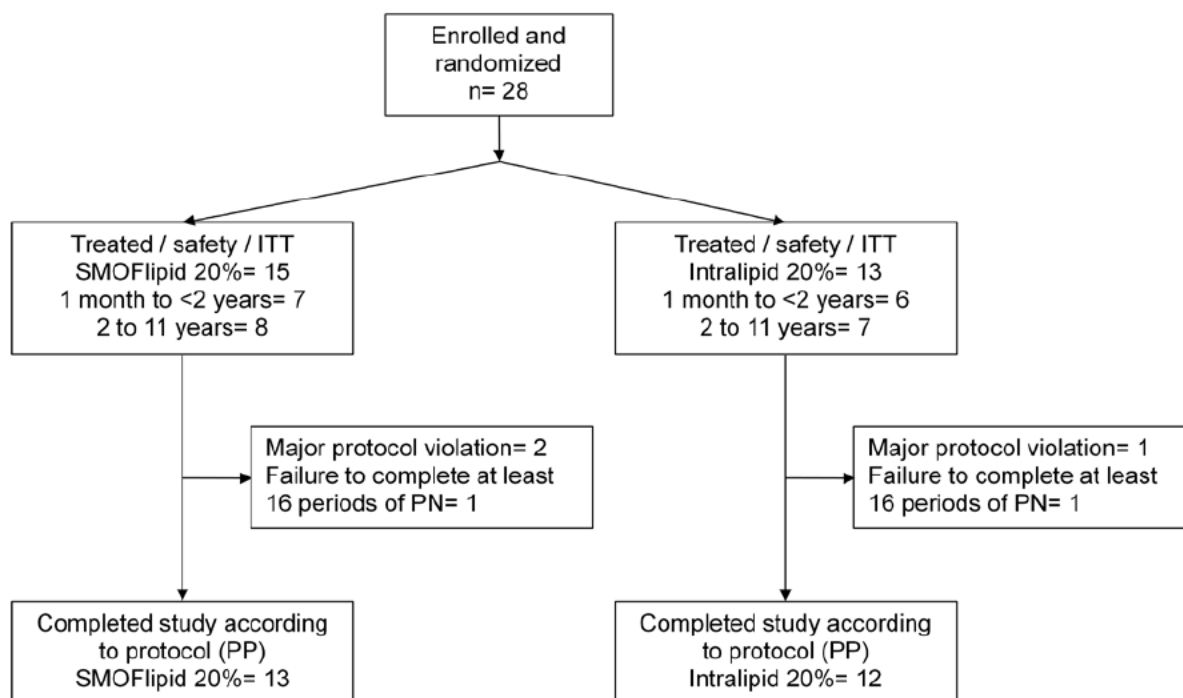
Clinical Review

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Figure 7: Flow of Patients in Study 00-SMOF-002



Body weight

(b) (4)

Body Height

(b) (4)

Body Mass Index (BMI)

(b) (4)

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Secondary efficacy

Retinol binding protein (RBP)

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Transthyretin /pre-albumin)

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Albumin

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Fatty acid pattern

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(b) (4)

Reviewer's comments:

(b) (4)

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(b) (4)

00-SMOF-004

A Phase 2b, double-blind, randomized, active-controlled, parallel-group, single-center study conducted from April 2004 (FPI) to February 2006 (LPO). The trial's primary objectives were to evaluate the safety and tolerability of 7 - 14 days (periods) of treatment with SMOF 20% compared to Intralipid 20% in premature infants. Secondary objective was to evaluate the efficacy of 7 - 14 days (periods) of treatment with SMOF 20% compared to Intralipid 20% in premature infants. The randomization had to be stratified with regards to the birth weight of the subjects at the time of inclusion. The three strata were to be 1000-1499 g, 1500-1 999 g and 2000-2500 g with the same number of subjects treated within each stratum.

The target patient population was preterm neonates 0 to 7 days of age with a gestational age of less than 34 weeks and a birth weight of 1000 to 2500 g. Patients were to require PN, including lipids, for at least 7 days. Exclusion criteria included the following: congenital severe heart, lung, or urinary anomalies; circulation failure with anuria; requirement for oxygenation treatment using a partial oxygen pressure (pO₂) >90 mm Hg for more than 60 minutes; inability to oxygenate despite maximum support (pO₂ <40 mm Hg for at least 2 hours); hepatic/hematolytic disease; sepsis score >3; or leukocytopenia, leukocytosis, granulocytosis, and/or thrombocytopenia as defined in the clinical study protocol.

Patients were screened for entry into these studies during the immediate prestudy period. After the last infusion of study treatment, all patients were to be followed up within 6 to 13 days after the end of study treatment.

The investigative treatment was Smoflipid 20% and the active comparator was Intralipid 20%.

The study treatments were to be administered for at least 7 consecutive periods but could continue for up to 14 periods. The recommended period of continuous lipid infusion was 20 to 24 hours, but could vary at the discretion of the investigator. Treatments were infused IV via a peripheral vein. The lipid emulsion was administered

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separately as one component of the PN using an infusion pump at a maximum rate of 0.125 g lipids/kg/h. The lipid dosing regimen was: 0.5 g lipids/kg on Day 1, 1.0 g lipids/kg on Day 2, 1.5 g lipids/kg on Day 3, and 2.0 g lipids/kg on Days 4 to 14. Additional oral/enteral intake comprising less than 30% of the total daily energy intake on Days 1 to 3 and less than 50% on Days 4 to 14 was permitted if clinically appropriate.

First order safety variable was serum triglyceride levels. Second order safety variables were clinical laboratory especially liver enzymes, cholesterol, AE-evaluation and vital signs.

First order efficacy variable was the Relative change in body weight between Day 0 and Day 8. Second order efficacy variables were CRP level, sepsis score, days with antibiotic therapy, the use of mechanical ventilation of oxygen therapy and the change in height during the treatment period.

Changes in fatty acid composition, phospholipid and lipid peroxidation were summarized as mechanism of action.

Efficacy data were analyzed for the ITT and PP populations, which included all patients who met the following predefined criteria:

- ITT: Received at least 1 dose of study treatment and underwent at least 1 post-baseline assessment
- PP (subset of the ITT population):
 - completed at least 7 periods of PN lipid-containing treatment and had no major protocol deviations

Patients were randomized in a stratified way. Three strata were generated according to birth weight: Stratum A (1000 - 1499 g), Stratum B (1500 and 1999 g) and Stratum C (2000 - 2500 g). Additionally to the analysis of the ITT and PP data set, all efficacy parameters were analyzed according to this stratification.

Results:

Table 21: Summary of Demographics Study 00-SMOF-004

Characteristic	SMOF lipid 20% (N=26)	Intralipid 20% (N=25)
Sex, n (%)	(b) (4)	
Female		
Male		
Race, n (%)		
White		
Age at time of informed consent (days)		
Mean (SD)		
Median (min-max)		
Gestational age (weeks)		
Mean (SD)		
Median (min-max)		
Body weight (g)		
Mean (SD)		
Median (min-max)		
Body height (cm)		
Mean (SD)		
Median (min-max)		

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BMI (kg/m²)	(b) (4)
Mean (SD)	
Median (min-max)	

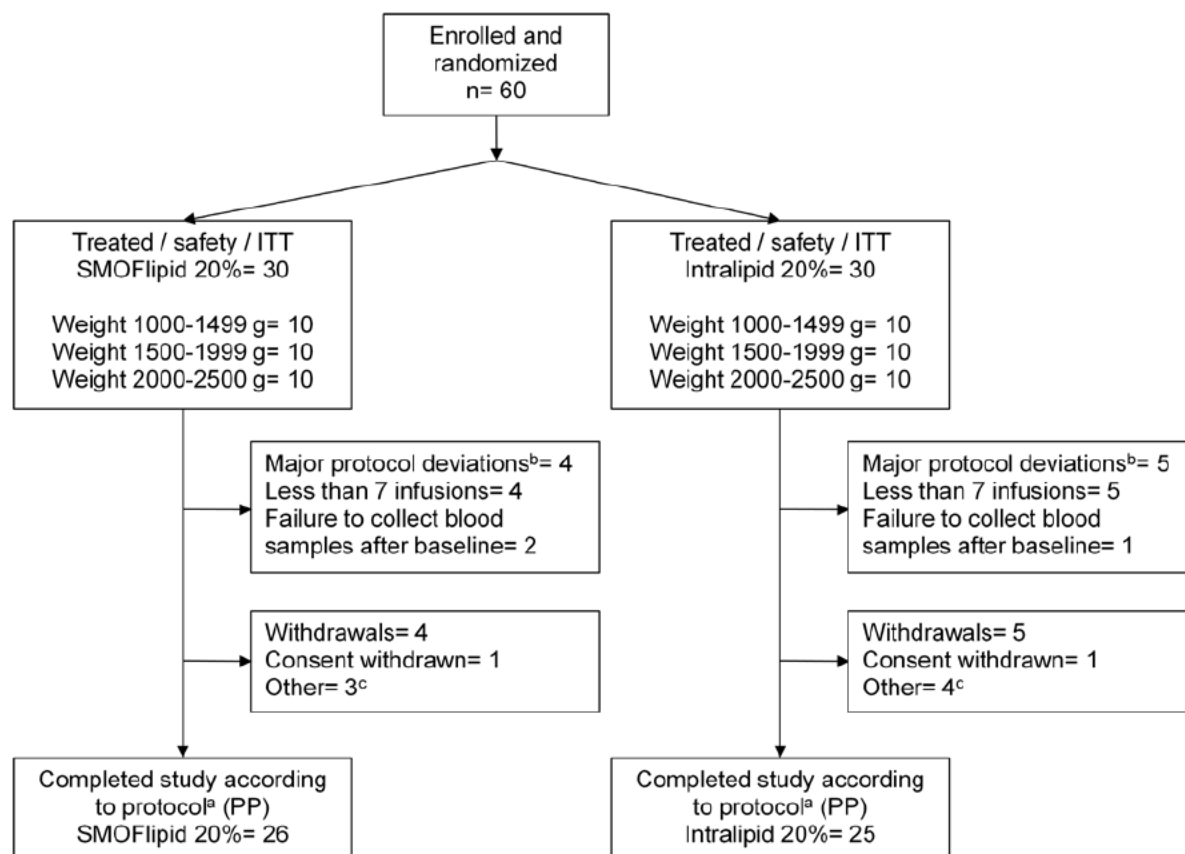
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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Figure 8: Flow of Patients in Study 00-SMOF-004



Body weight

(b) (4)

Second order efficacy variables

Body height

(b) (4)

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CRP

(b) (4)

Days on antibiotics

(b) (4)

Sepsis score

(b) (4)

Oxygen therapy

(b) (4)

03-SMOF-005

A Phase 3, double-blind, randomized, active-controlled, parallel-group, 2-center study conducted from May 2004 (FPI) to February 2006 (LPO). The target patient population was preterm neonates 0 to 7 days of age with a gestational age of less than 34 weeks and a birth weight of 500 to 2000 grams. Patients were to require PN, including lipids, for at least 7 days (main study phase) and a maximum of 14 days (complete study phase).

The primary objective of the study was to determine the safety of Smoflipid 20% compared to the standard lipid emulsion Intralipid 20% based on serum concentrations of triglycerides. Secondary objectives were the evaluation of additional safety criteria, such as other laboratory variables and adverse events. Also a comparison of key efficacy criteria such as body weight and height was planned.

Exclusion criteria included the following: congenital severe malformations or heart failure; multiple organ failure; hypoxic-ischemic encephalopathy; anuria due to circulation failure; oxygen saturation <80% for more than 2 hours; hepatic/hematolytic disease; thrombocytopenia (platelet count $<30 \times 10^9/L$, not due to placental dysfunction syndrome); severe acidosis (pH <7.0); or catecholamine therapy. Patients were also excluded if they had enteral nutrition with more than 20% of total energy intake at the beginning of lipid supplementation.

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Patients were screened for entry into these studies during the immediate prestudy period. After the last infusion of study treatment, all patients were to be followed up within 6 to 13 days after the end of study treatment.

The investigative treatment was Smoflipid 20% and the active comparator was Intralipid 20%.

The study treatments were SMOFlipid 20% and Intralipid 20%, which were to be administered for at least 7 consecutive periods but could continue for up to 14 periods. The recommended period of continuous lipid infusion was 20 to 24 hours, but could vary at the discretion of the investigator. Study treatments were infused IV via a peripheral indwelling cannula or via central infusion. The lipid emulsion was administered separately as one component of the PN using an infusion pump at a maximum rate of 0.17 g lipids/kg/h.

The lipid dosing regimen was:

1g/kg birth weight per day on Days 1 to 3; 2.0 g/kg birth weight on Day 4; 3.0 g/kg birth weight on Day 5; 3.5 g/kg birth weight per day on Days 6 to 14. If actual body weight exceeded birth weight during treatment, then dosing was to be adjusted according to actual body weight. For preterm neonates <34 gestational weeks and older than 7 days, the lipid dose regimen was 1.0 g/kg birth weight/d on Day 1, 2.0 g/kg birth weight/d on Day 2, 3.0 g/kg birth weight/d on Day 3, and 3.5 g/kg birth weight/d on Days 4 to 14. Additional oral/enteral intake comprising <30% on Days 1 to 3, <50% on Days 4 to 7, and <70% on Days 8 to 14 of the total daily lipid intake could be given if this was appropriate to the clinical situation and the patient's condition. Center 1 in this study did not consistently comply with the requirements of the study protocol regarding the dosage regimen for the parenteral lipid emulsion.

Table 22 Dosage Regimen for study medication (according to study protocol)

Fat per kg body weight and day	Day
1.0 g	1 - 3
2.0 g	4
3.0 g	5
3.5 g	6 -14

Safety variables were the primary parameter evaluated in this study:

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

The primary safety variable of the study was comparison of the change in serum triglycerides from baseline to study day 8/LVCF in both treatment groups. This target parameter was to be evaluated by testing for non-inferiority by applying Mann-Whitney statistic.

Secondary safety variables included:

- 1) Laboratory variables (hematology and biochemistry)
- 2) Adverse events (systemic and local)
- 3) Tolerability (global assessment of investigator, local tolerance measured by pre-defined Local Tolerance Scale)
- 4) Vital signs (temperature, heart rate, and blood pressure)

Efficacy variables included:

First order efficacy criteria:

- Body weight
- Body height

Second order efficacy criteria:

- Days on mechanical ventilation (oxygen therapy)

The safety population was defined as the data set that included all patients who received at least one dose of the trial medication and had at least one safety assessment afterwards. The ITT population was defined as all patients who received at least one dose of the trial medication and had at least one efficacy assessment afterwards. The per protocol (PP) population included all patients who did not show major protocol violations.

Results:

Table 23: Summary of Demographics Study 03-SMOF-005

Characteristic	Smoflipid 20% (N=23)	Intralipid 20% (N=23)
Sex, n (%)	(b) (4)	
Female		
Male		
Race, n (%)		
White		
Other (Moroccan/North African)		
Age on Day 1 (days)		
n		
Mean (SD)		
Median (min-max)		
Gestational age (weeks)		
n		
Mean (SD)		
Median (min-max)		
Birth weight (g)		
n		
Mean (SD)		
Median (min-max)		
Birth height (cm)		
n		
Mean (SD)		
Median (min-max)		
Head circumference (cm)		
n		
Mean (SD)		

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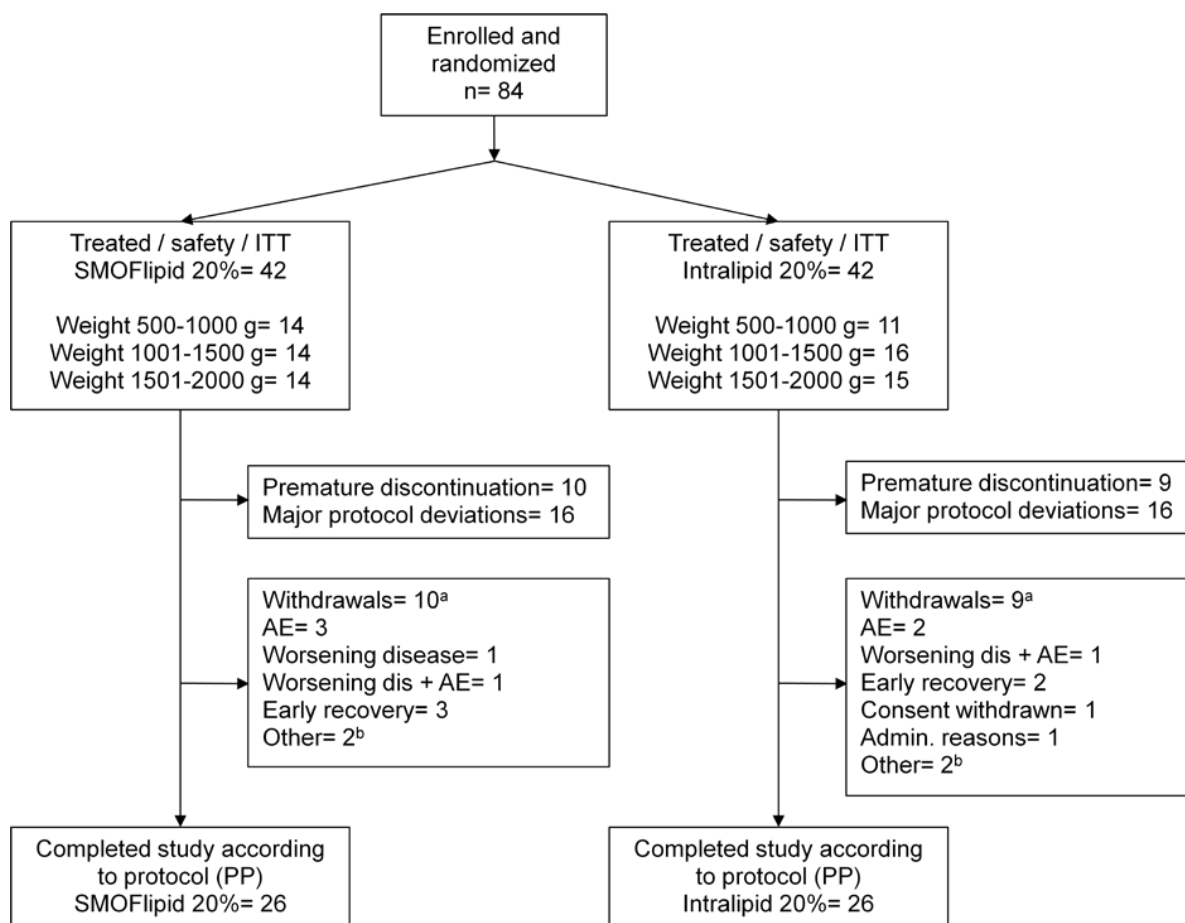
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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Median (min-max)

(b) (4)

Figure 9: Flow of Patients in Study 03-SMOF-005



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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

(b) (4)

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(b) (4)

Table 24: Age [day of life at start of infusion] overall, by centers and by strata; Safety/ITT Population

(b) (4)

(b) (4)

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Table 25: Gestational age [weeks] overall, by centers and by strata; Safety/ITT Population



(b) (4)

Table 26: Weight Distribution According to Birth Weight Strata and centers; safety/ITT Population¹⁾



(b) (4)

Triglyceride levels at baseline



(b) (4)

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Table 27: Triglyceride levels at baseline- Safety and ITT populations

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Exposure:

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Table 28: Duration of treatment (numbers of days with PN); Safety/ITT Population

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- Table 29: Parenteral nutrition – Fat intake [g/kg body weight]; Safety/ITT Population

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(b) (4)

Table 30: Mean daily dose in the main and complete study phase per stratum – Fat intake [g/kg body weight]; Safety/ITT Population

(b) (4)

Safety endpoint

Triglyceride levels

The primary study endpoint was the safety criterion serum triglycerides. Due to major discrepancies between the dosage prescribed in the protocol and the considerably lower actual administered amount in centre 1, confirmatory evaluation was based on all patients participating in centre 2. Triglycerides were being evaluated as change from baseline to day 8.

Triglyceride analysis

(b) (4)

Clinical Review

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

(b) (4)

Table 31: Triglycerides (mmol/l) from Baseline to Day 5 and Day 8, Center 2, Absolute Values and change from baseline; Safety/ITT Population

(b) (4)

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Additional efficacy criteria

Body weight

(b) (4)

Reviewer's comment:

(b) (4)

(b) (4)

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

(b) (4)

Body length

(b) (4)

Table 33: Body length (cm), Change of birth length at the last observation;
Safety/ITT Population

(b) (4)

Analysis of Fatty Acids in phospholipids of RBS

(b) (4)

Clinical Review

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

(b) (4)

(b) (4)

Table 34: Summary of fatty acids (relative amounts) in RBCs, Center 2, pre-treatment, post-treatment and change; ITT Population

(b) (4)



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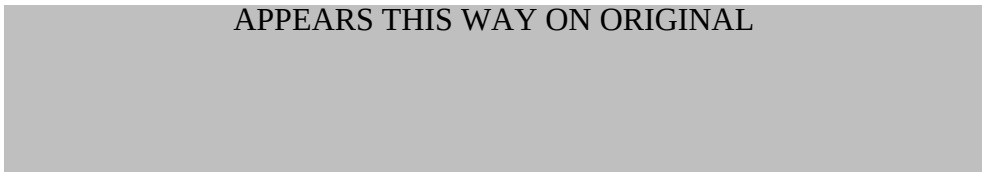
Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

(b) (4)



|

APPEARS THIS WAY ON ORIGINAL



Clinical Review

Karyn L. Berry, MD, MPH

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

APPEARS THIS WAY ON ORIGINAL



6 Review of Efficacy

Efficacy Summary

To assess the efficacy of Smoflipid 20%, the Applicant needed to demonstrate that the product adequately provided both, a supply of energy and essential fatty acids (to prevent essential fatty acid deficiency) as part of a parenteral nutrition regimen.

None of the submitted trials were adequately designed and powered to establish nutritional equivalence or superiority of Smoflipid to the currently marketed (b) (4) soybean oil lipid emulsion products. In addition, no study established that Smoflipid is superior or non-inferior to available therapy on a clinical outcome measure. However, the amount of calories provided by Smoflipid can be calculated since it is known and well established that the energy content of lipids is approximately 9 kcal/g. Therefore the need to establish efficacy in the clinical trials for Smoflipid as a source of energy is not necessary because Smoflipid's ability to provide adequate calories is evident by assessing its component contents.

There are concerns though related to the adequate supply of essential fatty acids in this product. Although, the Applicant has provided only limited data on essential fatty acids (triene/tetraene ratio) in adults, EFAD in adults who are receiving fat free PN generally takes longer to develop (e.g. 4 weeks) and can be corrected without concern for the potential long term neurologic and growth consequences that can occur in pediatric patients. Based on guidelines from ASPEN and the amount of essential fatty acids in Smoflipid, this may be adequate for adult patients. However, there is concern that the provision of EFA may not be adequate for premature neonates and the Applicant has not been able to lessen our concerns.

In this reviewer's opinion, the Applicant has demonstrated that Smoflipid 20% provides adequate calories and essential fatty acids for adults only. The Applicant has not provided sufficient data that Smoflipid provides adequate essential fatty acids to prevent EFAD in pediatric patients, particularly premature neonates. This reviewer recommends postmarketing clinical trials to further assess the provision of essential fatty acids for long term use in pediatric patients.

The submitted clinical trials were deficient in a number of areas related to trial design (e.g. identification of appropriate efficacy and safety endpoints, lack of statistical analysis plan and duration of trials to adequately assess nutritional and/or clinical outcomes. Parameters that were designed to be analyzed as safety variables (serum triglyceride and albumin levels, body weight, body height, etc) in the study reports, have been presented by the Applicant to support the claim of efficacy.

Clinical Review

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

The duration of the clinical trials varied from 5 to 7 days (3 adult trials), 10 to 14 days (1 adult trial) 7 to 14 days (two pre-term neonatal trials) and 4 weeks (one adult and one pediatric trials). Longer term (> 3 months) Smoflipid use has not been studied in either adult or pediatric patients. Longer duration trials in patients who require chronic parenteral nutrition are needed to adequately assess growth and prevention of essential fatty acid deficiency with Smoflipid.

The trials were not powered to show statistically significant changes in clinical outcomes and the Applicant used descriptive statistics to analyze the data. A formal statistics review was not performed by FDA staff for any of these studies. At the time of filing, the statistical reviewer, Behrang Vali stated the following in his filing review dated 12/10/2014: *"The submitted study results should be considered descriptive or observational only as they do not rely on appropriate inferential statistics or trial designs that would be considered adequate to support specific endpoint testing. At the time of filing, we considered this application as 'No Action Indicated'."*

Efficacy in adults was assessed primarily on the basis of Smoflipid's effect on triglyceride levels, fatty acid profiles and serum concentrations of albumin. In the pediatric populations, efficacy was assessed using the parameters of body weight and height, head circumference and fatty acid profile. Triglyceride levels and pre-albumin were also assessed.

In the Applicant's "pivotal" adult trial, FE-SM-03-DE, the study hypothesis was that the elimination of Smoflipid would be at least as fast as the elimination of Lipovenos 20%, based on serum triglyceride levels. The primary efficacy variable was the AUC of the difference between baseline serum triglyceride levels and levels at each measurement point up to Day 6 (corresponding to 5 days of infusion). This parameter was intended to demonstrate equivalence to the reference product in terms of its ability to provide energy. For the PP population, the Applicant demonstrated non-inferiority of the mean daily change from the baseline serum triglyceride AUC in the Smoflipid treatment group compared to the Intralipid group.

In pediatric trial 03-SMOF-005 (premature neonates), the primary objective was to determine the safety of Smoflipid 20% compared to the standard lipid emulsion Intralipid 20% based on serum concentrations of triglycerides. (b) (4)

[REDACTED]

In both pediatric trials that enrolled premature neonates, the duration of the trials, 7 to 14 days, with a mean of 8 days, may not be adequate to assess growth and essential fatty acid deficiency. Therefore, this reviewer recommends a trial of at least 28 days in this population.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

There were a number of issues in the 28 day pediatric study 00-SMOF-002. In this trial, which enrolled infants and children, no patients younger than 6 months or older than 81 months received Smoflipid, the trial enrolled small numbers of patients (15 in the Smoflipid treatment group and 13 in the Intralipid group and patients were allowed to receive up to 50% of calories via oral or enteral route. Significant oral/enteral feedings, which provide fat calories may potentially mask the development of EFAD. The data from this trial is limited.

In the other submitted pediatric clinical trials patients were also allowed oral/enteral intake, Oral/enteral feeding may also influence (b) (4) other laboratory values such as albumin, triglyceride levels and fatty acid profiles.

While efficacy data may possibly be extrapolated from the younger pediatric patients, safety cannot. Additional safety and efficacy data is needed for the entire pediatric age group (0 to 16 years).

6.1 Indication

(b) (4)

6.1.1 Methods

The clinical data from the Smoflipid clinical trials was reviewed to determine whether a clinical benefit was demonstrated in patients requiring parenteral nutrition.

6.1.2 Demographics

See Section 5.3 Discussion of Individual Studies/Clinical Trials for patient demographic characteristics.

6.1.3 Subject Disposition

See Section 5.3 Discussion of Individual Studies/Clinical Trials for patient disposition.

6.1.4 Analysis of Primary Endpoint(s)

The variables presented to support the claim of efficacy in this submission are categorized as follows by the Applicant:

- Lipid metabolism: triglyceride level and fatty acid profile
 - o Triglycerides: Triglyceride levels in plasma are also safety parameters in clinical trials. Disturbances in lipid metabolism may lead to hypertriglyceridemia. From a nutritional efficacy perspective, if patients' plasma triglyceride levels increase and remain within the normal range during the IV administration of lipids, this could indicate that triglycerides are effectively metabolized and potentially converted into energy.
 - o Fatty acid profile in cell membranes and plasma In the body, the triglyceride and fatty acid components of SMOFlipid 20% administered parenterally can be metabolized to supply energy, or incorporated as fatty acids into membranes. This submission focuses on fatty acid profiles for the essential fatty acids linoleic acid (C18:2 ω 6) and α -linolenic acid (C18:3 ω 3), as well as EPA (C20:5 ω 3), DHA (C22:6 ω 3), and ARA (C20:4 ω 6).
- Physical measures of nutritional status: body weight, body height, and head circumference (pediatric patients)
 - o Body weight is used as an indirect measure of nutritional status because it is representative of body energy stores and growth. During the developmental period, increasing body weight reflects growth, which depends on adequate energy supply. Weight assessments can be complicated by fluid retention and may vary with protein and electrolyte intake.
 - o Body height during the developmental period is an indirect measure of nutritional status. In children, infants and preterm neonates, adequate energy supply leads to normal and rapid growth (Going 2012).
 - o Head circumference is an indirect measure of nutritional status during the developmental period.
- Nutritional status: General nutritional parameters reflecting energy provision
 - o Albumin and prealbumin are markers that are used to evaluate protein synthesis and adequate nutrition.

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Table 35: Variables Presented to Support the Claim of Efficacy for SMOFlipid 20%

	Triglycerides	Fatty acid profile	Body height	Body weight	Head circumference	Albumin	Prealbumin	Other parameters analyzed
Adult trials								
FE-SM-03-DE	X	X (only conducted on subset of 33 pts)						Total chol, LOS
FE-SM-04-CH	X		X	X				
03-3CB7-001	X							
03-3CB8-001	X							
05-SMOF-006	X	X				X		

(b) (4)

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Triglycerides assessment

Adults

Study FE-SM-03

The primary endpoint was the serum concentration of triglycerides measured by the AUC of the difference between the pre-infusion value on day 1 and the value at each measurement point, up to day 6.

Table 36: Primary endpoint Study FE-SM-03

Serum concentration of triglycerides (mmol/l): mean daily AUC (difference from baseline)		
Per-Protocol Population	SMOF Group	Lipovenös Group
N	99	100
Serum concentration of triglycerides: mean daily AUC (difference from baseline)	0.7340	0.7197
Difference of treatment means	0.0142	
Lower limit of the one sided 95% confidence interval for the difference of the treatment means	-0.0891	

Source: Table 4.5.1.1

Per the Applicant, for the per-protocol population, the mean daily AUC (difference from baseline) for the serum concentration of triglycerides was 0.7340 mmol/l for the Smof group and 0.7197 mmol/L for the Lipovenos group. The lower limit of the one sided 95% confidence interval for this difference between the treatment means was -0.0891, demonstrating that the treatments were equivalent. However, as this value was not greater than zero, Smof was not shown to be superior to Lipovenos.

Mean and median triglyceride concentrations showed similar changes from Day 0 to Day 6 in both treatment groups, decreasing from Day 0 (screening, pre-surgery) to Day 1 (baseline, post-surgery and pre-infusion), then increasing from Day 1 to Day 2, and increasing more gradually until Day 5.

Table 37: Change in Triglyceride Concentrations (mmol/L) in Study FE-SM-03-DE

Population	SMOf lipid 20%					Lipovenös 20%				
	Day 0	Day 1	Day 3	Day 6	Change from baseline to Day 6	Day 0	Day 1	Day 3	Day 6	Change from baseline to Day 6
	Statistic	(screening) ^a				(baseline) ^b	(screening) ^a			
PP population (SMOf lipid 20% N=99; Lipovenös 20% N=100)										
Mean	1.44	0.92	1.74	1.87	0.95	1.41	0.89	1.64	1.93	1.03
SD	0.570	0.363	0.644	0.924	0.858	0.634	0.413	0.511	0.773	0.741
Median	1.29	0.83	1.58	1.63	0.80	1.26	0.86	1.61	1.80	0.89
IQR	1.01-1.72	0.66-1.18	1.28-2.18	1.31-2.23	0.40-1.36	1.03-1.63	0.63-1.06	1.31-1.88	1.41-2.31	0.50-1.43
ITT population (SMOf lipid 20% N=123; Lipovenös 20% N=121)										
Mean	1.42	0.92	1.79	1.93	1.02	1.40	0.88	1.66	1.92	1.03
SD	0.605	0.401	0.708	0.940	0.861	0.608	0.398	0.544	0.777	0.756
Median	1.28	0.83	1.65	1.78	0.84	1.27	0.86	1.59	1.79	0.89
IQR	0.98-1.67	0.61-1.16	1.29-2.18	1.32-2.32	0.45-1.46	0.99-1.65	0.62-1.05	1.31-1.88	1.39-2.32	0.46-1.44

While mean and median triglyceride values remained within the normal range throughout the study in both treatment groups, a number of individual values were observed outside the normal range in both treatment groups. In the SMOFlipid 20% group, 14 patients (11.1%) had increased triglyceride values at screening (presurgery); of these 14 patients, 3 had normal values at the final assessment, 8 had values that remained above the normal range, and no data were available for the remaining 3. Twenty-four patients (19.0%) in this group who had normal triglyceride values at screening had increased values at the final assessment.

In the Lipovenös 20% group, 11 patients (8.9%) had increased triglyceride values at screening; of these 11 patients, 5 had normal values at the final assessment, 5 had values that remained above the normal range, and no data were available for the remaining patient. Twenty-four patients (19.5%) in this group who had normal triglyceride values at screening had increased values at the final assessment. Five patients (4.1%) in this group had low triglyceride values at screening; of these, 4 had values within the normal range at the final assessment.

At the final assessment, 33 patients (26.2%) in the Smoflipid 20% group and 30 patients (24.4%) in the Lipovenös 20% group had triglyceride values outside the normal range. Of these patients, 18 in the Smoflipid 20% group and 14 in the Lipovenös 20% group had values outside the normal range considered related to study treatment; 11 in the Smoflipid 20% group and 10 in the Lipovenös 20% group had values outside the normal range considered both related to study treatment and clinically relevant; and 1 patient in the Smoflipid 20% group had a value outside the normal range that was considered both related to study treatment and clinically relevant, and reported as an AE. Overall, 2 patients (1.6%) in the Smoflipid 20% group and 2 (1.6%) in the Lipovenös 20% group experienced TEAEs of hypertriglyceridemia. The proportions of patients with triglyceride values within the normal range were similar between the treatment groups both at screening (83.3% Smoflipid 20%; 87.0% Lipovenös 20%) and at the final assessment (61.9% Smoflipid 20%; 65.0% Lipovenös 20%).

Study FE-SM-04-CH

Triglyceride concentrations were evaluated for both the PP and the ITT populations. In the PP population, mean and median triglyceride concentrations were higher in the Smoflipid 20% group than in the Lipovenös 20% group at baseline; in the ITT population, the treatment groups were similar at baseline. In the PP population, the mean and median triglyceride values showed an increase from baseline after the start of study treatment on Day 1 in both treatment groups; a larger increase was observed in the Lipovenös 20% group than in the Smoflipid 20% group. By the final assessment, the mean and median triglyceride values were at a level no higher than the baseline values in the Smoflipid 20% group, but were higher than at baseline in the Lipovenös 20%

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

group. In the ITT population, a similar pattern was seen, but the difference between the treatment groups was less pronounced.

In the PP population, mean and median triglyceride concentrations during the course of the study remained within the normal range (0.4 to 2.1 mmol/L) in both treatment groups, indicating that the infused lipids were eliminated efficiently in most patients. No individual shifts from a normal triglyceride value at screening to a value above the normal range at the final evaluation were reported in the SMOFlipid 20% group, while 2 patients (28.6%) in the Lipovenös 20% group shifted from values in the normal range at screening to values above the normal range at the final evaluation. One patient (14.3%) in each treatment group had a triglyceride value above the normal range at screening, but had a value within the normal range at the final evaluation.

In the ITT population, the mean triglyceride concentration was slightly above the normal range in the Smoflipid 20% group at Day 1 (2.18 mmol/L) and Days 11-14 (2.11 mmol/L), and in the Lipovenös 20% group at Day 1 (2.16 mmol/L). The median triglyceride concentration was within the normal range at all time points in the Smoflipid 20% group, but above the normal range at Days 2-5 (2.30 mmol/L) in the Lipovenös 20% group. In the SMOFlipid 20% group, 1 patient (9.1%) shifted from a normal triglyceride value at screening to a value above the normal range at the final evaluation, and one (9.1%) shifted from a high value at screening to a value within the normal range at final evaluation. In the Lipovenös 20% group, 2 patients (20.0%) shifted from normal at screening to high at final evaluation, and 2 (20.0%) shifted from high at screening to normal at final evaluation.

Clinical Review

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Table 38: Change in Triglyceride Concentrations (mmol/L) in Study FE-SM-04-CH

Population Statistic	SMOFlipid 20%					Lipovenös 20%				
	Baseline ^a	Day 1	Days 6-8	Final ^b	Change from baseline to final	Baseline ^a	Day 1	Days 6-8	Final ^b	Change from baseline to final
PP population (SMOFlipid 20% N=7; Lipovenös 20% N=7)										
n	7	7	7	7	7	7	7	7	7	7
Mean	1.54	1.71	1.26	1.34	-0.20	1.27	1.81	2.05	1.76	0.49
SD	0.56	0.77	0.84	0.36	0.51	0.54	0.48	0.90	0.85	0.74
Median	1.60	1.70	1.00	1.30	-0.30	1.10	1.80	2.10	1.90	0.10
IQR	1.10-2.00	1.20-1.80	0.60-1.60	1.00-1.70	-0.60 to 0.30	1.00-1.50	1.60-2.00	1.10-2.70	1.10-2.30	-0.20 to 1.20
ITT population (SMOFlipid 20% N=13; Lipovenös 20% N=10)										
n	11	12	12	13	11	10	10	10	10	10
Mean	1.53	2.18	1.47	1.60	0.13	1.57	2.16	1.90	1.62	0.05
SD	0.49	0.98	0.76	0.74	0.90	0.85	0.92	0.78	0.74	1.04
Median	1.40	1.85	1.46	1.50	-0.20	1.30	1.85	1.95	1.45	-0.10
IQR	1.10-2.00	1.55-3.05	0.85-1.98	1.10-1.80	-0.30 to 0.60	1.00-2.10	1.60-2.60	1.30-2.20	1.10-2.10	-0.20 to 0.90

^aIQR = interquartile range; ^bITT = intention to treat; ^cDD = per protocol; ^dSD = standard deviation

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NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Study 03-3CB7-001 (open label study)

Triglyceride levels were analyzed in the ITT population; no PP population was defined in this study. The postoperative patients in the study population had low mean and median triglyceride values at baseline. While the median triglyceride concentrations at baseline were similar between the treatment groups, the mean values were higher in the SmofKabiven group than in the Kabiven group, suggesting the presence of outliers with high values in this group. Mean and median triglyceride concentrations showed similar changes from screening to final assessment (LOCF) in both treatment groups; decreasing from screening (presurgery) to Period 1 (baseline, post-surgery and pre-infusion), increasing rapidly from Period 1 to Period 4, and the increasing more gradually until final assessment (LOCF). The mean and median increases were greater in the SmofKabiven group than in the Kabiven group.

Mean and median triglyceride concentrations during the course of the study remained within the normal range in both treatment groups. At the end of the study, values outside the normal range were reported for 2 patients in each treatment group (in each case 1 high value and 1 low value), but they were not assessed by the Applicant as clinically relevant. Of the 11 patients in each treatment group who had a triglyceride value below the lower limit of normal at baseline, 9 in the SmofKabiven group and 10 in the Kabiven group had a value within the normal range at the final evaluation (LOCF). No abnormal triglyceride values in either treatment group were reported by the Applicant as AEs during the course of the study.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Table 39: Change in Triglyceride Concentrations (mg/dL) in Study 03-3CB7-001

		SmofKabiven (N=26)				Kabiven (N=27)				
Statistic	Screening ^a	Period 1	Final (LOCF) ^c	Change from baseline to final	Screening ^a	Period 1	Final (LOCF) ^c	Change from baseline to final	Period 1	Final
		(baseline) ^b				(baseline) ^b				
n	16	24	18	24	24	8	24	20	24	24
Mean	156.81	87.71	156.44	162.25	74.54	125.38	77.25	132.65	144.00	66.75
SD	84.31	55.32	38.37	65.89	60.52	52.93	29.84	46.15	50.60	48.64
Median	120.50	72.00	145.50	167.00	80.00	117.50	72.50	124.50	137.00	61.50
IQR	90.50-234.00	55.50-91.00	129.00-179.00	111.50-211.00	27.50-124.00	95.00-132.00	58.50-89.50	101.00-158.50	115.50-170.50	29.50-96.00

Clinical Review

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NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Study 03-3CB8-001 (open label study)

Triglyceride concentrations were evaluated for the ITT population; no PP population was defined. There were no differences in mean or median serum triglyceride concentrations between the treatment groups at baseline. In both treatment groups, mean and median triglyceride concentrations increased from baseline (Day 1 LOCF) to Day 4 (LOCF); mean values then decreased between Day 4 (LOCF) and the follow-up visit (LOCF) in both groups, while the median values remained stable through the follow-up visit (LOCF). Larger increases in the mean and median values were seen in the SmofKabiven Peripheral group than in the Kabiven Peripheral group.

The upper quartile triglyceride values in each treatment group remained below the upper limit of normal throughout the study (reference range: <200 mg/dL). In the SmofKabiven Peripheral group, 5 patients (20.8%) had triglyceride values above the upper limit of normal at the follow-up visit (LOCF); 2 of these patients had values within the normal range and 3 had increased values at baseline (LOCF). Two patients (8.3%) in this group had low triglyceride values at baseline (LOCF); one of these patients had a normal value at the follow-up visit (LOCF). In the Kabiven Peripheral group, 2 patients (8.7%) had triglyceride values above the upper limit of normal at the follow-up visit (LOCF); both had had values within the normal range at baseline (LOCF). One patient (4.3%) in this group had had a low triglyceride value at baseline (LOCF); this patient continued to have a value below the normal range at the follow-up visit (LOCF). No triglyceride values outside the normal range in either treatment group were reported as AEs in the course of the study.

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Table 40: Change in Triglyceride Concentrations (mg/dL) in Study 03-3CB8-001

Statistic	SmofKabiven Peripheral (N=27)				Kabiven Peripheral (N=25)			
	Baseline (Day 1 LOCF) ^a	Day 4 (LOCF)	Follow-up (LOCF) ^b	Change from baseline to follow-up (LOCF)	Baseline (Day 1 LOCF) ^a	Day 4 (LOCF)	Follow-up (LOCF) ^b	Change from baseline to follow-up (LOCF)
n	24	24	24	24	23	23	23	23
Mean	122.2	140.9	135.8	13.5	116.8	124.3	114.7	-2.0
SD	61.5	72.1	73.6	59.5	64.4	70.8	52.4	77.6
Median	104.5	116.5	115.5	-2.5	105.0	109.0	110.0	12.0
IQR	82-140	103-157	87-155	-17 to 35	80-149	75-135	81-130	-39 to 32

Clinical Review

Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Study 05-SMOF-006

Triglyceride concentrations were evaluated for both the evaluable and the safety populations (equivalent to PP and ITT populations). There were no differences in mean or median serum triglyceride concentrations between the treatment groups at baseline. Mean and median triglyceride values remained stable and within the normal range over time in both treatment groups.

In the evaluable population 1 patient (3.7%) in the SMOFlipid 20% group and 3 patients (10.3%) in the Intralipid 20% group shifted from a normal value at baseline to a value above the upper limit of normal at Week 4/end of study. In the safety population 2 patients (6.5%) in the SMOFlipid 20% group and 4 patients (10.5%) in the Intralipid 20% group shifted from a normal value at baseline to a value above the upper limit of normal at Week 4/end of study.

Clinical Review

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NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Table 41: Change in Triglyceride Concentrations (mmol/L) in Study 05-SMOF-006

Population Statistic	SMOf lipid 20%				Intralipid 20%			
	Baseline (Day 0)	Week 1	Week 4/EOS ^a	Change from baseline to Week 4/EOS	Baseline (Day 0)	Week 1	Week 4/EOS ^a	Change from baseline to Week 4/EOS
Evaluable population (SMOf lipid 20% N=28; Intralipid 20% N=29)								
n	27	26	27	27	29	27	29	29
Mean	1.45	1.29	1.26	-0.18	1.45	1.29	1.26	-0.19
SD	0.856	0.668	0.689	0.732	0.667	0.797	0.710	0.607
Median	1.22	1.10	1.10	0.00	1.30	1.10	1.00	-0.11
IQR	0.78-1.90	0.72-1.70	0.81-1.48	-0.49 to 0.13	0.93-1.84	0.80-1.56	0.65-1.72	-0.60 to 0.10
Safety population (SMOf lipid 20% N=34; Intralipid 20% N=39)								
n	32	31	31	31	39	35	38	38
Mean	1.36	1.27	1.31	-0.08	1.40	1.30	1.39	-0.01
SD	0.829	0.661	0.746	0.823	0.639	0.766	0.964	0.913
Median	1.13	1.09	1.10	0.00	1.30	1.10	1.15	-0.06
IQR	0.76-1.75	0.71-1.70	0.77-1.68	-0.48 to 0.25	0.88-1.84	0.78-1.60	0.68-1.77	-0.41 to 0.29

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NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Reviewer's comments: For any given intravenous lipid emulsion product, plasma triglyceride levels are dependent on the rate of lipid infusion as well as the rate of conversion of that lipid to fatty acids by lipase.

Per review of the results of the clinical trial most patients had triglyceride levels within normal ranges, which suggest that the infused lipids were eliminated efficiently. As previously discussed plasma triglyceride levels that increase during IV lipid administration and are higher than the normal range may indicate that triglycerides are not being effectively metabolized and may lead to problems related to hypertriglyceridemia and require decrease in lipid dose and therefore decrease in potential energy. The Applicant states that elevated triglyceride values seen in some patients at the final assessment may be related to timing of blood sampling post infusion.

Fatty Acid Profile - Adult Trials

Study FE-SM-03-DE

Fatty acid profiles were analyzed in a PP subset of 33 patients enrolled at 2 prespecified study centers. Data for the essential fatty acids (linoleic acid and α -linolenic acid) and other fatty acids (i.e. EPA, DHA, and ARA) are reported. There were no differences in fatty acid profiles between the treatment groups at baseline. The mean proportion of linoleic acid showed an increase in the Lipovenös 20% group and decreased (in free fatty acids and plasma phospholipids) in the SMOFlipid 20% group. The mean proportion of α -linolenic acid in both free fatty acids in plasma and in fatty acids in plasma, leukocyte, and platelet phospholipids showed a greater increase from Day 1 (pre-infusion) to Day 6 in the Lipovenös 20% group than in the SMOFlipid 20% group. For most of the fatty acid analyses, mean proportions of both EPA and DHA increased in the SMOFlipid 20% group, but decreased in the Lipovenös 20% group, and had higher values at Day 6 in the SMOFlipid 20% group. The mean proportion of ARA showed a greater decrease in the Lipovenös 20% group than in the SMOFlipid 20% group. Mead acid was measured as a free fatty acid in plasma, and had a low mean value (≤ 0.01 mol%) in both treatment groups at both Day 1 and Day 6.

Table 42: Changes in Proportions of Free Fatty Acids (mol%) in Plasma in Study FE-SM-03-DE – Per-Protocol Subset

Fatty acid parameter

SMOFlipid 20% (N=19)

Lipovenös 20% (N=14)

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Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
C18:2ω6 (linoleic acid)						
Day 1	18	20.70 (3.647)	20.68 (19.09-21.98)	14	20.59 (2.175)	20.17 (18.74-21.58)
Day 6	18	19.25 (2.472)	18.58 (17.50-21.07)	14	30.91 (4.222)	32.07 (28.20-34.39)
Change	18	-1.45 (3.154)	-1.01 (-2.19 to 0.48)	14	10.31 (5.184)	12.06 (7.19-13.48)
C18:3ω3 (α-linolenic acid)						
Day 1	18	0.47 (0.139)	0.44 (0.36-0.56)	14	0.35 (0.193)	0.33 (0.29-0.48)
Day 6	18	0.72 (0.282)	0.72 (0.60-0.91)	14	1.48 (0.604)	1.39 (1.18-1.65)
Change	18	0.25 (0.344)	0.34 (0.04-0.48)	14	1.13 (0.628)	0.98 (0.79-1.34)
C20:5ω3 (EPA)						
Day 1	18	0.43 (0.354)	0.42 (0.16-0.63)	14	0.38 (0.374)	0.32 (0.24-0.37)
Day 6	18	3.05 (1.083)	2.73 (2.55-3.25)	14	0.32 (0.109)	0.31 (0.26-0.44)
Change	18	2.62 (1.045)	2.41 (2.10-2.69)	14	-0.06 (0.338)	0.05 (-0.13 to 0.10)
C22:6ω3 (DHA)						
Day 1	18	3.68 (1.159)	3.67 (2.82-4.09)	14	3.13 (0.692)	2.98 (2.84-3.30)
Day 6	18	6.48 (1.036)	6.91 (5.77-7.27)	14	2.64 (0.664)	2.63 (2.38-3.03)
Change	18	2.80 (1.343)	2.89 (1.72-3.53)	14	-0.50 (0.740)	-0.41 (-1.00 to 0.20)
C20:4ω6 (ARA)						
Day 1	18	8.57 (1.385)	8.79 (7.37-9.33)	14	8.13 (2.050)	7.69 (7.19-8.87)
Day 6	18	7.56 (1.100)	7.33 (6.80-8.53)	14	5.84 (1.271)	-5.86 (4.72-6.61)
Change	18	-1.02 (1.805)	-0.81 (-2.46 to -0.20)	14	-2.29 (1.916)	-2.37 (-3.13 to -1.12)

Study 05-SMOF-006

There were no differences in fatty acid profiles between the treatment groups at baseline. The mean proportion of linoleic acid decreased in the SMOFlipid 20% group and increased in the Intralipid 20% group. The mean proportion of α-linolenic acid in both plasma lipoproteins and RBC phospholipids showed greater increases from baseline to Week 4/end of study in the Intralipid 20% group than in the SMOFlipid 20% group. Mean proportions of both EPA and DHA increased in the SMOFlipid 20% group, but decreased in the Intralipid 20% group (except for DHA, which showed a small increase in RBC phospholipids). The mean proportion of ARA decreased in the SMOFlipid 20% group and increased in the Intralipid 20% group.

Table 43: Changes in Proportions of Fatty Acids (%) in Plasma Lipoproteins in Study 05-SMOF-006 – Evaluable Population

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Karyn L. Berry, MD, MPH

NDA 207648

Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

Fatty acid

parameter

		SMOFlipid 20% (N=28)			Intralipid 20% (N=29)	
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
C18:2ω6 (linoleic acid)						
Day 0	14	36.82 (9.603)	40.00 (32.90-43.37)	20	36.94 (9.533)	35.69 (28.73-45.89)
Week 4/EOS ^a	14	33.79 (8.115)	33.84 (29.75-37.65)	20	44.24 (7.725)	46.57 (38.24-51.00)
Change	14	−3.03 (7.547)	−2.71 (−7.81 to 0.93)	20	7.29 (12.817)	10.35 (−1.27 to 15.24)
C18:3ω3 (α-linolenic acid)						
Day 0	14	0.51 (0.300)	0.53 (0.24-0.69)	20	0.51 (0.334)	0.44 (0.25-0.75)
Week 4/EOS ^a	14	0.40 (0.188)	0.30 (0.27-0.55)	20	0.64 (0.364)	0.58 (0.42-0.85)
Change	14	−0.11 (0.232)	−0.05 (−0.30 to 0.10)	20	0.13 (0.295)	0.14 (0.01-0.37)
C20:5ω3 (EPA)						
Day 0	14	0.38 (0.282)	0.34 (0.13-0.48)	20	0.51 (1.076)	0.28 (0.13-0.41)
Week 4/EOS ^a	14	3.21 (2.747)	2.30 (1.40-3.51)	20	0.35 (0.380)	0.25 (0.12-0.33)
Change	14	2.83 (2.609)	1.91 (1.22-3.15)	20	−0.16 (0.824)	−0.06 (−0.12 to 0.06)
C22:6ω3 (DHA)						
Day 0	14	0.71 (0.414)	0.58 (0.36-1.06)	20	0.88 (1.147)	0.58 (0.46-0.82)
Week 4/EOS ^a	14	2.08 (1.654)	1.50 (1.08-2.90)	20	0.84 (0.493)	0.77 (0.54-0.99)
Change	14	1.37 (1.529)	0.99 (0.71-1.46)	20	−0.04 (0.746)	0.06 (−0.09 to 0.21)
C20:4ω6 (ARA)						
Day 0	14	6.99 (4.848)	5.25 (3.74-9.80)	20	5.98 (1.739)	6.01 (4.50-7.13)
Week 4/EOS ^a	14	5.89 (3.724)	4.32 (3.07-9.05)	20	6.00 (2.235)	5.78 (4.00-7.64)
Change	14	−1.10 (2.750)	−0.48 (−2.97 to 0.34)	20	0.02 (2.074)	0.02 (−1.16 to 0.64)

Reviewer's comments: The Applicant states that even though the Holman index (ratio of mead acid to ARA) was not calculated in this study, mead acid was measured as a free fatty acid in plasma, and had a low mean value (≤ 0.01 %mol) in both treatment groups at both Day 1 and Day 6. The Applicant reports that based on the measured mean mead acid values that the mean Holman index would be well below 0.2 at both Day 1 and Day 6 in both treatment groups. EFAD in the adult leads to recognizable symptoms of which dermatological are the most prominent. EFAD is generally reversible in adults with administration of essential fatty acids, While the the mean values in this small population provides limited information on essential fatty acids, this issue will be further addressed and studied in neonates, a population in which EFAD is far more serious and associated with possible permanent sequela related to neurological development.

Albumin

Study 05-SMOF-006

Albumin concentration was evaluated in both the evaluable and the safety populations. There were no differences in mean or median albumin concentration between the treatment groups at baseline. Mean and median albumin values remained stable during the course of the study in both treatment groups.

In the evaluable population at baseline, 8 patients (29.6%) in the SMOFlipid 20% group and 9 patients (31.0%) in the Intralipid 20% group had albumin values below the lower limit of normal. By Week 4/end of study, 3 of these patients in each treatment group had values within the normal range. Three patients (11.1%) in the SMOFlipid 20% group, and none in the Intralipid 20% group, had normal albumin values at baseline, and low values at Week 4/end of study. In the safety population, 1 event of hypoalbuminemia in the SMOFlipid 20% group was reported as an AE

Table 44: Albumin Values Over Time (g/L) in Study 05-SMOF-006 –
Evaluable and Safety Populations

Population						
Statistic						
	SMOFlipid 20%			Intralipid 20%		
	Baseline	Week 4/EOS	Change	Baseline	Week 4/EOS	Change
Evaluable population (SMOFlipid 20% N=28; Intralipid 20% N=29)						
n	27	27	27	29	29	29
Mean	36.98	37.11	0.14	37.81	38.42	0.61
SD	7.273	6.139	3.596	5.891	6.169	3.268
Median	37.00	37.00	0.00	37.00	40.00	0.00
IQR	31.00-41.00	33.00-42.00	-3.00 to 3.00	34.00-41.00	33.00-42.30	-1.00 to 3.00
Safety population (SMOFlipid 20% N=34; Intralipid 20% N=39)						
n	32	32	32	38	38	38
Mean	36.81	36.46	-0.36	38.72	38.38	-0.35
SD	7.595	7.178	3.872	5.822	6.262	4.680
Median	37.00	37.00	-0.45	38.00	39.00	-1.00

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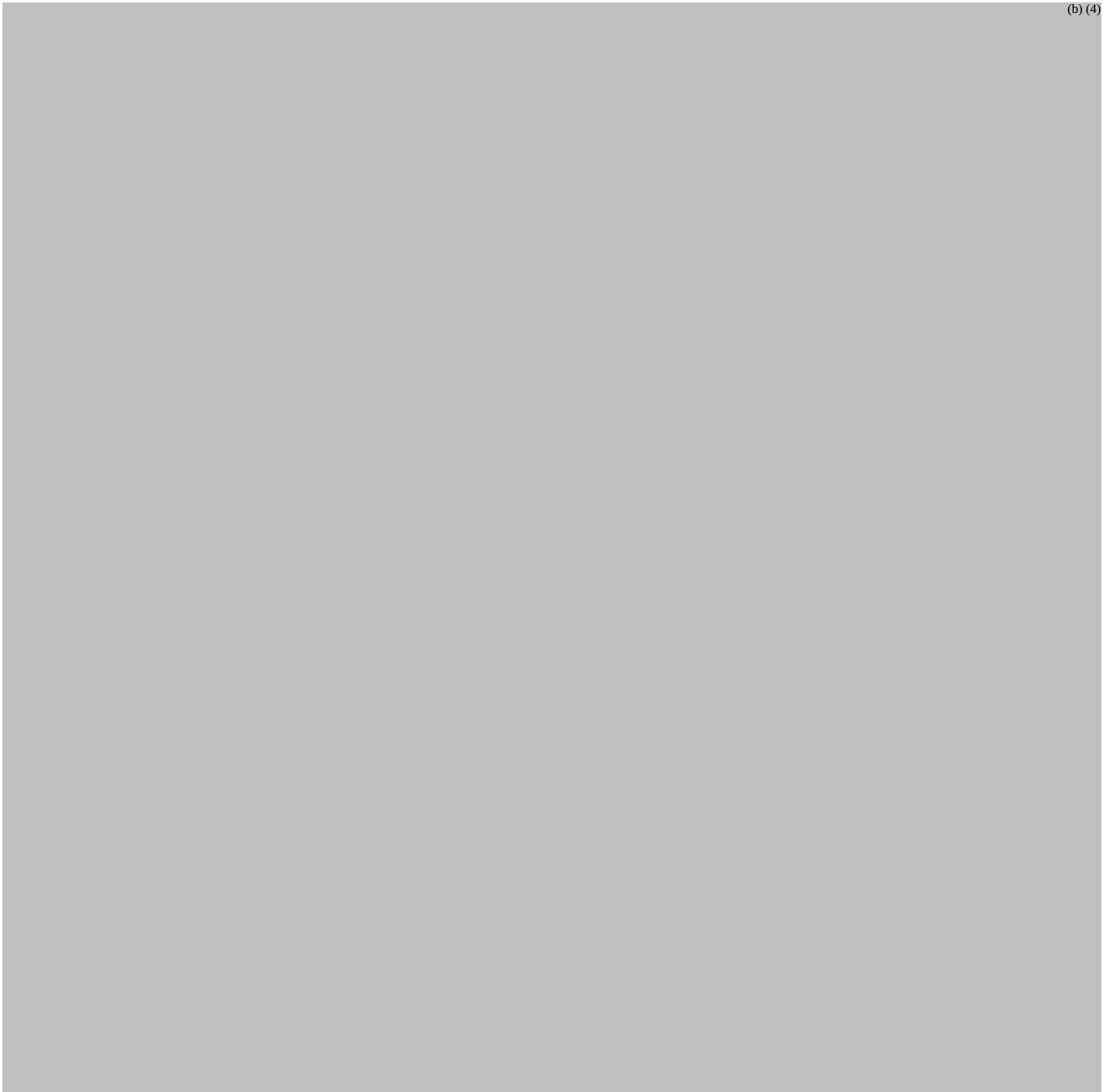
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IQR	31.00-42.50	32.50-42.00	-3.05 to 2.50	34.10-44.00	33.00-42.30	-2.80 to 3.00
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6.1.5 Analysis of Secondary Endpoints(s)

Adult trials

Study FE-SM-03-DE

Eicosanoid synthesis: Mean concentrations of EPA-derived LTB₅ increased to a greater extent following administration of SMOFlipid 20% compared with Lipovenös 20% (p: 0.0013, ANOVA), whereas mean concentrations of ARA derived LTB₄ increased following administration of Lipovenös 20% and decreased following administration of SMOFlipid 20%.

Vitamin E (α-tocopherol and γ-tocopherol): α-Tocopherol and γ-tocopherol concentrations were measured in plasma for the 33 patients included in the PP subset of patients enrolled at 2 prespecified study centers. Mean α-tocopherol and γ-

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tocopherol levels increased from Day 1 to Day 6 in both treatment groups. The change in α -tocopherol levels was significantly greater for the Smoflipid 20% group

Table 49: Vitamin E - α -tocopherol (mmol/l)

Vitamin E - α -tocopherol (μ mol/l)						
Per-Protocol Sub-group	N	Mean	SD	LCLM	UCLM	Median
SMOF Group						
day 1	19	14.46	6.508	11.326	17.600	13.40
day 6	19	34.16	10.324	29.182	39.134	34.30
day 6-day 1	19	19.69	12.169	13.829	25.560	20.10
Lipovenös Group						
day 1	14	11.56	2.261	10.259	12.870	11.25
day 6	14	17.57	2.937	15.876	19.267	16.80
day 6-day 1	14	6.01	3.909	3.750	8.264	5.20

Table 50: Vitamin E - γ -tocopherol (mmol/l)

Vitamin E - γ -tocopherol (μ mol/l)						
Per-Protocol Sub-group	N	Mean	SD	LCLM	UCLM	Median
SMOF Group						
day 1	19	0.73	1.449	0.028	1.425	0.00
day 6	19	3.31	1.487	2.594	4.027	3.40
day 6-day 1	19	2.58	2.271	1.490	3.679	3.10
Lipovenös Group						
day 1	14	1.27	2.604	-0.232	2.775	0.00
day 6	14	10.47	4.317	7.979	12.964	11.40
day 6-day 1	14	9.20	6.058	5.702	12.698	11.20

Length of stay in hospital: For the PP population as a whole, the mean (standard deviation [SD]) length of stay in the hospital was 15.7 (6.3) days in the SMOFlipid 20% group and 17.8 (13.2) days in the Lipovenös 20% group. These data demonstrated high

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interpatient variability; the median values were similar in both treatment groups (14.5 days for SMOFlipid 20%, 14.0 days for Lipovenös 20%).

Length of stay in ICU: For the PP population as a whole, the mean (SD) length of stay in the ICU was similar in the 2 treatment groups: 4.7 (9.4) days in the SMOFlipid 20% group and 5.2 (10.5) days in the Lipovenös 20% group. As for length of stay in hospital, there was high interpatient variability in both groups; the median value was 3.0 days in each group

6.1.6 Other Endpoints

NA

6.1.7 Subpopulations

Efficacy data were not analyzed by subgroups based on intrinsic or extrinsic factors in the studies conducted in adults.

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant has not explored new dosing schedules. Dosing regimens are the same as those for Intralipid. Dosing of lipid emulsions in both adult and pediatric patients is individualized by the treating physician based on the individual caloric needs of the patient using guidelines published by national and international nutrition societies, such as ASPEN and ESPEN.

Table 51: Protocol specified dose regimens for Smoflipid 20% in clinical trials in adults

Study	Type of subject	Dose regimen	Planned duration of treatment
FE-SM-01-BE	Healthy subjects	1 g/kg/h for 6 min, then approximately 0.15 g/kg/h for total of 4 h	4 hours
FE-SM-02-DE	Healthy subjects	0.125 g/kg/h for total of 6 h	6 hours
FE-SM-03-DE	Adult patients	1.5 g/kg/d	5 days
05-SMOF-006	Adult patients	1-2 g/kg/d	4 weeks
FE-SM-04-CH	Adult patients	up to 2.0 g/kg/d	10-14 days
03-3CB7-001	Adult patients	stepwise dosing from 0.57 g/kg/d to 1.14 g/kg/d	5-7 days
03-3CB8-001	Adult patients	up to 1.13 g/kg/d	5-7 days

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

The Applicant's proposed recommended dose of Smoflipid 20% in adults is 1.0 to 2.0 g/kg/d, corresponding to 5 to 10 mL/kg/d; not to exceed a dose of 2.5 g/kg/d.

Reviewer's comments: Based on a review of the literature, the proposed dosing regimen for adults of 1 to 2 g/k/d appears adequate, especially in the acute setting. For long term HPN treatment (>6 months) in adults, it is recommended that the provision of intravenous lipid should not exceed 1 g/kg/day. The daily requirement for essential fatty acids is 7-10 g. which corresponds to 14-20 g LCT fat from soya oil and 30-40 g LCT fat from olive/soya oil. This dose of Smoflipid should therefore provide adequate essential fatty acids for long term adult IV lipid emulsion treatment. (Staun M, 2009. None of the Applicant's submitted adult clinical trials used a dose higher than 2 g/kg/d. However, as discussed in Section 5.2, the applicant has based their proposed dosing on ASPEN guidelines that recommend that the fat content of PN formulations not exceed 2.5 g/kg/day. This reviewer therefore, recommends including the "not to exceed" dose of 2.5 g/k/d in the dosing section of the label.

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This is not applicable to intravenous lipid emulsion products. There is no data that lipid emulsions have efficacy that persists beyond their metabolic use as a source of calories and essential fatty acids. Tolerance, i.e., the need for ever increasing doses to have the same effect, has not been described with lipid emulsions.

6.1.10 Additional Efficacy Issues/Analyses

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7 Review of Safety

Safety Summary

A total of 10 clinical studies were included in the safety evaluation of SMOFlipid 20%. This includes 2 studies in healthy volunteers, 5 studies in adult patients, and 3 studies in pediatric patients. The trial conducted in China, was not included in the ISS and is briefly discussed as a supportive trial in Section 7.7 Additional Submissions/Safety Issues. A total of 338 subjects received Smoflipid 20% (22 healthy adults; 229 adult patients; 15 infants/children and 72 preterm neonates). A total of 19 patients died in the studies (9 patients [2.8%] in the SMOFlipid 20% group and 10 patients [3.2%] in the comparator group). Four of these deaths occurred in preterm neonates (2 deaths in the Smoflipid group and 2 deaths in the Intralipid group). None of the adult or pediatric deaths in the Smoflipid 20% treatment groups were attributed to the drug.

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Smoflipid (lipid injectable emulsion), for intravenous use/ Smoflipid (lipid injectable emulsion, USP), 20%

The most common SOC in which TEAEs were reported was Gastrointestinal Disorders, Smoflipid 55/316 (17.4%) and comparator 51/315 (16.2%). This may reflect that the majority of the patients in the adult studies were post-operative patients who had undergone abdominal surgery. The most common preferred terms were nausea, which occurred in 20 patients (6.3%) in the Smoflipid group and 26 patients (8.3%) in the comparator group and vomiting, which occurred in 16 patients (5.1%) in the Smoflipid group and 12 patients (3.8%) in the comparator group.

Three safety issues that are of particular concern are: 1) The potential for essential fatty acid deficiency, 2) development of PNALD possibly related to the phytosterol content of plant derived lipid formulations and 3) the question of whether increased amounts of omega 3 fatty acids confer a safety benefit.

Essential Fatty Acids

Only two specific fatty acids are generally considered to be “essential.” They are both long chain (18-carbon) polyunsaturated fatty acids (PUFA) that cannot be synthesized by mammals. Alpha linolenic acid (ALA) is the precursor of the n-3 family of PUFA, in which the first double bond in the molecule is 3 carbons away from the methyl terminus. Linoleic acid (LA) is the precursor of the n-6 PUFA family, in which the first double bond in the molecule is 6 carbons from the methyl terminus.

Mammals lack the requisite enzymes to insert a double bond at the n-3 or n-6 position (counting from the methyl end) of the fatty acid chain (McCowen 2005).

Docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6), metabolites of EFA, are important structural components of the highly specialized membranes lipids of the human central nervous system and are therefore particularly important for the neonate. Inadequate provision of EFA in the adult leads to a recognizable EFA deficiency syndrome of which dermatological manifestations are the most prominent. The adult form is easily reversible; in the infant EFA deficiency may have more far-reaching and possibly permanent consequences for neurological development (Uauy et al. 2001), (Innis 2003).

Evaluation of essential fatty acids is both an efficacy and safety concern for intravenous lipid emulsions. Smoflipid 20% contains significantly lower amounts of the essential fatty acids, LA and ALA, compared to Intralipid 20%. As previously discussed, pediatric patients, particularly preterm neonates, are most at risk for long term developmental complications related to essential fatty acid deficiency.

PNALD/Phytosterols

Phytosterols are plant sterols that are poorly absorbed by the gut and compete with the absorption of cholesterol. Increased oral phytosterol consumption can lower plasma

cholesterol levels. However, phytosterols are also contained in intravenous lipid formulations. In contrast to the intestinal route, where the absorption is approximately 5 %, all of the phytosterols contained in intravenous lipid formulations reach the liver. Phytosterols have been implicated as one of several potential causative factors of parenteral nutrition associated liver disease. PNALD is believed to occur in stages starting with parenteral nutrition associated cholestasis (PNAC), the predominant presentation in infants. As PNAC progresses to PN-associated liver disease (PNALD), the process can lead to a high incidence of morbidity and mortality (Rangel et al. 2012).

None of the studies in this NDA submission were designed to investigate the belief that a lower content of omega 6 fatty acids associated with a higher content of omega 3 fatty acids confers a safety benefit, such as anti-inflammatory effects and immune modulation. Although there is insufficient data to support these claims, there is a strong bias in favor of alternative lipid emulsion products that have increased omega 3 fatty acids and decrease omega 6 fatty acids (Vanek 2012). The Applicant does not propose to include any related claims in the label.

To further assess the risks of EFAD, PNALD/phytosterols and the safety benefits of omega 3 fatty acids additional clinical trials are needed in both the adult and pediatric populations.

7.1 Methods

The safety results of the 10 clinical trials comprising the Smoflipid clinical program are summarized. All patients who received at least one dose of the study medication are included in the safety analysis.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 10 clinical studies were included in the safety evaluation of SMOFlipid 20%. This includes 2 studies in healthy volunteers, 5 studies in adult patients, and 3 studies in pediatric patients. This safety review will primarily focus on the patient trials.

Table 55: Summary of Clinical Studies Included in the Safety Evaluation

Study Population	Study Identifier	Study Treatment	Comparator	Number of Patients in Safety Population (SMOF lipid 20%/ comparator)
Healthy volunteers	FE-SM-01-BE	SMOF lipid 20%	Lipovenös 20%	10 (10/10)
Healthy volunteers	FE-SM-02-DE	SMOF lipid 20%	Lipovenös 20%	12 (12/12)
Adult patients	FE-SM-03-DE	SMOF lipid 20%	Lipovenös 20%	249 (126/123)
Adult patients	FE-SM-04-CH	SMOF lipid 20%	Lipovenös 20%	32 (16/16)
Adult patients	03-3CB7-001	SmofKabiven	Kabiven	53 (26/27)
Adult patients	03-3CB8-001	SmofKabiven Peripheral	Kabiven Peripheral	52 (27/25)
Adult patients	05-SMOF-006	SMOF lipid 20%	Intralipid 20%	73 (34/39)
Children, infants	00-SMOF-002	SMOF lipid 20%	Intralipid 20%	28 (15/13)
Preterm neonates	00-SMOF-004	SMOF lipid 20%	Intralipid 20%	60 (30/30)
Preterm neonates	03-SMOF-005	SMOF lipid 20%	Intralipid 20%	84 (42/42)

7.1.2 Categorization of Adverse Events

Clinical safety outcomes were evaluated by the assessment of adverse events (AE), serious adverse events (SAE), changes in laboratory safety parameters, and changes in vital signs.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant stated that the safety data from the 10 clinical studies were pooled in order to create larger safety datasets for analysis, with all analyses based on the safety population (i.e., all patients who received at least 1 dose of study treatment).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 22 healthy volunteers and 631 patients were included in the pooled safety analysis. All 22 of the healthy volunteers received both SMOFlipid 20% and the comparator (Lipovenös 20%) in crossover studies. Of the 631 patients enrolled into the 8 patient studies, 459 were adult patients (229 receiving SMOFlipid 20% and 230 receiving the comparator) and 172 were pediatric patients (87 receiving SMOFlipid 20% and 85 receiving the comparator), including 144 preterm neonates (gestational age <37 weeks) (72 receiving SMOFlipid 20% and 72 receiving the comparator), 13 infants (1 month to <2 years) (7 receiving SMOFlipid 20% and 6 receiving the comparator), and 15 children (2 years to <12 years) (8 receiving SMOFlipid 20% and 7 receiving the comparator). There were 101 patients who received 28-days of treatment (SMOFlipid 20% = 49; comparator = 52).

In the studies in adult patients, there were more male patients than female patients in both treatment groups (57% males in the pooled SMOFlipid 20% group; 61% males in the pooled comparator group). Mean age was similar in both groups (57 years in the pooled SMOFlipid 20% group; 58 years in the pooled comparator group), and a similar proportion of

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patients in both treatment groups were >65 years of age (33% in the pooled SMOFlipid 20% group; 37% in the pooled comparator group).

7.2.2 Explorations for Dose Response

Explorations for dose response were not conducted because the doses of lipid emulsions were determined according to the needs of the patient (mostly based on calorie requirements) which were in turn determined according to clinical practice and nutritional society recommendations prevailing when these studies were conducted,

7.2.3 Special Animal and/or In Vitro Testing

No special animal testing was reported by the Applicant.

7.2.4 Routine Clinical Testing

For all laboratory parameters, mean, median, SD, 25% and 75% quartiles, minimum and maximum values were calculated for baseline, endpoint, and on-treatment. Laboratory assessments included complete blood count, chemistries, liver function tests, triglyceride levels, cholesterol levels, fatty acid profiles.

7.2.5 Metabolic, Clearance, and Interaction Workup

Smoflipid lipid emulsion contains a triglyceride core surrounded by phospholipids and its distribution and metabolism are similar to that of endogenously synthesized chylomicrons. The applicant evaluated appropriate clinical chemistry parameters such as triglyceride clearance and no significant differences were found.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 7 Safety overview

7.3 Major Safety Results

7.3.1 Deaths

A total of 19 patients died in the studies (9 patients [2.8%] in the SMOFlipid 20% group and 10 patients [3.2%] in the comparator group). Of these 19 patients, 2 in each treatment group died during the treatment period of the study and the remaining 15

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patients died during follow-up. One SAE leading to death in the Intralipid 20% group was considered related to the study treatment (Enterobacter sepsis).

Four deaths occurred after study completion. These 4 patients were all in study FE-SM-03-DE, including 3 in the SMOFlipid 20% group and 1 in the Lipovenös 20% group. The cause of death for patient 9075 (Lipovenös 20%) was reported as multi-organ failure. For the 3 SMOFlipid 20% patients, the cause of death was unknown.

A total of 15 patients died in the adult studies (7 patients [3.1%] in the SMOFlipid 20% group and 8 patients [3.5%] in the comparator group). Two patients died during the treatment period and the remaining 13 patients died during follow-up. None of the SAEs leading to death in 11 of the 15 cases were considered related to the study treatment. No SAEs leading to death were reported for the remaining 4 patients.

Four patients (2 patients in the SMOFlipid 20% group and 2 patients in the Intralipid 20% group) died in the preterm neonate studies (all deaths occurred in the 03-SMOF-005 study). All 4 patients who died were male. The 2 SMOFlipid 20% patients were lighter in weight (0.6 kg and 0.6 kg) than the 2 Intralipid 20% patients (1.0 kg and 1.1 kg). In the SMOFlipid 20% group, the deaths occurred during treatment, while in the Intralipid 20% group, the deaths occurred during follow-up. One SAE in an Intralipid 20% preterm infant who died was considered related to the study treatment (Enterobacter sepsis). There were no SAEs leading to death in study 00-SMOF-004 preterm neonates or study 00-SMOF-002 in children.

Reviewer's comments: After review of the patient narratives, the adult deaths occurred in patients who had undergone significant gastrointestinal surgery and the pediatric deaths appeared to be the result of events related to prematurity. This reviewer agrees with the Applicant's assessment that it was unlikely that deaths were related to the study drug.

Table 56: Summary of Deaths- All patients

Study identifier	Treatment group	Patient number	Study phase and study day at death ^a	Age at enrollment	Sex	Race	SAE (preferred term)	Treatment-related AE?
FE-SM-03-DE	SMOFlipid 20%	9055	Post-treatment, Day 3	72 years	Male	White	Pneumonia aspiration	No
FE-SM-03-DE	SMOFlipid 20%	9118 ^b	Post-treatment, Day 21	77 years	Male	White	No SAE reported	–
FE-SM-03-DE	SMOFlipid 20%	9173 ^b	Post-treatment, Day 7	56 years	Male	White	No SAE reported	
FE-SM-03-DE	SMOFlipid 20%	9174 ^b	Post-treatment, Day 25	39 years	Female	White	No SAE reported	–
FE-SM-03-DE	SMOFlipid 20%	9190	Post-treatment, Day 4	64 years	Male	White	Sepsis	No
FE-SM-03-DE	SMOFlipid 20%	9258	Post-treatment, Day 10	64 years	Male	White	Ascites	No
							Multi-organ failure	No
FE-SM-03-DE	Lipovenös 20%	9034	Post-treatment, Day 9	57 years	Male	White	Respiratory failure	No
FE-SM-03-DE	Lipovenös 20%	9075 ^{b,c}	Post-treatment, Day 17	71 years	Female	White	No SAE reported	–
FE-SM-03-DE	Lipovenös 20%	9081	Post-treatment, Day 29	46 years	Male	White	Disease progression	No
FE-SM-03-DE	Lipovenös 20%	9093	Post-treatment, Day 14	90 years	Female	White	Multi-organ failure	No
FE-SM-03-DE	Lipovenös 20%	9096	Post-treatment, Day 33	62 years	Male	White	Respiratory failure	No
FE-SM-04-CH	Lipovenös 20%	0004	Treatment, Day 2	87 years	Male	White	Pneumonia aspiration	No
FE-SM-04-CH	Lipovenös 20%	0034	Treatment, Day 6	96 years	Female	White	Abdominal pain ^d	No
03-3CB8-001	SmofKabiven peripheral	0099	Post-treatment, Day 7	69 years	Male	White	Dyspnoea	No
							Anaemia	No
							Hepatic necrosis	No
							Haemorrhage	No
							Liver abscess	No
							Sepsis	No
							Left ventricular failure	No

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Study identifier	Treatment group	Patient number	Study phase and study day at death ^a	Age at enrollment	Sex	Race	SAE (preferred term)	Treatment-related AE?
03-3CB8-001	Kabiven peripheral	0001	Post-treatment, Day 22	75 years	Female	White	Sepsis Pneumonia Multi-organ failure	No No No
03-SMOF-005	SMOFlipid 20%	0111	Treatment, Day 4	1 day	Male	White	Infection Toxic shock syndrome	No No
03-SMOF-005	SMOFlipid 20%	0132	Treatment, Day 7	5 days	Male	White	Pneumothorax	No
03-SMOF-005	Intralipid 20%	0134	Post-treatment, Day 13	3 days	Male	White	Enterobacter sepsis Multi-organ failure Sepsis Pancytopenia Metabolic acidosis	Yes No No No No
03-SMOF-005	Intralipid 20%	0230	Post-treatment, Day 20	9 days	Male	White	Multi-organ failure	No

AE = adverse event; SAE = serious adverse event.

^a Relative to the start of study treatment.

Four deaths were reported in patients after they had completed study FE-SM-03-DE (3 patients in the SMOFlipid 20% group; 1 patient in the Lipovenös 20% group); no

SAEs were reported in the clinical database for these patients. These deaths are, therefore, not included in tables summarizing SAEs that led to death. For further information see Section 4.3.

^c Death subsequently reported to be due to multi-organ failure.

^d Verbatim term given as 'abdominal pain in a case of anastomotic insufficiency' in the CRF.

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7.3.2 Nonfatal Serious Adverse Events

There were no SAEs reported in the healthy volunteer studies. A total of 23 (7%) patients reported SAEs in the SMOFlipid 20% pooled group and 31 (10%) patients reported SAEs in the comparator pooled group.

Twenty-one patients in the Smoflipid group and 29 patients in the Comparator group had serious adverse events. The overall frequency of treatment-emergent SAEs was lower in the SMOFlipid 20% pooled group (6.6%) than in the comparator pooled group (9.2%). The most common treatment-emergent SAE in both groups was sepsis (5 patients in the SMOFlipid 20% pooled group and 5 patients in the comparator pooled group), followed by multi-organ failure (1 patient in the SMOFlipid 20% pooled group and 4 patients in the comparator pooled group), respiratory failure (2 patients in each pooled group), abdominal pain (1 patient in the SMOFlipid 20% pooled group and 2 patients in the comparator pooled group), and device related sepsis (1 patient in the SMOFlipid 20% pooled group and 2 patients in the comparator pooled group). The treatment-emergent SAEs of device related sepsis were all reported in the adult 28-day study 05-SMOF-006.

Table 57: Summary of Treatment-Emergent Serious Adverse Events Occurring in at Least 2 Patients in Any Pooled Group – All Patients

MedDRA preferred term, n (%) of patients	SMOFlipid 20% pooled (N=316)	Comparator pooled (N=315)
Patients with at least 1 treatment-emergent SAE	21 (6.6)	29 (9.2)
Sepsis	5 (1.6)	5 (1.6)
Respiratory failure	2 (0.6)	2 (0.6)
Patent ductus arteriosus repair	2 (0.6)	0
Peritonitis	2 (0.6)	0
Multi-organ failure	1 (0.3)	4 (1.3)
Abdominal pain	1 (0.3)	2 (0.6)
Device related sepsis	1 (0.3)	2 (0.6)
Pleural effusion	0	2 (0.6)

Applicant's table

Reviewer's comments: No specific safety signals were identified for Smoflipid.

7.3.3 Dropouts and/or Discontinuations

Twenty-five (8%) patients in the SMOFlipid 20% pooled group and 22 (7%) patients in the comparator pooled group withdrew from the study due to a TEAE. The most common TEAEs leading to study withdrawal were vomiting, hyperglycemia, and nausea. Both vomiting and hyperglycemia led to study withdrawal in more patients in the Smoflipid 20% pooled group than in the comparator pooled group (5 patients vs. 0 patients for vomiting and 5 patients vs. 1 patient for hyperglycemia).

In adults, twenty-one (9%) patients in the Smoflipid 20% pooled group and 20 (9%) patients in the comparator pooled group withdrew from the study due to a TEAE. The most common TEAEs leading to study withdrawal were nausea, vomiting, hyperglycemia, and sepsis. Vomiting, hyperglycemia, and sepsis led to withdrawal from the study in more patients in the Smoflipid 20% pooled group than in the comparator pooled group (5 patients vs. 0 patients for vomiting, 4 patients vs. 1 patient for hyperglycemia, and 3 patients vs. 0 patients for sepsis).

In pediatric patients, four (5%) patients in the Smoflipid 20% pooled group and 2 (2%) patients in the Intralipid 20% pooled group withdrew from the study due to a TEAE. All the events were reported in the preterm infant studies. In the Smoflipid group the reported TEAE were: intraventricular hemorrhage/hyperkalemia, pneumothorax, hyperglycemia and hypercalcemia. Only the TEAE of hyperglycemia was reported as possibly related to the study drug. In the Intralipid group the reported TEAEs were hepatitis and staphylococcal sepsis. Neither was reported as related to the study drug.

7.3.4 Significant Adverse Events

There were no significant adverse events reported in the development program.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.1. Three safety issues relevant to the class of products, intravenous lipid emulsion, that are of particular relevance have been identified: The potential for essential fatty acid deficiency, possible toxicities related to the phytosterol content of plant derived lipid formulations and the question whether the higher content of omega-3 fatty acids in Smoflipid as opposed to (b) (4) soybean oil lipid emulsions confers a safety benefit.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common SOC in which TEAEs were reported was Gastrointestinal Disorders, which may reflect that the majority of the patients in the adult studies were post-operative patients who had undergone abdominal surgery. This was followed by Infections and Infestations, Metabolism and Nutrition Disorders, and General Disorders and Administration Site Conditions.

Table 58: System Organ Classes for all Treatment-Emergent Adverse Events –All Patients

MedDRA System Organ Class, n (%) of patients	SMOFlipid 20% pooled (N=316)	Comparator pooled (N=315)
Patients with at least 1 TEAE	152 (48.1)	163 (51.7)
Gastrointestinal Disorders	55 (17.4)	51 (16.2)
Infections and Infestations	44 (13.9)	48 (15.2)
Metabolism and Nutrition Disorders	27 (8.5)	23 (7.3)
General Disorders and Administration Site Conditions	20 (6.3)	27 (8.6)
Blood and Lymphatic System Disorders	19 (6.0)	14 (4.4)
Nervous System Disorders	16 (5.1)	14 (4.4)
Respiratory, Thoracic and Mediastinal Disorders	15 (4.7)	19 (6.0)
Investigations	15 (4.7)	18 (5.7)
Vascular Disorders	10 (3.2)	16 (5.1)
Hepatobiliary Disorders	8 (2.5)	13 (4.1)
Cardiac Disorders	8 (2.5)	7 (2.2)
Musculoskeletal and Connective Tissue Disorders	8 (2.5)	6 (1.9)
Injury, Poisoning and Procedural Complications	7 (2.2)	5 (1.6)
Skin and Subcutaneous Tissue Disorders	6 (1.9)	10 (3.2)
Renal and Urinary Disorders	6 (1.9)	5 (1.6)
Surgical and Medical Procedures	6 (1.9)	4 (1.3)
Psychiatric Disorders	5 (1.6)	5 (1.6)
Neoplasms Benign, Malignant and Nonspecified (including cysts and polyps)	1 (0.3)	2 (0.6)

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Reproductive System and Breast Disorders	1 (0.3)	0
Congenital, Familial and Genetic Disorders	0	1 (0.3)
Ear and Labyrinth Disorders	0	1 (0.3)
Eye Disorders	0	1 (0.3)
Immune System Disorders	0	1 (0.3)

The overall frequency of TEAEs within the SOC of Gastrointestinal Disorders was similar for the 2 pooled treatment groups. The most common TEAEs in this SOC were nausea, vomiting, flatulence, abdominal pain, dyspepsia, and diarrhea

Table 59: Treatment-Emergent Adverse Events in the System Organ Class of Gastrointestinal Disorders Occurring in at Least 2 Patients in Any Pooled Group – All Patients

MedDRA preferred term, n (%) of patients	SMOf lipid 20% pooled (N=316)	Comparator pooled (N=315)
Patients with at least 1 TEAE	55 (17.4)	51 (16.2)
Nausea	20 (6.3)	26 (8.3)
Vomiting	16 (5.1)	12 (3.8)
Flatulence	10 (3.2)	4 (1.3)
Abdominal pain	8 (2.5)	5 (1.6)
Dyspepsia	5 (1.6)	1 (0.3)
Diarrhoea	3 (0.9)	4 (1.3)
Constipation	2 (0.6)	0
Dry mouth	2 (0.6)	0
Peritonitis	2 (0.6)	0
Paralytic ileus	1 (0.3)	2 (0.6)
Necrotising colitis	0	2 (0.6)

The TEAEs occurring in the SOC of General Disorders and Administration Site Conditions in more than 1 patient of any pooled group. The overall frequency of TEAEs reported in the SOC of General Disorders and Administration Site Conditions was similar for the 2 pooled treatment groups. The most common TEAE in this SOC was pyrexia, which was reported in 15 patients in each of the pooled treatment groups.

Table 60 Treatment-Emergent Adverse Events in the System Organ Class of General Disorders and Administration Site Conditions Occurring in at Least 2 Patients in Any Pooled Group – All Patients

MedDRA preferred term, n (%) of patients

	SMOf lipid 20% pooled (N=316)	Comparator pooled(N=315)
Patients with at least 1 TEAE	20 (6.3)	27 (8.6)
Pyrexia	15 (4.7)	15 (4.8)
Multi-organ failure	1 (0.3)	4 (1.3)
Chills	1 (0.3)	2 (0.6)
Medical device complication	0	3 (1.0)

Hepatic

Overall, 8 (2.5%) patients treated with SMOFlipid 20% and 13 (4.1%) of patients treated with the comparator experienced events in the SOC of Hepatobiliary Disorders; this includes 9 adult patients (3 [1.3%] in the SMOFlipid 20% pooled group and 6 [2.6%] patients in the comparator pooled group; and 12 preterm neonates (5 [6.9%] patients in the SMOFlipid 20% pooled group and 7 [9.7%] patients in the Intralipid 20% pooled group. In adult patients, the most commonly reported preferred terms in this SOC were cholestasis and cytolytic hepatitis (each reported in 2 [0.9%] patients in the SMOFlipid 20% pooled group and 2 [0.9%] patients in the comparator pooled group); all of these events were assessed by the investigator as being at least possibly related to study treatment. In preterm neonates, the most commonly reported preferred term in this SOC was hyperbilirubinemia 4 [5.6%] patients in the SMOFlipid 20% pooled group; 5 [6.9%] patients in the Intralipid 20% pooled group), all of which were assessed by the investigator as being at least possibly related to study treatment

Adult Patients

The SOC in which TEAEs were most commonly reported was Gastrointestinal Disorders, This was followed by Infections and Infestations and Metabolism and Nutrition Disorders in the SMOFlipid 20% pooled group, and by Infections and Infestations and General Disorders and Administration Site Conditions in the comparator pooled group. There were no SOC for which there was a notably higher frequency of events in the SMOFlipid 20% pooled group compared to the comparator pooled group.

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Table 61: Preferred Term for all Treatment-Emergent Adverse Events ($\geq 1\%$) – Adult Patients

	Smoflipid group (pooled) N = 249		Comparator group (pooled) N = 230	
Number (%) of subjects with at least one AE	114 (49.8)		121 (52.6)	
Preferred term n (%)				
Nausea	20	(8.7)	26	(11.3)
Vomiting	15	(7)	12	(5.2)
Hyperglycemia	12	(5.2)	5	(2.2)
Flatulence	10	(4.4)	4	(1.7)
Pyrexia	9	(3.9)	11	(4.8)
Abdominal pain	8	(3.5)	5	(2.2)
Hypertension	6	(2.6)	9	(3.9)
Blood triglycerides increased	6	(2.6)	4	(1.7)
Sepsis	5	(2.2)	4	(1.7)
Dyspepsia	5	(2.2)	1	(0.4)
Urinary tract infection	4	(1.7)	3	(1.3)
Anemia	4	(1.7)	2	(0.9)
Device related infection	4	(1.7)	2	(0.9)
Headache	3	(1.3)	7	(3.0)
Diarrhea	3	(1.3)	4	(1.7)
Pneumonia	3	(1.3)	4	(1.7)
Pruritus	3	(1.3)	4	(1.7)
Liver function test abnormal	3	(1.3)	3	(1.3)
Hypertriglyceridemia	3	(1.3)	2	(0.9)
Tachycardia	3	(1.3)	1	(0.4)
Dyspnea	3	(1.3)	1	(0.4)
Leukocytosis	3	(1.3)	0	0

Reviewer's comments: GI disorders were most likely more common in the adult population as the majority of the patients in the adult studies were post-operative patients undergoing abdominal surgery.

Pediatric

The most common SOC in which TEAEs were reported was Infections and Infestations.

Table 62: System Organ Classes for all Treatment-Emergent Advers Events – Pediatric Patients

MedDRA System Organ Class, n (%) of patients	SMOFlipid 20% pooled (N=87)	Intralipid 20% pooled (N=85)
Patients with at least 1 TEAE	38 (43.7)	42 (49.4)

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Infections and Infestations	21 (24.1)	23 (27.1)
Blood and Lymphatic System Disorders	13 (14.9)	11 (12.9)
Respiratory, Thoracic and Mediastinal Disorders	8 (9.2)	5 (5.9)
General Disorders and Administration Site Conditions	7 (8.0)	8 (9.4)
Metabolism and Nutrition Disorders	7 (8.0)	8 (9.4)
Hepatobiliary Disorders	5 (5.7)	7 (8.2)
Nervous System Disorders	5 (5.7)	2 (2.4)
Gastrointestinal Disorders	3 (3.4)	7 (8.2)
Surgical and Medical Procedures	3 (3.4)	3 (3.5)
Investigations	2 (2.3)	3 (3.5)
Cardiac Disorders	1 (1.1)	2 (2.4)
Vascular Disorders	1 (1.1)	1 (1.2)
Injury, Poisoning and Procedural Complications	1 (1.1)	0
Congenital, Familial and Genetic Disorders	0	1 (1.2)
Eye Disorders	0	1 (1.2)

In the pediatric group, Infections and Infestations was the SOC in which TEAEs were reported with the highest frequency. The overall frequency of TEAEs within the SOC of Infections and Infestations was similar for the 2 pooled treatment groups. The most common TEAE in this SOC was nosocomial infection Smoflipid 10 (11.5%) and comparator 6 (7.1%).

Reviewer's comments: Increase in TEAEs in this SOC may reflect that preterm neonates are at increased risk of infections.

The overall frequency of TEAEs within the SOC of General Disorders and Administration Site Conditions was similar for the 2 pooled treatment groups, Smoflipid 6 (6.9%) and comparator 4 (4.7%)

7.4.2 Laboratory Findings

For most laboratory parameters, small changes were seen over the course of the studies. An increase was seen in prothrombin time (Quick test) (18% in the SMOFlipid 20% pooled group and 17% in the comparator pooled. Minimal decreases were seen in mean creatinine values and C-reactive protein was also decreased in both groups.

Changes were also seen in liver function tests, with decreases seen in mean total bilirubin and AST, and increases seen in mean GGT and alkaline phosphatase levels.

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Mean ALT levels remained virtually unchanged in the SMOFlipid 20% pooled group, but increased in the comparator pooled group.

Liver Function test

Mean alkaline phosphatase levels increased over the course of the study in both pooled groups. A few patients had values that increased from normal at baseline to greater than $2.5 \times \text{ULN}$ at endpoint (5 patients [2%] in the SMOFlipid 20% pooled group and 9 patients [4%] in the comparator pooled group). In contrast, increases in mean GGT levels from baseline to endpoint were reflected in a greater number of patients having a potentially clinically relevant change in GGT. The Applicant notes that the percentage of patients having a potentially clinically relevant change was lower in the SMOFlipid 20% pooled group (16%) than in the comparator pooled group (25%).

Mean ALT levels were relatively unchanged in the SMOFlipid 20% pooled group, but increased in the comparator pooled group over the course of the study; only 3% of patients in the SMOFlipid 20% pooled group and 5% of patients in the comparator pooled group had potentially clinically relevant increases in ALT over the course of the study. For AST and total bilirubin levels, decreases in mean values were seen from baseline to endpoint, but only a small percentage of patients had potentially clinically relevant changes in these parameters. For bilirubin, fewer patients in the SMOFlipid 20% pooled group had notable changes compared to the comparator pooled group.

Table 63: Number of Patients with Potentially Clinically Relevant Changes in Liver Function Tests – All Patients

Parameter, n (%) of patients	SMOFlipid 20% pooled (N=316)	Comparator pooled (N=315)
Total bilirubin, n^a	223	230
Change from $\leq 1.5 \times \text{ULN}$ to $> 1.5 \text{ ULN}$	1 (0.4)	7 (3.0)
AST, n^a	174	187
Change from $\leq 3.0 \times \text{ULN}$ to $> 3.0 \text{ ULN}$	3 (1.7)	4 (2.1)
ALT, n^a	226	241
Change from $\leq 3.0 \times \text{ULN}$ to $> 3.0 \text{ ULN}$	6 (2.7)	11 (4.6)
GGT, n^a	218	232
Change from $\leq 2.5 \times \text{ULN}$ to $> 2.5 \text{ ULN}$	34 (15.6)	59 (25.4)
Alkaline phosphatase, n^a	208	216
Change from $\leq 2.5 \times \text{ULN}$ to $> 2.5 \text{ ULN}$	5 (2.4)	9 (4.2)

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7.4.3 Vital Signs

An increase was observed in diastolic and systolic blood pressure in both treatment groups, with the increases being greater in the SMOFlipid 20% (diastolic blood pressure mean change was 3.1, systolic blood pressure mean change was 3.3) pooled group compared to the comparator (diastolic mean change of 2.0 and systolic mean change of 1.1) pooled group. For the other parameters (heart rate and body temperature), no clinically relevant changes were observed over the course of the study.

7.4.4 Electrocardiograms (ECGs)

No ECGs were conducted in the submitted patient studies.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant did not conduct any special safety studies/clinical trials.

7.4.6 Immunogenicity

Lipid emulsions have a very low potential to elicit an immunological reaction so because naturally occurring fatty acids do not elicit an immune response. However, allergic reactions to excipients and impurities are possible. Chief of these would be soy protein allergies.

In contrast, as previously discussed, there is a bias in the nutritional community about whether Smoflipid (and similar products) may lead to less immune suppression than lipid formulations with higher omega-6 PUFA content, such as Intralipid. The Applicant has not provided data to support this hypothesis.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Explorations for dose response are not applicable to this submission because the doses of lipid emulsions were determined according to the needs of the patient (mostly based on calorie requirements) which were in turn determined according to clinical practice and society recommendations prevailing when these studies were conducted.

7.5.2 Time Dependency for Adverse Events

The exposure time (e.g. duration of trials) was limited in the majority of adult and pediatric trials, which restricts the ability to assess adverse events over time.

7.5.3 Drug-Demographic Interactions

Subgroup analyses were performed for the following groups of patients: Adult patients, Children and infants and Preterm neonates.

Adults

In the sex subgroup analysis, related TEAEs occurred more frequently in females in the SMOFlipid 20% pooled group than in females in the comparator pooled group (20/99 [20%] vs. 11/90 [12%]).

The TEAE profile was similar between patients 18 to 65 years and those >65 years. The only treatment difference of note in patients >65 years was a greater frequency of anemia in the SMOFlipid 20% pooled group (4/76 [5%]) compared to the comparator pooled group (0/86 [0%]). Fewer treatment-emergent SAEs were reported for patients >65 years who received SMOFlipid 20% (5/76 [7%] vs. 11/86 [13%] in the comparator group).

In patients > 75 years of age treatment-emergent adverse events were more frequently reported in the SMOFlipid 20% pooled group compared to the comparator pooled group (14/23 [61%] vs. 9/21 [43%]).

Pediatrics

In children and infants there were no clinically relevant differences between treatments for the safety subgroup analyses based on sex or age.

Preterm neonates

In the male subgroup, there was a lower frequency of TEAEs in the SMOFlipid 20% pooled group (44%) compared to the Intralipid 20% pooled group (56%). However, the number of SAEs was similar between the 2 groups. In the female subgroup, the TEAEs was lower in SMOFlipid 20% pooled group compared to the Intralipid 20% pooled group (45% compared to 53%); however, the number of SAEs was similar between the 2 groups. When comparing males and females directly, there were more related TEAEs, SAEs, and deaths in males compared to females.

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7.5.4 Drug-Disease Interactions

No drug-disease interactions were explored.

7.5.5 Drug-Drug Interactions

The Applicant reports that no specific clinical drug-drug interaction studies were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

None were conducted

7.6.2 Human Reproduction and Pregnancy Data

No adequate or well-controlled studies with Smoflipid 20% in pregnant women. The Applicant reports that no animal reproduction studies have been conducted with Smoflipid 20%. It is not known whether SMOFlipid 20% can affect reproduction capacity or can cause fetal harm when administered to a pregnant woman. It is not known whether the components of SMOFlipid 20% are present in human milk.

A consult was requested from the Division of Pediatric and Maternal Health Review. Dr. Kasten, the medical reviewer, concluded that there are no data on Smoflipid use during pregnancy or lactation to inform the benefit/risk assessment; Limited clinical data on use of other lipid infusions and practice guidelines from ACOG support use of TPN with a lipid infusion in the rare instances where a pregnant woman is unable to consume sufficient nutrients to maintain her weight; There are no data on the use of TPN and lipid infusions during breastfeeding. However, there are no serious adverse events in adult patients identified that would warrant limitation of breastfeeding. See Dr. Kasten's full review dated September 23, 2015 for proposed labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

Under the Pediatric Research Equity Act (PREA), all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless requirement is waived, deferred, or inapplicable. Based on new active ingredients in Smoflipid, PREA would apply.

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Prior to submission of this application, the Division determined that additional safety information would be needed in the pediatric population that would be collected as post-marketing studies. The Applicant agreed to conduct two studies: The agreed initial Pediatric Study Plan (iPSP) includes two studies; a neonatal study intended to demonstrate the superiority of SMOFlipid when compared to Intralipid with respect to liver safety and a long-term safety study in the pediatric population with a minimum duration of three months.

In comments to the Applicant on 11/10/2014, the FDA stated: *We agree that extrapolating efficacy from neonates to infants, children and adolescents is reasonable. Extrapolation of data from one pediatric population to another under PREA generally refers only to efficacy and not to safety or dosing (Section 505B (a)(2)(B)(ii) of the FD&C Act). However, we agree, to assess safety, that two safety studies, a 28 day study in neonates and a 3 month study in infants, children and adolescent pediatric patients requiring long term PN is acceptable. The infant population should not be limited to pediatric patients 6 months of age and older, but should also include infants under 6 months of age down to the neonatal period*

On December 17, 2014, the Division met with Pediatric Review Committee (PeRC) to discuss the Applicant's submitted initial Pediatric Study Plan. At that time, PeRC agreed with the Division's plan to extrapolate efficacy data.

(b) (4)

Additional long-term safety data is needed in a sufficient number of patients. Careful attention must be paid to monitoring growth, nutritional parameters, and essential fatty acids. Studies must be performed in pediatric patients using adequate and consistent dosing of lipid (e.g. 2-3 g/kg/d); studies will need to address the full age span (pre-term and term neonates, toddlers, children and adolescents).

(b) (4)

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(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the event of an overdose, fat overload syndrome may occur. Fat overload syndrome is a rare condition that results from the excess accumulation of lipids in the serum. It is characterized by hyperlipidemia, fever, fat infiltration, hepatomegaly with or without jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorder, hemolysis and reticulocytosis, abnormal liver parameters, and coma, which resolve when the lipid infusion is discontinued. The cause may be genetic or the fat metabolism may be altered due to a change in clinical status.

Drug abuse is not applicable to this application. The Applicant reports that withdrawal or rebound effects with SMOFlipid 20% have not been reported.

7.7 Additional Submissions / Safety Issues

The Applicant submitted study SMOF-001-CP3 as a supportive safety study. Two hundred and twelve adult patients were enrolled in the study (106 in the Smoflipid group and 106 in the Intralipid group) that was conducted for 5 days in patients receiving PN who had undergone GI surgery. There was a similar incidence of adverse events (AEs)

in the study and control groups. A total of 88 patients reported 155 AEs (43 patients in the Smoflipid group and 45 patients in the Intralipid group). The Applicant reported that 4 patients (3 patients in the Smoflipid group and 1 patient in the Intralipid group) had 7 serious adverse events. SAEs reported in the Smoflipid group were pneumonia, wound dehiscence, abdominal infection, upper GI bleeding and delayed wound healing. SAE reported in the Intralipid group was wound dehiscence. Overall, as was seen in the other studies, GI symptoms, such as nausea and vomiting comprised the most number of AEs.

8 Postmarket Experience

Smoflipid 20% is approved or registered in 63 countries. The Applicant reports that no actions relating to safety have been taken by regulatory authorities or the marketing authorization holder. Since first registration in 2004, the Applicant estimated that 917,000 patients have been treated with SMOFlipid 20%.

The Applicant submitted a Periodic Safety Update Report that covered the period from March 1, 2011 to February 28, 2014. During the reporting interval no actions have been taken or have been proposed for safety reasons. Based on the available safety data for SMOFlipid evaluated in this PSUR no change of the risk-benefit ratio of the product was identified.

Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling discussions are ongoing at the time of this review. The label will provide information and data to support the use of Smoflipid 20% in adult patients. This reviewer therefore recommends that the label include only the five adult studies [REDACTED] (b) (4)

[REDACTED] The efficacy section of the label should include the three (3) randomized, double blind, active control studies only and the safety section should include all five (5) studies (n=229)

9.3 Advisory Committee Meeting

No Advisory Committee (AC) was held for this submission.

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9.4 Financial Disclosure

Clinical Investigator Financial Disclosure

Application Number: 207648

Submission Date(s): September 26, 2014

Applicant: Fresenius Kabi

Product: Smoflipid 20% (Lipid emulsion)

Reviewer: Karyn L. Berry, MD

Date of Review: October 26, 2015

Covered Clinical Study (Name and/or Number): FE-SM-01-BE; FE-SM-02-DE; FE-SM-03-DE; FE-SM-04-CH; 03-3CB7-001; 03-3CB8-001; 05-SMOF-006; SMOF-001-CP3; 00-SMOF-002; 00-SMOF-004; 03-SMOF-005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of principal investigators identified: <u>48</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NA Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: NA	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

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minimize potential bias provided: NA		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: NA	Yes ☐	No ☐ (Request explanation from applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARYN L BERRY
12/23/2015

ANIL K RAJPAL
12/24/2015
I concur with Dr. Berry.