NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	207648
Priority or Standard	Priority
Submit Date(s)	
Received Date(s)	June 22, 2021
PDUFA Goal Date	
Division/Office	Division of Hepatology and Nutrition (DHN)
Review Completion Date	
Established/Proper Name	SMOFlipid 20%, lipid injectable emulsion
(Proposed) Trade Name	
Pharmacologic Class	Solution for parenteral nutrition, fat emulsion.
Code name	
Applicant	Fresenius Kabi
Dosage form	Injectable
Applicant proposed Dosing Regimen	• For preterm and term neonates (b) (4) and infants (1 month to <2 years of age), the recommended initial dose is 0.5 to 1.0 g/kg/day (2.5 to 5.0 mL/kg/day) followed by successive increases of 0.5 to 1.0 g/kg/day in relation to the patient's ability to metabolize and eliminate lipids up to 3.0 g/kg/day. It is recommended to not exceed a daily dose of 3.0 g/kg/day (15 mL/kg/day). The infusion rate should not exceed 0.15 g/kg/hour. • For children (2 to <12 years of age), the recommended initial dose is 1.0 to 2.0 g/kg/day (5.0 to 10.0 mL/kg/day) followed by successive increases of 0.5 to 1.0 g/kg/day up to 3.0 g/kg/day (15 mL/kg/day). • For adolescents (12 to <17 years of age), the recommended dose is 1.0 to 2.0 g/kg/day (5.0 to 10.0 mL/kg/day) and should not exceed 2.5 g/kg/day (12.5 mL/kg/day). • In preterm and term neonates (b) (4), Smoflipid should be infused continuously over 20 to 24 hours. The recommended duration of infusion for Smoflipid in infants (1 month to <2 years of age), children (2 to <12 years of age), and adolescents (12 to <17 years of age) is between 12 and 24 hours, depending on the clinical situation. The administration flow rate is determined by dividing the volume of lipid by the duration of the infusion.
Applicant Proposed Indication(s)/Population(s)	A source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not

<table>
<tr><td></td><td>possible, insufficient, or contraindicated</td></tr>
<tr><td>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</td><td></td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s) (if applicable)</td><td>Add pediatric population</td></tr>
<tr><td>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</td><td></td></tr>
<tr><td>Recommended Dosing Regimen</td><td>
<table>
<tr><th>Pediatric Age group</th><th>Initial Dose</th><th>Maximum Dose</th><th>Duration of infusion</th></tr>
<tr><td>Birth to 2 years of age (including preterm and term neonates*)</td><td>0.5 to 1 g/kg/day

Increase the dose by 0.5 to 1 g/kg/day</td><td>3 g/kg/day</td><td>20 to 24 hours for preterm and term neonates

12 to 24 hours for patients
1 month to 2 years</td></tr>
<tr><td>2 to <12 years of age</td><td>1 to 2 g/kg/day

Increase the dose by 0.5 to 1 g/kg/day</td><td>3 g/kg/day</td><td>12 to 24 hours</td></tr>
<tr><td>12 to 17 years of age</td><td>1 to 2 g/kg/day</td><td>2.5 g/kg/day</td><td>12 to 24 hours</td></tr>
</table>
* The neonatal period is defined as including term, post-term, and preterm newborn infants. The neonatal period for term and post-term infants is the day of birth plus 27 days. For preterm infants, the neonatal period is defined as the day of birth through the expected age of delivery plus 27 days (i.e., 44 weeks post-menstrual age).
</td></tr>
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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Fresenius Kabi (FK) submitted a pediatric efficacy supplement (S-005) for SMOFlipid, new drug application (NDA) 207648, on June 22, 20211. SMOFlipid was approved for adults in July 2016 as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. The Agency did not grant pediatric approval at the time of adult approval in 2016 citing a lack of evidence for safety and efficacy.

In the original NDA submission, FK submitted the findings from its three sponsored pediatric studies. The studies were of short duration with two (00-SMOF-002, 00-SMOF-004) lasting up to 14 days, and one (03-SMOF-005) lasting for four weeks. All of the studies used Intralipid 20%, which was approved in the US in 1981 and is 100% soybean-oil based, for the control. While most of the safety and efficacy endpoint findings in the pediatric trials were equivalent in both treatment arms, the Division[1] was concerned that use in pediatric patients, especially preterm neonates, required additional evaluation.

The Agency's key efficacy concern about SMOFlipid was the adequacy of essential fatty acid (EFA) supply, a lack of which can lead to EFA deficiency (EFAD) and can cause permanent neurological impairment, particularly in premature neonates. The key safety concern was the development of parenteral nutrition-associated cholestasis (PNAC) which can progress to parenteral nutrition-associated liver disease (PNALD), which is associated with a high incidence of morbidity and mortality.[2] PNALD, which is increasingly referred to as intestinal failure-associated liver disease (IFALD), may cause cirrhosis, portal hypertension, and end stage liver disease. PNAC is defined, by expert consensus, as a conjugated or direct bilirubin level of >2 mg/dL, after at least two weeks of PN and with no other identified cause.[3]

Bilirubin levels provide a means to diagnose and evaluate the clinical course of PNAC. Rising levels of conjugated or direct bilirubin correlate with increasing cholestasis. Decreasing levels correlate with improvement. PNALD progresses from PNAC and is associated with long-term or permanent liver dysfunction.

[1] The review division responsible for the original NDA review was the Division of Gastrointestinal and Inborn Error Products; in March 2020, the Division of Hepatology and Nutrition was created and took over responsibility for regulation of parenteral nutrition products.
[2] Rangel, S. J., et al., & 2011 American Pediatric Surgical Association Outcomes and Clinical Trials Committee (2012). Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. *Journal of pediatric surgery*, *47*(1), 225–240. https://doi.org/10.1016/j.jpedsurg.2011.10.007
[3] Kathleen Gura and Scott A. Elisofon. Intestinal failure-associated liver disease in infants. UpToDate. Content updated Feb 01, 2022.

When FK was granted approval for SMOFlipid use in adults, they were given a path forward for a pediatric indication through two Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs). (1) PMR 3002-1 was intended to compare the safety of SMOFlipid to a soybean oil-based intravenous lipid emulsion (ILE) in neonates treated for at least 28 and up to 84 days and (2) PMR 3002-2 was intended to evaluate the safety and efficacy of SMOFlipid given for up to 90 days in pediatric patients 3 months of age or older (see Section 3.1).

To comply with PMR 3002-1 the sponsor conducted SMOF-018-CP3. However, due to a lower-than-expected incidence of PNAC, FK's interim analysis showed that a much larger study would be needed than originally anticipated. FK sought permission from the Division in April 2020 to complete the study with the currently enrolled patients, and the Division agreed because it was impracticable for FK to enroll the large number of patients that would be needed to reach a statistical endpoint. In the modifications to the original trial design, the primary objective was changed from confirmatory to exploratory. The results of SMOF-018-CP3 were submitted to the Agency on April 30, 2021 and were also included in the pediatric efficacy supplement which was submitted on June 22, 2021. The efficacy supplement sought a pediatric indication and relied on the results from the four FK-sponsored pediatric studies and the findings from a literature review.

SMOFlipid 20% is an injectable lipid emulsion which is administered intravenously. It was developed to provide an ILE that was closer to that obtained through "normal oral nutrition" and to optimize the fatty acid profile used in parenteral nutrition (PN). Compared to older, predominately soybean oil-based ILEs, SMOFlipid contains a (b) (4) SMOFlipid is a fixed physical mixture of four different oils. It combines soybean oil, medium chain triglycerides (MCTs) (b) (4) olive oil, and fish oil. Phytosterols are plant-derived compounds that are similar in structure to cholesterol. Although they are believed to have health benefits when ingested enterally, they are associated with PNALD when delivered intravenously as part of an ILE. In addition to containing only about 50% of the total phytosterols of Intralipid, SMOFlipid contains (b) (4) mg/L α-tocopherol (vitamin E), (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

After reviewing the sponsor's pediatric efficacy supplement which relied on extrapolation of adult efficacy, the results of its four pediatric trials and literature review, along with the literature review conducted by the agency, we conclude that SMOFlipid has efficacy at least equivalent to soybean oil-based ILEs.

The safety profile of SMOFlipid is superior to soybean oil-based ILEs.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

SMOFlipid belongs to the pharmacotherapeutic group "solution for parenteral nutrition, fat emulsion." It contains, in fixed combination, soybean oil 30%, medium chain triglycerides (MCT) 30%, olive oil 25%, and fish oil 15%.

Intravenous(IV) lipid emulsions (ILEs) such as SMOFlipid are intended for patients who lack the capacity to absorb adequate nutrients to maintain or recover body mass and function and cannot tolerate enteral feeding. Gastrointestinal dysfunction can preclude normal enteral intake and can be due to a primary process such as short bowel syndrome or gastroschisis, or secondary to other medical problems such as sepsis or respiratory distress. Administration of ILEs to patients in which adequate enteral nutrition is not feasible reduces the amount of glucose that would otherwise have to be administered to achieve the necessary calorie intake. The administration of concentrated glucose solutions can cause hyperglycemia, especially in more severely ill patients, which is associated with adverse events including immunosuppression and a higher incidence of infectious complications.[4] ILEs supply between 20 and 50 percent of energy needs and essential fatty acids, which are especially critical in infants for growth, neurological development, and skin integrity.

The US pediatric population is currently prescribed ILEs that are derived from four different lipid sources:

- 1) 100% soybean oil:
  - Intralipid 10% emulsion (NDA 017643), was the first ILE approved in the U.S. (1975), but it is rarely used because of adverse events related to the higher concentrations of phospholipid which interferes with lipoprotein lipase activity.
  - Intralipid 20% emulsion (NDA 18499) was subsequently approved in 1981.
  - Intralipid 30% emulsion (NDA 019942), approved in 1993, is not intended for direct administration, it must be diluted to 10% or 20% concentration for infusion.
  - Nutrilipid 10% and 20% lipid injectable emulsion (NDA 019531) were approved in 1993. Nutrilipid 20% Pharmacy Bulk Package is not intended for direct intravenous administration.
- 2) 80% olive oil/20% soybean oil:
  - Clinolipid 20% (NDA 204508), was approved in 2013 for adult use.
- 3) Soybean oil 30%, medium chain triglycerides (MCT) 30%, olive oil 25%, and fish oil 15%. Soybean oil/Fish oil/medium chain

[4] Waitzberg DL, Torrinhas RS, and Jacintho TM. "New Parenteral Lipid Emulsions for Clinical Use"; J Parenteral Enteral Nutr 2006; 30:351-367.

triglycerides (MCT) (b) (4) /olive oil/, SMOFlipid (used off-label in pediatric patients):

- SMOFlipid 20% (NDA 207648) approved in July 2016.

- 4) 100% fish oil triglycerides:
  - Omegaven (NDA 210589), approved in July 2018 (Orphan drug designation). Indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC).

Soybean oil contains high levels of phytosterols and pro-inflammatory omega-6 (ω-6) fatty acids, both of which have been implicated in the multifactorial pathogenesis of parenteral nutrition-associated cholestasis (PNAC) including impaired bile flow, proinflammatory effects,[5,6,7,8] and the development of hepatic steatosis. As a result, the more recently developed ILEs, including SMOFlipid and Omegaven (fish oil triglycerides) (NDA 210589), have avoided using soybean oil as the predominate fat source, or in the case of Omegaven, at all.

The efficacy supplement presented the findings of three previously submitted pediatric trials (00-SMOF-002, 00-SMOF-004, 03-SMOF-005), the data from the most recently conducted pediatric trial (SMOF-018-CP3), and evidence from the published literature. After reviewing the sponsor's submission and examining postmarket data, it is our conclusion that SMOFlipid has equivalent efficacy to soybean oil-based lipid emulsions based on anthropometric measures and the incidence of EFAD.

With regard to safety, postmarket data confirms that PNALD has been reported with SMOFlipid use; however, study Smof-018-CP3 showed lower rates of, PNAC, as defined consensus definition of a conjugated bilirubin level of > 2 mg/dL, compared to Intralipid, a 100% soybean oil-based ILE. The primary endpoint of SMOF-018-CP3 was a conjugated bilirubin > 2 mg/dL (confirmed 7 days later), during the first 28 days of study treatment. SMOFlipid In the SMOFlipid arm, a total of 2/83 (2.4%) and 3/78 (3.8%) of SMOFlipid and Intralipid patients, respectively, reached the primary endpoint. However, in the next 29-84 days, six additional patients in the Intralipid group developed PNAC (24% [6/25]), while no additional patients in the SMOFlipid group developed PNAC.

[5] Carter BA, Taylor OA, Prendergast DR, Zimmerman TL, Von Furstenberg R, Moore DD, Karpen SJ. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. Pediatr Res. 2007;62(3):301-6.

[6] El Kasmi KC, Anderson AL, Devereaux MW, Vue PM, Zhang W, Setchell KD, Karpen SJ, Sokol RJ. Phytosterols promote liver injury and kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med. 2013;5(206):206ra137.

[7] Kurvinen A, Nissinen MJ, Andersson S, Korhonen P, Ruuska T, Taimisto M, Kalliomaki M, Lehtonen L, Sankilampi U, Arikoski P, Saarela T, Miettinen TA, Gylling H, Pakarinen MP. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. J Pediatr Gastroenterol Nutr. 2012;54(6):803-11.

[8] Rangel SJ, Calkins CM, Cowles RA, Barnhart DC, Huang EY, Abdullah F, Arca MJ, Teitelbaum DH, American Pediatric Surgical Association O, Clinical Trials C. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2012;47(1):225-40.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Intravenous(IV) lipid emulsions (ILEs) are intended for patients who lack the lack the capacity to absorb adequate nutrients to maintain or recover body mass and function and cannot tolerate enteral feeding. ILEs provide between 20 and 50 percent of energy needs. Without ILEs, the amount of glucose needed to supply the necessary calories and meet energy requirements would pose a risk of adverse effects including hyperglycemia, particularly in critically ill patients, which is associated with immunosuppression and a higher rate of infectious9 complications. ILEs supply energy and essential fatty acids which are especially critical in infants for neurological development, growth, and skin integrity. • A postmarket safety evaluation conducted by the Division of Pharmacovigilance 1 (DPV-1) identified 8 cases of EFAD in pediatric patients receiving SMOFlipid10. Of the eight, three patients were	Based on the totality of evidence, SMOFlipid is a safe and effective ILE option in the pediatric population. According to an evaluation of postmarket cases, EFAD has been observed in patients receiving SMOFlipid. Healthcare professionals should remain vigilant for clinical signs and symptoms of EFAD such as failure to thrive and skin abnormalities, and perform routine testing of EFA levels to detect EFAD and take corrective measures. The published literature supports the safety of SMOFlipid for short to medium term use in

[9] Waitzberg DL, Torrinhas RS, and Jacintho TM. "New Parenteral Lipid Emulsions for Clinical Use"; J Parenteral Enteral Nutr 2006; 30:351-367.
[10] Wolf, Lisa M., Division of Pharmcovigilance, Pharmcovigilance Review for NDA 207648 Smoflipid. Dec 9, 2021.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	underdosed. The dosing was not reported in one of the eight patients. The median time to onset was 38 days. • Long-term use of parenteral nutrition (PN) has been associated with PN associated cholestasis (PNAC). PNAC is defined by expert consensus11 as a direct or conjugated bilirubin level of ≥ 2 mg/dL in the absence of other liver dysfunction. To diagnose PNAC, at least a 2-week duration of exposure to an ILE is required. In FK's most recent study, SMOF-018-CP3, which compared SMOFlipid to Intralipid, PNAC was observed more frequently in patients receiving Intralipid than SMOFlipid. The incidence of PNAC increased in Intralipid patients with exposure beyond 28 days, but no PNAC occurred in SMOFlipid patients beyond 28 days of exposure. However, a neonatal literature assessment12 determined that PNAC has been identified with SMOFlipid use in postmarket evaluation. • SMOFlipid contains about 50% less phytosterol than 100% soybean oil-based ILEs.	neonates, with the median treatment duration of 12-16 days in most of the reviewed randomized controlled trials (RCTs)13. PNAC is more likely to develop in patients receiving Intralipid than SMOFlipid with long-term use, based on the findings of SMOF-018-CP3.
Current Treatment Options	The following ILEs are used in pediatric patients: • 1) Intralipid NDA 100% soybean oil: Intralipid (10%, 20%, 30%) approved in January 1981, and Nutrilipid (10%, 20%) approved in May 1993; • 2) Clinolipid 80% olive oil/20% soybean oil: Clinolipid approved in 2013, (but with adult indication only); • 3) SMOFlipid (20%) derived from soybean oil/medium chain	Omegaven is classified as an orphan drug that is indicated for treatment in patients with PNAC. It is derived exclusively from fish oil and contains predominately omega-3 (ω-3) fatty acids, (b) (4) .

[11] https://www.regulations.gov/document?D=FDA-2012-N-0001-0093
[12] Baer, Gerri R. Neonatal-Perinatal Medicine Consultation for NDA 207648/S-005 – Smoflipid Neonatal Literature Assessment. November 15, 2021.
[13] Ibid.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	triglycerides (MCT) (b) (4) olive oil/fish oil, approved for adults in July 2016, and used off-label in pediatric patients; • 4) Omegaven, derived from 100% fish oil triglycerides: approved in July 2018.	SMOFlipid contains (b) (4) Based on its composition, SMOFlipid offers advantages over exclusively soybean oil-based ILEs. SMOFlipid and Omegaven have different indications.
Benefit	• SMOFlipid use is associated with lower rates of PNALD compared to soybean oil-based ILEs, particularly with longer term use. • The efficacy of SMOFlipid regarding growth in neonates and lipid measures in older children appears to be no different than the other ILEs with which it has been compared.	SMOFlipid has lower levels of phytosterols and proinflammatory fatty acids than other marketed ILEs. The most recent pediatric study SMOF-018-CP3 compared SMOFlipid to Intralipid in neonates and infants and found lower levels of PNALD in SMOFlipid than Intralipid patients after 28 days of exposure.
Risk and Risk Management	PNALD and EFAD have been detected in patients receiving SMOFlipid. Patients who receive SMOFlipid should be monitored regularly using clinical evaluation and laboratory screening for PNALD and EFAD. .	SMOFlipid offers advantages to 100% soybean oil-based ILEs. However, routine screening for PNALD and other safety measures such as liver function studies and hematologic evaluations should be conducted routinely. EFAD has been detected in pediatric patients receiving long term SMOFlipid. However, EFAD frequently resolved with increasing the dose of SMOFlipid.

2 Therapeutic Context

2.1. Analysis of Condition

Parenteral nutrition (PN) is indicated for infants and children who are unable to achieve adequate nutrition through oral intake or enteral feeding and require supplemental nutritional support for seven days or more. In some instances, the gastrointestinal tract cannot be accessed at all, and total parenteral nutrition (TPN), an admixture of solutions that includes dextrose and amino acids, along with vitamins, minerals, and electrolytes, is required.

Fat is also a necessary component of PN and is supplied by ILEs, such as SMOFlipid, that are infused in conjunction with the other solutions. The goal of an ILE is to provide dietary fuel, (ILEs supply between 20 and 50 percent of energy needs), and to supply essential fatty acids (EFAs) that cannot be synthesized by the body and must come from an external source, by either the enteral or parenteral route.

PN, which began in clinical practice in the 1950s and 1960s, was an infusion of amino acids and dextrose solutions. The absence of a lipid component resulted in hepatic steatosis and essential fatty acid deficiency (EFAD).[14, 15] Intralipid, a soybean oil-based ILE was approved in Sweden in 1962. In 1975, Intralipid 10% became the first lipid emulsion to be approved for use in the U.S., followed by Intralipid 20% in 1981. Intralipid 30% and Nutrilipid 10%, also 100% soybean oil-based received U.S. approval in 1993. Newer formulations of ILEs, which are not exclusively soybean oil-based have been developed within the past few years with the goal of improving clinical outcomes, particularly in neonates and children.

Fatty acids (FAs), which are hydrocarbons, exist in three forms, triglycerides, phospholipids, and cholesterol esters, and are characterized by their length and other molecular characteristics such as the location of double bonds.

FAs have several critical roles which include regulating cellular pathways and signaling, cell membrane structure, transcription factor activity, and gene expression. EFAs are vital for neurocognitive development and growth, particularly in neonates and infants.[16] The polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA) and arachidonic acid (ARA) are essential for growth and brain development and act as precursors to eicosanoids, cell-

14 “Fat-Free Parenteral Alimentation of Infants.” Nutrition reviews 32.5 (1974): 134–136. Web.
[15] Faulkner WJ, Flint LM, Jr. Essential fatty acid deficiency associated with total parenteral nutrition. Surgery, gynecology & obstetrics. 1977;144(5):665-7.
[16] Baker, R, et al. Parenteral nutrition in infants and children. UpToDate. Literature review current through: Jul 2021. | This topic last updated: Jun 26, 2020.

signaling molecules that regulate inflammation, immunity, and vasoreactivity.[17] There are three types of PUFAs, omega(ω) ω-6, ω-3, and ω-9. The ω-6 eicosanoids are proinflammatory and ω-3 eicosanoids are less inflammatory.

Although TPN saves the lives of patients who are unable to tolerate enteral nutrition, its long-term use is sometimes associated with hepatic complications such as parenteral nutrition-associated cholestasis (PNAC) which progresses to parenteral nutrition-associated liver disease (PNALD), now more commonly referred to as intestinal failure-associated liver disease or (IFALD). PNALD has been defined by expert consensus as direct or conjugated bilirubin (DBil) level ≥ 2.0 mg/dL in the absence of other liver dysfunction[18] in patients who have received PN for at least 2 weeks.[19] IFALD is characterized by progressive cholestasis and biliary fibrosis in children, and steatohepatitis in adults. Premature infants and children with intestinal failure (IF) or short bowel syndrome are particularly susceptible to IFALD and, as in the case of adults, the duration of the exposure to PN is a key contributing factor. The longer the exposure to PN, the more at risk patients are for developing PNALD.

More recently developed ILEs, which no longer rely on it as the sole source of fat or even include it at all, have been developed with the goal of mitigating the risk of liver dysfunction associated with PN. For several decades, soybean oil (SO)-derived ILEs have been the most commonly used ILEs in the United States.[20] Soybeans have an exceptionally high content of linoleic acid (LA), an ω-6 fatty acid. High ω-6 to ω-3 ratios, combined with a lack of antioxidant protection, induce inflammation and oxidative stress. SO is also rich in phytosterols, which are plant-derived compounds, that when delivered intravenously reduce biliary flow and contribute to intestinal failure–associated liver disease (IFALD).[21] More recently developed ILEs have evolved to include replacing SO, at least in part, with other fat sources, including olive, coconut, and fish oils. By modifying the ILEs' biological properties, the fatty acid profile is diversified, the phytosterol concentration is decreased, and the antioxidant capacity is increased. These compositional changes alter the ILE's ability to modulate inflammation, oxidation, and disease.

2.2. Analysis of Current Treatment Options

The ILEs used in the pediatric population are derived from: 1) 100% soybean oil, including Intralipid and Nutrilipid, 2) 80% olive oil/20% soybean oil, Clinolipid, 3) fish oil/medium chain

[17] Calkins, Kara and Robinson, Daniel. 2020. Intravenous Lipid Emulsions in the NICU. NeoReviews- An Official Journal of the American Academy of Pediatrics. February 01, 2020; Volume 21, Issue 2. e109-e119; DOI: https://doi.org/10.1542/neo.21-2-e109.
[18] The public consensus on the definition of PNAC was developed at the 2012 FDA Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) workshop, to define PNAC by Dbil level ≥ 2 mg/dL in the absence of other liver disorders in patients with a need for PN for > 2 weeks.
[19] Blackmer, A. Parenteral Nutrition: Complications of Long-Term Use in Pediatric Patients. Pharmacy Times. Health-System Edition, July 2015, Volume 4, Issue 4.
[20] Fell, G. L., Nandivada, P., Gura, K. M., & Puder, M. (2015). Intravenous Lipid Emulsions in Parenteral Nutrition. *Advances in nutrition (Bethesda, Md.)*, *6*(5), 600–610. (https://doi.org/10.3945/an.115.009084).
[21] Ibid.

triglycerides (MCT) from (b) (4)/olive oil/soybean oil, SMOFlipid (used off-label in pediatric patients), and 4) 100% fish oil triglycerides, Omegaven. Soybean oil contains high levels of phytosterols and an unfavorable ratio of inflammatory ω-6 to ω-3 fatty acids which are associated with IFALD. As a result, the more recently developed ILEs have avoided using soybean oil as the predominate fat source, or at all.

Intralipid was approved in 1975 and was the first intravenous lipid emulsion product to be approved in the United States (U.S.). It is indicated as a source of calories and fatty acids in adult and pediatric patients when enteral nutrition is insufficient. Intralipid is derived from soybean oil which has high levels of phytosterols and ω-6 fatty acids which are proinflammatory. Nutrilipid, also approved in 1975, essentially has the same composition as Intralipid.

Clinolipid was approved in the U.S. for use in adults in 2013. It is a mixture of 80% refined olive oil and 20% refined soybean oil in a 4:1 ratio (olive:soy). The amount of soybean oil, which is rich in omega (ω)-6 fatty acids, in Clinolipid, is less than that of other previously approved soybean oil-containing ILES, such as Intralipid. Clinolipid (b) (4) concerns that it did not provide sufficient amounts of ω-6 fatty acids to prevent essential fatty acid deficiency (EFAD), which can lead to long-term neurological and growth deficiencies, in pediatric patients, especially premature infants.[22]

SMOFlipid was approved in 2016 for use in adults, contains a combination of four different oils, soybean oil, medium chain triglycerides (b) (4) olive oil and fish oil, and was developed to optimize the fatty acid profile of the lipid emulsion used in PN. SMOFlipid is indicated for use in adults as a source of calories and EFAs in adults when enteral nutrition is not sufficient to provide nutritional needs.

Omegaven (fish oil triglycerides) was approved in 2018 and indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC). However, it is not indicated for the *prevention* of PNAC and monitoring for EFAD is recommended in patients receiving Omegaven due its composition which is mainly ω-3, and lower in ω-6. The clinically apparent manifestations of essential fatty acid deficiency in premature infants, which can include inflamed skin, delayed wound healing, hematologic disturbances such as bleeding, and decreased growth, are due mainly to ω-6 fatty acid deficiency.

[22] Clinical Review for NDA 204508 Clinolipid, January 13, 2013. Klaus Gotlieb, MD, MS, MBA, Division of Gastroenterology Inborn Errors Products (DGIEP). In March 2020 DGIEP was subdivided into three divisions. The Division of Hepatology and Nutrition (DHN) is now responsible for regulation of parenteral nutrition products.

Table 1. Approved Intravenous Lipid Emulsion Products

Product (s) Name, Lipid Source, Date of Approval	Relevant Indication	Dosing/ Administration	Important Safety and Tolerability Issues
Intralipid 20%, Soybean oil 1972	A source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days)	Premature: infants starts at 0.5 g fat/kg body weight/24 hours (2.5 mL Intralipid® 20%) and may be increased in relation to the infant's ability to eliminate fat. The maximum dosage recommended by the American Academy of Pediatrics is 3 g fat/kg/24 hours . The initial rate of infusion in older pediatric patients should be no more than 0.05 mL/minute for the first 10 to 15 minutes. If no untoward reactions occur, the rate can be changed to permit infusion of 0.5 mL of Intralipid® 20%/kg/hour. The daily dosage should not exceed 3 g of fat/kg of body weight[3] Intralipid® 20% should make up no more than 60% of the total caloric input to the patient	•Contraindicated in patients with disturbances of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia. •Deaths in preterm infants after infusion of intravenous fat emulsion have been reported in the medical literature.
Nutrilipid Soybean oil 1975	A source of calories and essential fatty acids for parenteral nutrition and as a source of essential fatty acids when a deficiency occurs when oral or enteral nutrition is not possible, insufficient, or	Preterm and term infants (<1 year) and pediatric patients 1 to 10 years: initial dosage 1 to 2 g/kg/day, maximum dosage 3 g/kg/day. Pediatric patients 11 to <17 years: initial dosage 1 gm/kg/day, maximum dosage 2.5 g/kg/day. Adults: initial 1 to 1.5 g/kg/day, maximum dosage 2.5 g/kg/day.	Warnings: •Death in preterm infants, • Autopsy findings of intravascular fat accumulation in the lungs •Increased free fatty acid levels

<table>
<tr><td></td><td>contraindicated</td><td></td><td></td></tr>
<tr><td>Clinolipid 80% olive oil 20% soybean oil

CLINOLIPID injection provides sufficient amounts of essential fatty acids (EFA) in pediatric patients. 2013</td><td>Indicated in adults for providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated.</td><td>No labeled pediatric dosage</td><td>•Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported in the medical literature.
•Autopsy findings included intravascular fat accumulation in the lungs.
•Preterm infants and low birth weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion.</td></tr>
<tr><td>SMOFlipid 20%</td><td>Is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated</td><td>Proposed pediatric dosing:
The target dose is 3 g/kg/day.
In pediatric patients that were already receiving PN before starting study treatment, the lipid dose either stayed at 3 g/kg/day or increased in 1 g/kg/d steps to a maximum of 3 g/kg/d.

In pediatric patients that had not started PN prior to study participation, lipid dose was increased stepwise using the following regimen:
<table><tr><td>Study Day</td><td>Patients < 1500 g</td><td>Patients > 1500 g</td></tr><tr><td>1</td><td>1.0 g/kg/day</td><td>2.0 g/kg/day</td></tr><tr><td>2</td><td>2.0 g/kg/day</td><td>3.0 g/kg/day</td></tr><tr><td>3+</td><td>3.0 g/kg/day</td><td>3.0 g/kg/day</td></tr></table></td><td>The omega-6: omega-3 fatty acid ratio and Medium Chain Triglycerides in SMOFlipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.

• Deaths in preterm infants have been reported in literature.
• Autopsy findings included intravascular fat accumulation in the lungs.
• Preterm and low-birth-weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion.</td></tr>
<tr><td>Omegaven 100% fish oil triglycerides. 2018</td><td>A source of calories and fatty acids in pediatric</td><td>Recommended dosage depends on age, energy expenditure, clinical status, body weight, tolerance, ability to metabolize, and consideration of additional</td><td>•Risk of Death in Preterm Infants due to Pulmonary Lipid Accumulation

•Monitoring and Laboratory Tests: Routine laboratory monitoring is recommended,</td></tr>
</table>

	patients with PNAC	energy sources given to the patient Pediatric patients: 1 g/kg/day; this is also the maximum daily dose	including monitoring for essential fatty acid deficiency.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NDA 207648 for SMOFlipid (lipid injectable emulsion, USP), 20%, was submitted on September 25, 2014, with the indication for supply of calories and essential fatty acids, as part of parenteral nutrition (PN), when oral or enteral nutrition is impossible, insufficient, or contraindicated. The intended population was adults and the pediatric population (including newborns).

On July 13, 2016, the FDA approved NDA 207648 for SMOFlipid under regulatory pathway 505(b)(1), for use in adults.

- SMOFlipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

A complete response (CR) letter was also issued on July 13, 2016 for the pediatric indication, due to a lack of long-term data:

> "We have determined that you have not provided sufficient evidence to determine that SMOFLIPID (lipid injectable emulsion) is safe and effective in pediatric patients from birth through 16 years of age. In order to address this deficiency additional studies in these populations are required."

Two PREA PMRs were issued with the adult approval to address the deficiencies included in CR letter.

PREA PMR 3002-1

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 3002-5.

Regulatory history of PMR 3002-1

- Final protocol agreed to September 21, 2015 for study SMOF-018-CP3, "A Prospective, Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compared the Safety and Efficacy of SMOFlipid 20% to Intralipid 20% in Hospitalized Neonates and Infants Requiring 28 Days of Parenteral Nutrition"
- Primary objective: Show superiority in the safety of SMOFlipid over Intralipid 20% as measured by the number of study patients with conjugated bilirubin > 2 mg/dL (i.e., the commonly accepted threshold for a diagnosis of cholestasis) during the first 28 days of study treatment.
- Designed as a sequential 2-stage adaptive study with an interim analysis.
- An interim analysis was performed after 100 patients in the Per-Protocol (PP) Population (50 in each arm) had completed 28 days of PN with lipid emulsions.
    - Based on the findings of the interim analysis, the sample size needed to demonstrate **superiority** for the primary objective with 80% power would be **4828** neonates (2414 in each treatment arm).
    - The sample size needed to demonstrate noninferiority with 80% power would require **1196** neonates (598 per treatment arm).
- FK-requested Type C meeting April 2020[23]
    - In response to FK's interim analysis, and the impracticability of the enrolling the study as originally planned, the Division agreed the study could be completed with the current number of enrolled patients, and that the requested analysis of genetic polymorphisms in FADS could be deferred to the study developed to address PMR 3002-2 in an older pediatric population, 3 months to 16 years.

PREA PMR 3002-2

Randomized controlled trial to evaluate the safety and efficacy of SMOFLIPID (lipid injectable emulsion) administered for at least 90 days in pediatric patients, compared to standard of care soybean oil based lipid emulsion administered for the same duration. Continue treatment for all patients who remain on parenteral nutrition (PN) for up to 1 year. The study should enroll an adequate number of patients 3 month 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

[23] FK was satisfied with the preliminary comments shared on April 16, 2020; therefore, the actual meeting was cancelled.

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 3002-5.

Regulatory history of PMR 3002-2

- Final protocol agreed to October 13, 2017 for study "Prospective, Randomized, Double-Blind, Parallel-Group, Active-Controlled, Multicenter Study to Compare Safety and Efficacy of SMOFlipid to Intralipid 20% in Pediatric Patients of 3 Months to 16 Years of Age Requiring Parenteral Nutrition for at Least 90 Days and up to 1 Year"
- Primary objective: evaluate the efficacy and safety of SMOFlipid compared to a standard-of-care lipid emulsion, a 100% soybean oil lipid emulsion (Intralipid) administered in pediatric patients 3 months to 16 years of age who require PN to meet their nutritional needs for at least 90 days and up to 1 year.
- Delays at the study sites in initiating this study due to the logistical complexity of conducting a long-term study in home PN patients.
- Few clinical study sites were willing to participate in the proposed study, leading to limited patient recruitment.
- On February 5, 2021, FK proposed converting the RCT to a single arm safety study to supplement the safety information about SMOFlipid use in older children.
- Following a discussion with PeRC, DHN issued a deferral extension for PMR 3002-2 on March 2, 2021 while the pediatric efficacy supplement is reviewed.

To fulfill PMR-3002-1, IND 102137 was submitted on August 21, 2015 for study SMOF-018-CP3. FK and DGIEP[24] discussed the study design between November 2012 and January 2015 at several meetings. The primary objective of the study was to show superiority in safety of SMOFlipid over Intralipid. A deferral extension was submitted by FK on July 5, 2019 and a pre-defined interim analysis was conducted because the number of patients needed for the analysis was reached in June, 2019.

Under NDA 207648, Supplement 005 was submitted on June 22, 2021 to evaluate the safety and efficacy of SMOFlipid in pediatric patients.

[24] The Division of Gastroenterology and Inborn Errors Products (DGIEP) was subdivided into three divisions in March 2020. The Division of Hepatology and Nutrition (DHN) is now responsible for regulation of parenteral nutrition products.

3.2. Summary of Presubmission/Submission Regulatory Activity

Three company-sponsored studies were conducted in neonates, infants, and children who required PN with lipids, and the clinical study reports (CSRs) were provided for studies 00-SMOF-002, 03-SMOF-005 and 00-SMOF-004 in the original NDA submission.

The first study, **00-SMOF-002**, was a phase 2b, double-blind randomized, active-controlled, parallel group, single-center study conducted from May 2003 to May 2005. The primary objective of the study was to evaluate the safety and efficacy of treatment with SMOFlipid 20% compared to Intralipid 20% in infants, toddlers, and children. Twenty-eight patients were enrolled and randomized with the objective of obtaining equal strata and a comparable age distribution. Fifteen patients received SMOFlipid (seven patients were less than two years of age), and 13 pediatric patients received Intralipid (six patients were less than two years of age).

The study treatment was 27 days in both treatment groups. The SMOFlipid group had a younger population with five of the seven patients being less than one year of age. In the Intralipid group, three of the six patients were less than one year of age. Triglyceride concentrations, along with liver enzymes, total cholesterol, adverse reactions, and vital signs were analyzed as a safety parameters. Mean and median triglyceride concentrations showed a small increase from day-0 to Week-4 in the SMOFlipid group and a small decrease in the Intralipid group.

FK reported that an increase in omega-3 fatty acids was observed in the SMOFlipid group, which was attributed to the higher omega-3 content of the product, compared to Intralipid. The efficacy profiles were otherwise similar between the two groups.

None of the patients in the study developed EFAD, however, several factors in the study design may have contributed to this outcome. For example, only 18% of patients in the study were dependent solely on PN for calories, which is a key risk factor for developing EFAD, and study patients were allowed up to 50% of their intake from enteral sources. In addition, the relatively short study duration of 27 days may not have been long enough for patients to develop EFAD.

The second study, **00 SMOF-004** was a phase 2b, double-blind, randomized, active-controlled, parallel-group, single-center study conducted from April 2004 to February 2006. The trial's primary objective was to evaluate the safety and tolerability of 7 to 14-day periods of treatment with SMOFlipid 20% compared to Intralipid 20% in premature infants. Not all patients were treated for 14 days, with a mean treatment period of 12 days in the SMOFlipid group and nine days in the Intralipid group. The secondary objective was to evaluate the efficacy of SMOFlipid 20% compared to Intralipid 20%. Safety variables included laboratory evaluation of serum triglycerides as the first order variable. Second order safety variables included liver function studies and cholesterol levels, and clinical assessments of AEs and vital signs. The primary efficacy variable was the change in body weight from day 0 to day 8. Secondary efficacy variables included C-reactive protein (CRP) level, sepsis score, mechanical ventilation and oxygen requiring, and change in length.

The target population was preterm neonates 0-7 days of age with a gestational age of less than 34 weeks and a birth weight between 1000 and 2500 grams, requiring PN (including lipids) for at least 7 days. Subjects were randomized to one of three strata according to birth weight, Stratum A, 1000-1499 g, Stratum B, 1500-1999 g, or 2000-2500 g, Stratum C, with the same number of subjects treated within each stratum.

The exclusion criteria included: congenital anomalies of the heart, lungs, or urinary tract; circulation failure with anuria; oxygen requiring using a partial oxygen pressure (pO2) >mm Hg for more than 60 minutes; inadequate oxygenation despite maximum support of pO2 <mm Hg for at least 2 hours; hepatic/hematolytic disease; sepsis score >3; or leukocytopenia, leukocytosis, granulocytosis, and/or thrombocytopenia as defined by the study protocol.

Sixty patients were randomized, (Group I- SMOF 30, and Group II- Intralipid 30), 51 patients were treated according to protocol (SMOF 26, Intralipid 25). Twenty patients (SMOF 10, Intralipid 10) belonged to Stratum A (birth weight 1000 to 1499 g), 20 patients (SMOF 10, Intralipid 10) to Stratum B (birth weight 1500 to 1999 g) and 20 patients (SMOF 10, Intralipid 10) to Stratum C (birth weight 2000 to 2500 g).

Treatment emergent AEs:

All AEs were of mild or moderate intensity, and no serious AEs were reported. During the study treatment period, 29 adverse events (AEs) were observed in 13/30 (43.3%) of patients in Group I (SMOFlipid) and in 14/30 (46.7%) in Group II (Intralipid). The rate of occurrence of treatment emergent AEs (TEAEs) were comparable in both groups and were observed to decrease with increasing in birth weight. In Stratum A, 6/10 (60.0%) and 7/10 (70.0%) patients in Group I and II experienced AEs, whereas in Stratum B,5/10 (50.0%) and 4/10 (40.0%) patients, respectively, and in Stratum C 2/10 (20.0%) and 3/10 (30.0%) patients, respectively, experienced AEs.

By system organ class (SOC), infections and infestations were the most frequently reported, 11/30 (36.7%) and 8/30 (26.7%) in Groups I and II, respectively. Nosocomial infection was the most frequent preferred term in this SOC, 7/30 (23.3%) in Group I and 5/30 (16.7%) in Group II. Respiratory, thoracic and mediastinal disorders, 6/30 (20%) and 3/30 (10%), in Groups I and II, respectively, was the second most frequently reported SOC. Apnea was the most frequent preferred term reported in this SOC, 4/30 (13.3%) in Group I and 3/30 (10%), in Group II. Groups I and II had similar rates of AEs with infections and infestations being the most frequently reported SOC, followed by respiratory, thoracic and mediastinal disorders. No important differences were observed between treatment arms.

The laboratory safety parameters did not reveal noticeable differences between the treatment groups. However, preterm infants in the SMOFlipid group had plasma levels of fatty acids that reflected a higher omega-3 fatty acid and alpha tocopherol profile than those in the Intralipid group, which most likely was due to the composition of fatty acids in SMOFlipid. While no EFAD

was detected in any study subject, the relatively short duration of the study may have limited the ability to detect EFAD in this patient population.

Efficacy

In the SMOFlipid group, relative growth increased at a similar rate in all strata. In the Intralipid group, the lower weight strata showed a slightly faster growth than the higher weight strata.

The third study, **03-SMOF-005** was a phase 3, double-blind, randomized, active-controlled, parallel group, 2-center study conducted from May 2004 to February 2006. The primary objective of the study was to determine the safety of SMOFlipid 20% compared to Intralipid 20% based on the serum concentrations of triglycerides over a period of seven to 14 days. The secondary objectives were the evaluation of safety criteria including other laboratory values and adverse events, and efficacy criteria such as changes in body weight and height.

The study enrolled premature infants, but also those with a birth weight as low as 500 grams, and stratified according to birth weight (500-1000, 1001-1500, and 1501-2000 grams), and treatment group (SMOFlipid vs. Intralipid). The study initially included 84 patients, who were enrolled in two centers. Due to protocol deviations in center 1, the efficacy analyses were based on 52 patients who were enrolled at center 2, which was in compliance with the protocol. The primary study endpoint was measure of serum triglycerides with lower levels preferable; there was no overall difference between patient groups.

The study was initially powered to demonstrate non-inferiority of SMOFlipid to Intralipid on the triglyceride endpoint. However, the exclusion of data from center 1 for noncompliance resulted in a smaller than anticipated patient population, and the test for non-inferiority failed because the confidence interval was exceeded. The sponsor concluded that the study was inadequately powered and that the results did not necessarily indicate that SMOFlipid failed the test for non-inferiority.

The results of these three FK-sponsored pediatric studies 00-SMOF-002, 000-SMOF-004, and 03-SMOF-005 were submitted with the original NDA review for SMOFlipid. The review team did not find sufficient evidence that the studies demonstrated safety and efficacy of SMOFlipid in the pediatric population. Two PREA PMRS, 3002-1 and 3002-2, were issued to further evaluate the safety and efficacy of SMOFlipid in pediatric patients.

On April 30, 2021, the final study report for FK-sponsored study SMOF-018-CP3, was submitted to address PMR 3002-1 to evaluate the safety and efficacy of SMOFlipid in hospitalized neonates and infants requiring 28 days of parenteral nutrition.

Table 2. FK-Sponsored Controlled Studies to Support Efficacy and Safety

Trial Identity	Trial Design/ number/demographics of patients enrolled	Efficacy Variables	Results
Controlled Studies to Support Efficacy and Safety			
00-SMOF-002	Phase 2b, single center, double-blind, randomized, active-controlled, parallel group 28 patients, 1 month to ≤ 2 years of age and children 2-11 years of age 4-week study	Primary: changes in body weight, body height/length, and BMI from Day 0 to Day 29. Secondary: included changes in retinol binding protein (RBP), prealbumin, and albumin.	No notable differences were detected between the treatment groups with respect to changes in the mean or median body weight and height after 4 weeks of study treatment. Changes in RBP, albumin, and prealbumin from were negligible in both treatment groups.
00-SMOF-004	Phase 2b, Single center, randomized, double-blind, parallel, active controlled study 60 patients, premature infants < 34 weeks gestational age 7-14 days	Primary: the percentage change in body weight from Day 0 to Day 8. Secondary: C-reactive protein level, sepsis score, days with antibiotic therapy, the use of mechanical ventilation or oxygen therapy, change in length during the treatment period and evaluation of the fatty acid pattern in erythrocytes, phospholipids, alpha-tocopherol and lipid peroxidation in plasma	The sponsor reported comparable weight gain between the treatment groups. No changes in mean or median body height/length in either treatment group. No notable differences between treatment groups in fatty acid profiles Intralipid group: Lower weight strata showed slightly faster growth than higher weight strata. Mean α-linolenic acid in RBC phospholipids increased in both treatment groups, but to a greater extent in the Intralipid group. In contrast, mean EPA levels increased to a greater extent in the SMOFlipid group.

			An evaluation of T:T ratios was not performed. No differences in CRP levels, sepsis scores, days on antibiotic therapy, use of mechanical ventilation.
03-SMOF-005	Phase 3, Two-center, randomized, double-blind, parallel, active controlled study 84 patients Premature infants in need of PN including fat, for at least 7 days 7-14 days	Efficacy variables included changes in body weight, height/length, and time to end of artificial or supportive ventilation; head circumference, fatty acid profiles, changes in serum triglyceride levels were also evaluated	The short duration of the study may not be adequate to assess growth parameters. The two-center study had a discrepancy in the weight gain. There were no statistically significant differences between groups for changes from Baseline to final assessment/LOCF for any of the anthropometric parameters. Mean and median triglyceride concentrations during the course of the study remained within the normal range (<1.6 mmol/L) in both treatment groups.
SMOF-CP3-0018-	Phase 3, prospective, randomized, controlled, double-blind, multi-center, parallel-group	Conjugated bilirubin > 2 mg/dL during the first 28 days of study treatment,	Dropout rate by day-28 was around 60%. Initial treatment- 28 days, PN can be extended to 84 days if still needed.

4 Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

Four company-sponsored studies have been conducted with SMOFlipid in the pediatric (preterm, neonatal, infant, and children) population. The largest, and most recent of the trials, SMOF-0180-CP3, a prospective, controlled, double-blind, parallel-group, phase 3 study randomized a total of 161 subjects (intention to treat (ITT)), with 83/78 in the SMOFlipid/control arms, respectively.

Table 3. Listing of Clinical Trials Relevant to this NDA

Trial Identity/ No. of patients enrolled	Trial Design/ No. of Centers and Countries	Regimen/ schedule/ route	Key Study Endpoints	Treatment Duration/ Follow Up	Study Population
00-SMOF-002/ 28 patients	Phase 2b, single center, double-blind, randomized, active-controlled, parallel group/ Single center, Europe (Hungary)	PN treatment was to be administered for 4 to 7 periods per week during 4 consecutive weeks. Concomitantly fat emulsion was to be administered for 4 to 5 periods per week. The infusion rate of 0.125 g fat/kg body weight (bw)/hour was recommended and should preferably not have exceeded 0.15 g fat/kg bw/hour. Daily amount approx. 2 g lipids/kg bw x day. All patients were to receive Intralipid 20% as a part of the PN regimen, one week prior to the start of the study treatment period (run-in period).	First order: serum triglycerides, Second order: clinical laboratory findings including liver function studies, cholesterol, AE evaluation	One week initial run-in period (Intralipid 20%), four weeks study treatment period with study medication.	Male and female, Age: 1 month – 11 years. Expected stable disease requiring PN for at least four weeks
00-SMOF-004/ 60 patients	Phase 2b, Single center, randomized, double-blind, parallel, active controlled study/ Single center, Europe (Hungary)	0.5 g fat/kg bw on Period (Day) 1 1.0 g fat/kg bw. on Period (Day) 2 1.5 g fat/kg bw. on Period (Day) 3 2.0 g fat/kg bw on Periods (Days) 4-14	First order safety variables Serum triglycerides	7-14 days	Premature male and female infants < 34 weeks gestational age
00-SMOF-005/ 84 patients	Phase 3, two centers, randomized, double-blind, parallel, active controlled study/ Two centers, Europe, (Germany and Hungary)	1.0 g fat/kg bw on day 1, 2 and 3, 2.0 g fat/kg bw on day 4, 3.0 g fat/kg bw on day 5, 3.5 g fat/kg bw on days 6-14.	Primary: Change in Serum triglyceride level	7-14 days	Premature infants in need of PN including fat, for at least 7 days
SMOF-CP3-0018-CP3/ 161 patients	Phase 3, prospective, randomized, controlled, double-blind, parallel-group	Neonates (newborns (0-27 days) < 1500 g: At 1 g/kg/day, 2 g/kg/day and first dose of 3 g/kg/day Neonates ≥ 1500 g: At first dose of 3 g/kg/day/	Primary: Conjugated bilirubin > 2 mg/dL during the first 28 days of study	Initial treatment-28 days, PN can be extended to 84 days if still	hospitalized preterm and term neonates/ infants requiring 28

		14 centers in US	treatment Secondary: Efficacy: anthropometric measurement, Fatty acid evaluation, Holman Index Secondary Safety: Time to PNAC, changes serum chemistry findings	needed	days of PN

4.2. Review Strategy

The Division reviewed the pediatric efficacy supplement, submitted on June 22, 2021 which included the following components:

- The results of FK-sponsored clinical trial, SMOF-CP3-018, which was submitted on April 30, 2021. The trial was developed and conducted to address PMR 3002-1, to evaluate the safety and efficacy of SMOFlipid in neonates and infants.
- Historical trial data from the original NDA submission including three FK-sponsored studies in pediatric patients (neonates, infants, and children).
- Literature review

In addition, the Division consulted:

- The Office of Pediatric Therapeutics:
  - 6/22/21: For the pediatric efficacy supplement under review, DHN requested DPMH assistance in reviewing the safety and efficacy of study SMOF-018-CP3 to expand the indication, dosing, and labeling in neonates.
- The Division of Pediatric and Maternal Health:
  - 6/28/21 DHN requested assistance by the Pediatric team in reviewing and interpreting the safety and efficacy data of pediatric age groups.
  - 6/28/21 DHN requested Maternal Health's assistance for evaluating proposed changes in the PI sections 8.1 and 8.2.
- Office of Surveillance and Epidemiology (OSE)-The Division of Pharmacovigilance (DPV):

- 11/1/21: The SMOFlipid pediatric efficacy supplement under review had limited information about EFAD in neonates, infants, and older children. DHN requested that OSE-DPV conduct a FAERS search and a literature search for cases of EFAD in patients taking SMOFlipid.

- OSE-The Division of Medication Error Prevention and Analysis (DMEPA)
  9/3/21: DHN requested OSE-DMEPA to review the PI and provide recommendations from a medication error prevention perspective.
- OSE-The Division of Epidemiology (DEPI):
  - 7/21/21: DHN requested OSE-DEPI's assistance in reviewing the methodology and approach in literature submitted to support dosing and labeling in older pediatric patients.
  - In addition, DHN requested an assessment of whether the literature provided by the Applicant was adequately representative of the published literature about the safety of SMOFlipid in neonates, infants, and children.

5 Statistical and Clinical and Evaluation

5.1. Review of Relevant Individual Trials Used to Support Efficacy

5.1.1. Smof-018-CP3

Trial Design

Title: A Prospective, Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare Safety and Efficacy of SMOFlipid 20% to Intralipid 20% in Hospitalized Neonates and Infants Requiring 28 Days of Parenteral Nutrition. This was a prospective, randomized, controlled, double-blind, parallel-group, multicenter phase 3 study that was conducted in 14 study centers in the US. The primary objective of the study was to show the superiority in safety of SMOFlipid to Intralipid. The primary safety outcome was measured as the number of pediatric study patients in each treatment group with conjugated bilirubin > 2 mg/dL during the first 28 days of study treatment, confirmed by a second sample collected 7 days later. To determine efficacy, the study evaluated if SMOFlipid safely provided essential fatty acids and sufficient energy to provide for adequate growth and development in these pediatric patients.

The sponsor developed Smof-018-CP3 to address the Agency's postmarketing requirement for SMOFlipid (PMR 3002-1).

The individual study duration for each pediatric patient was from the time of enrollment to up to 92 (±1) days after the first PN and included the following phases:

- Initial treatment phase: 28 days from Baseline (Day 1) to Day 29/end of treatment (EOT)
- Treatment extension phase: Day 30 to Day 85/EOT (56 days from Day 30) if PN was still

Indicated.
- Follow-up phase: 7 days after EOT

Study Endpoints - Efficacy

- Fatty acids in plasma and red blood cell membranes (change from Baseline)
- Holman index[25]
- Body weight (change from baseline)
- Body Length (change from baseline)
- Head circumference (change from baseline)
- Time to full or enteral feeds
- Length of stay in hospital
- Number of pediatric patients who complete PN treatment without lipid minimization

Statistical Analysis Plan

An estimated 200 pediatric patients were planned to be enrolled. Based on the results of the interim analysis and after seeking advice from the FDA, Fresenius Kabi terminated the study because the statistical goal of superiority could not be reached with a reasonable number of pediatric patients in a realistic time frame. Therefore, the analysis of the primary objective was changed from confirmatory to exploratory, and all parameters were evaluated descriptively to support overall safety and efficacy of SMOFlipid in neonates.

Protocol Amendments

The original protocol, version 1.0, was dated July 24, 2015, and did not enroll any patients. The study started under protocol version 2.0, dated October 9, 2015. Version 2.0 had only minor administrative amendments from version 1.0.

FK made significant changes to version 2.0 citing difficulty enrolling the previously proposed number of patients within a reasonable timeframe. Under IND 102137, Version 3.0, dated October 5, 2020, the reduced number of enrollees changed the statistical interpretability of the trial findings, and the analysis of the primary objective was changed from confirmatory to

[25] The Holman Index is used to diagnose biochemical EFAD. It is determined by calculating the ratio of triene (i.e., Mead acid) to tetraene (i.e., arachidonic acid) ratio (T:T) ratio in plasma. A T:T ratio of > 0.2 is considered biochemical EFAD.

exploratory. The key changes from version 2.0 to 3.0 were:

- Changes in the study design and statistical evaluation:
  - The prerequisite for interim analysis was changed. The updated design was to perform analysis with 100 patients who completed the study "per protocol" (defined as at least 14 days on study treatment). Version 2.0 required 100 patients (50 per group) who had completed 28 days on the study drug.
  - Futility criterion was added for continuation of the study after interim analysis.
  - Hypothesis testing was updated for the case of study stop for futility.
  - Changes in safety endpoints due to hospital standards per FDA request.
    - Deleted "cumulative number of days of conjugate bilirubin levels > 1.5 mg/dL", since levels were measured only weekly and the endpoint could not be measured as written initially.
    - Indices of major neonatal morbidities were added as endpoints. These included bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), and late-onset sepsis in premature and low birth weight neonates.

  - Changes in the units in which the daily documentation of the study drugs, dextrose, and amino acids were recorded.
  - Changes in which specialized laboratories were to be used for study assessments.
  - COVID-19 outbreak (March 2020): adaptations were implemented in the off-site monitoring activities, which included virtual monitoring visits, including remote source data verification (SDV).

5.1.2. Study Results

Compliance with Good Clinical Practices

A statement of compliance is included.

Financial Disclosure

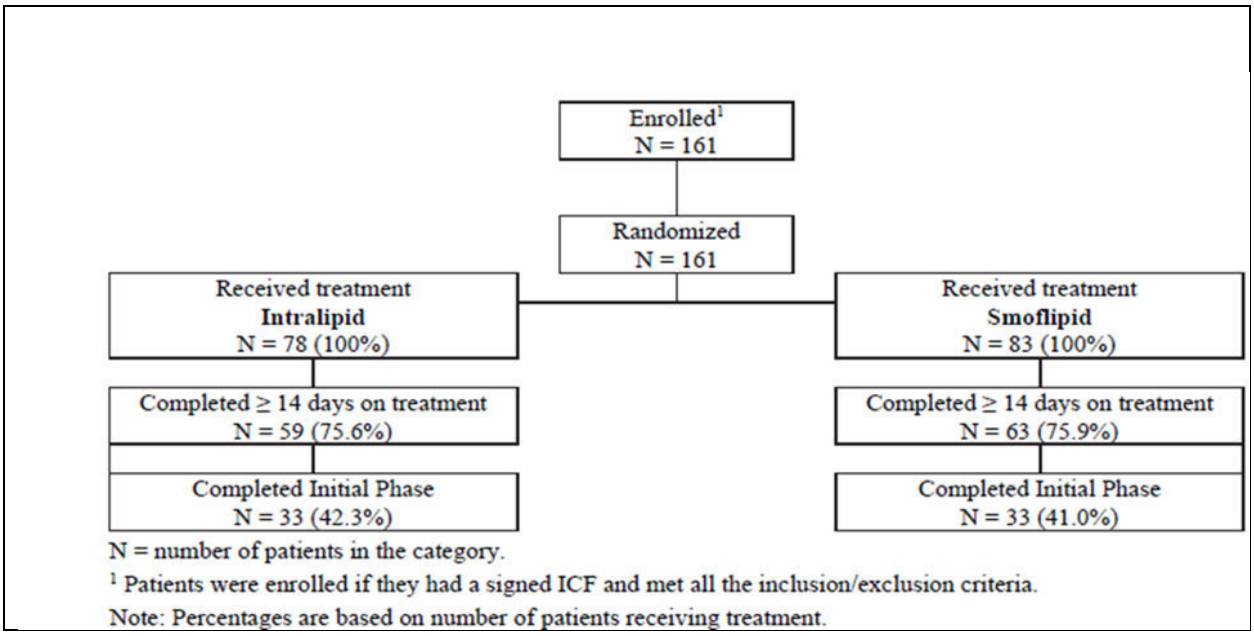
The applicant submitted appropriate documentation that financial disclosures were obtained, and there was nothing to disclose with regards to study SMOF-018-CP3.

Patient Disposition

In total, 161 patients were enrolled and randomized to receive either SMOFlipid (83 patients) or Intralipid (78 patients). All patients received at least one dose of the study drug and were included in the safety analysis set and ITT set. Of these, about three quarters of patients in each group (Intralipid: 59 patients; SMOFlipid: 63 patients) completed at least 14 days on treatment, and about 40% (33 patients in each group) completed the initial phase of the study, i.e., 28 days

on treatment. Of the approximately 60% of patients in each group who discontinued the study early, the most frequently reported reason was that the patient weaned off study product earlier than Day 28 (SMOFlipid: 53.0%; Intralipid: 55.1%).

Figure 1. Disposition of Patients in Protocol SMOF-018-CP3



Clinical Study Report of SMOF-018-CP3, p. 61, study-rpt-smof-cp3.pdf.

Patient Dropout

The patient dropout rate over the duration of the trial was progressive and occurred at similar rates in both treatment arms. By Day-14 of the study, nearly one fourth of the patients had discontinued treatment, (SMOFlipid 24.1%; Intralipid 24.4%). By the end of the initial treatment phase, Day-28, around 60% of patients were no longer receiving treatment. By Day-84, the final study day, around 5% of patients continued to receive treatment, with 3.6% of SMOFlipid, and 5.1% of Intralipid patients remaining.

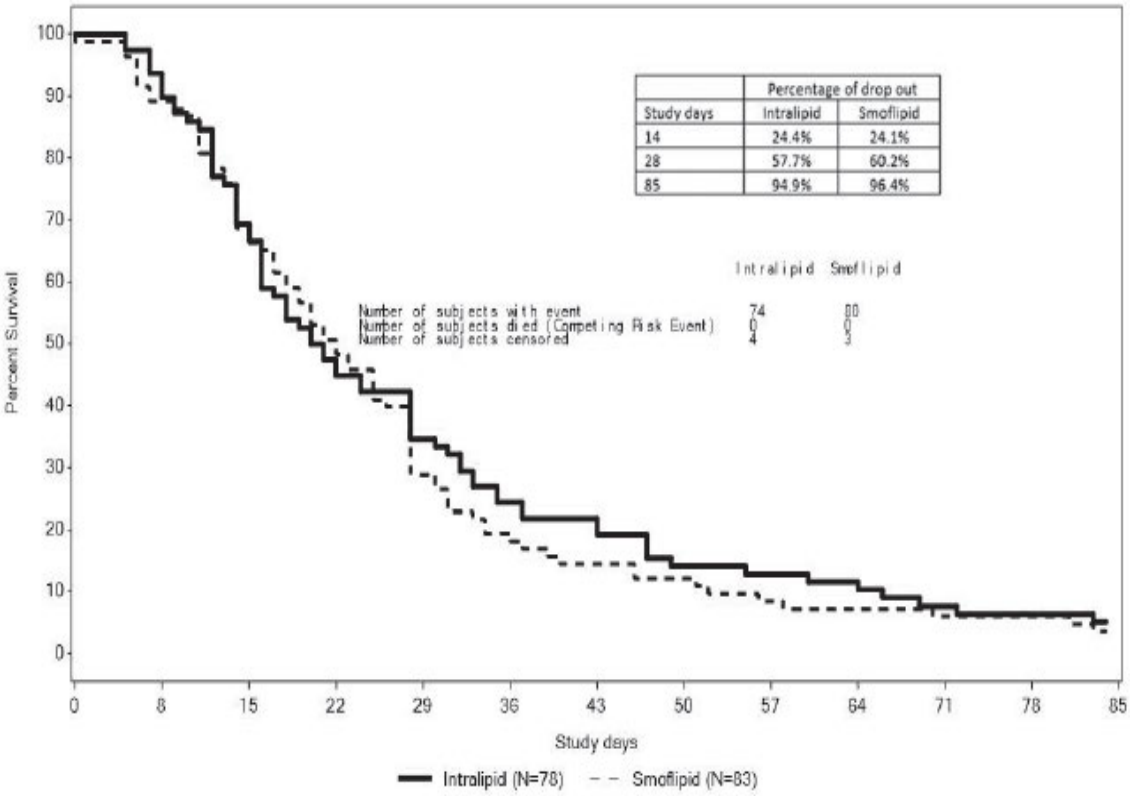
Table 4. Numbers of Patients Receiving Study Treatment During Study SMOF-018-CP3 – Intention-to-Treat Population

Study Period	Smoflipid (N = 83), n	Intralipid (N = 78), n
Days 1 through 7	83	78
Days 8 through 14	74	74
Days 15 through 21	58	55
Days 22 through 28	42	37
Days 29 through 35	25	27
Days 36 through 42	16	19
Days 43 through 49	12	17
Days 50 through 56	10	11
Days 57 through 63	8	10
Days 64 through 70	6	9
Days 71 through 77	5	6
Days 78 through 84	5	5

Note: the Intention-to-Treat Population was equivalent to the Safety Analysis Population

Source: **STUDY SMOF-018-CP3 CSR TABLE 14.3.5.4**

Figure 2. Survival Curve of Patient dropout by Treatment Arm over Days of Treatment



Protocol Violations/Deviations

Major protocol deviations were reported in 22 (26.5%) patients in the SMOFlipid group and 20 (25.6%) patients in the Intralipid group, most of which were that the patient did not receive study drug for at least 14 days (SMOFlipid: 24.1%; Intralipid: 24.4%). The second most common deviation, reported in 2 patients in each group, (SMOFlipid 2.4%; Intralipid 2.6%) was "inclusion/exclusion criteria." After excluding patients with major protocol deviations from the population, the resulting "per protocol" (PP) set comprised 61 (73.5%) patients in the SMOFlipid group and 58 (74.4%) patients in the Intralipid group.

Minor protocol deviations were reported in 72 (86.7%) of patients in the SMOFlipid group and 71 (91.0%) in the Intralipid group. The most common minor protocol deviation in both treatment arms was "protocol required evaluation not completed," in 58 (74.4%) of the Intralipid arm, and 55 (66.3%) in the SMOFlipid arm, all of which were attributed to physician decision, with an additional 4 (4.8%) of the Intralipid subjects having the additional attribution of parent/guardian decision.

Over the duration of the study, laboratory parameters were not measured according to the protocol. “Any liver test” was not measured at baseline screening in 43 (51.8%) of SMOFlipid and 48 (61.5%) of Intralipid patients and during treatment in 68 (81.9%) of SMOFlipid and 58 (74.4%) of Intralipid patients.

Because the primary endpoint of the study was the measure of direct bilirubin, the review team requested additional data from the sponsor to determine whether bilirubin levels had been measured with adequate frequency. The Sponsor explained that many of the participating study sites did not evaluate conjugated bilirubin in their clinical practice and that the conjugated bilirubin analyses were performed, independently of the other liver tests, at a central laboratory. For the initial treatment phase, i.e., the first 28 days of treatment, in which the primary outcome was evaluated, the sites collected 100% (733/733) of the expected samples. For the treatment extension phase of the study (Days 29-85), 107 out of 113 expected samples were received (95%). Based on this additional information, the review team felt assured that the primary endpoint has been rigorously measured.

The second most common category of minor protocol deviation was “investigational new drug issues” which was present in 54 (65.1%) of SMOFlipid patients and 60 (76.9%) of Intralipid patients.

Demographic and Baseline Characteristics

Table 6 summarizes the demographic and baseline characteristics of patients participating in study SMOF-018-CP3. Despite randomization, there were some imbalances in the patient populations in the treatment arms. The SMOFlipid group had more patients greater than 28-days of age than the Intralipid group (7.2% vs. 3.8%). Other differences included a greater percentage of males in the SMOFlipid arm than the Intralipid arm (53% vs. 42%). Additionally, the Intralipid arm had more Black patients than the SMOFlipid arm (14% vs. 5%) whereas the SMOFlipid arm had more Hispanic/Latino patients that the Intralipid arm (20% vs. 10%).

Table 5. Summary of Demographic and Baseline Characteristics (safety analysis set)

	Intralipid (N=78) SMOFlipid	**SMOFlipid (N=83) n (%)**	**Total (N=161)**
Sex			
Male	33 (42.3)	44 (53.0)	77 (47.8)
Female	45 (57.7)	39 (47.0)	84(52.4)
Age			
Chronological age (days)[1], mean (SD)	8.3 (12.16)	11.4 (21.58)	9.9 (17.67)
Age Category Newborn (0-27 days) Infant (≥28 days)	 75 (96.2) 3 (3.8)	 77 (92.8) 6 (7.2)	 152 (94.4) 9 (5.6)

Postmenstrual age at birth (days), mean (SD)	238.4 (23.98)	243.2 (24.27)	240.9 (24.18)
Underlying Disease Type, N%) **No NEC** **NEC**	 72 (92.3) 6(7.7)	 74 (89.2) 9 (10.8)	 146 (90.7) 15 (9.3)
Body weight (kg), n **mean (SD)** **Z-score, mean (SD)** Category for age, n (%) Low Normal High	n = 74 2.25 (0.663) -0.90 (0.969) 12 (15.4) 62 (79.5) 0	n = 82 2.44 (0.871) -1.06 (1.090) 20 (24.1) 62 (74.7) 0	n = 156 2.35 (0.783) -0.98 (1.034) 32 (19.9) 124 (77.0) 0
Head circumference (cm), n mean (SD) **Z-score , mean (SD)** **Category for age, n(%)** Low Normal High	n = 73 31.28 (2.798) -0.76 (1.184) 9 (11.5) 62 (79.5) 2 (2.6)	n = 78 31.69 (3.225) -0.97 (1.249) 20(24.1) 57 (68.7) 1 (1.2)	n =151 31.49 (3.024) -0.87 (1.218) 29 (18.0) 119 (73.9) 3 (1.9)
Duration of per-treatment (days), n mean (SD)	n = 45 8.8 (8.25)	n = 49 7.3 (7.50)	n = 94 8.0 (7.86)
Race			
White	57 (73.1)	65 (78.3)	122 (75.8)
Black or African American	11 (14.1)	4 (4.8)	15 (9.3)
Asian	1 (1.3)	2 (2.4)	3 (1.9)
American Indian or Alaska Native	2 (2.6)	2 (2.4)	4 (2.5)
Native Hawaiian or Other Pacific Islander	1(1.3)	0	1 (0.6)
Other[1]	6 (7.7)	10 (12.0)	16 (9.9)
Ethnicity			
Hispanic or Latino	8 (10.3)	17 (20.5)	25 (15.5)
Not Hispanic or Latino	70 (89.7)	66 (79.5)	136 (84.5)

Clinical Study Report of SMOF-018-CP3, p. 65/117, study-rpt-smof-cp3.pdf.
1 Chronological age = post-natal age
2 Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other Baseline Characteristics

Disease characteristics

All patients had medical history events which were reported by system organ class (SOC). The most frequently reported was gastrointestinal, which was present in all patients, 161 (100%). The other most commonly reported medical conditions, respiratory, "other," and cardiovascular were present in 87 (54.0%), 72 (44.7%), and 63 (39.1%), respectively. Of particular significance, hepatic was reported in 2 (2.4%) in the SMOFlipid group and 2 (2.6%) in the Intralipid group. In general, the prevalence of medical history conditions was fairly consistent between SMOFlipid and Intralipid patients and was consistent with the usual pathology of neonates and infants requiring PN.

Table 6. Summary of Medical History (Safety Analysis Set)

Table 14.1.4.3
Summary of Medical History (Safety Analysis Set)

Medical History Code	Intralipid (N=78)	Smoflipid (N=83)	Total (N=161)
Overall	78(100.0%)	83(100.0%)	161(100.0%)
Allergy	0	0	0
HEENT	8 (10.3%)	12 (14.5%)	20 (12.4%)
Respiratory	42 (53.8%)	45 (54.2%)	87 (54.0%)
Cardiovascular	30 (38.5%)	33 (39.8%)	63 (39.1%)
Gastrointestinal	78(100.0%)	83(100.0%)	161(100.0%)
Hepatic	2 (2.6%)	2 (2.4%)	4 (2.5%)
Genitourinary	6 (7.7%)	7 (8.4%)	13 (8.1%)
Immunologic	0	2 (2.4%)	2 (1.2%)
Hematologic/Lymphatic	26 (33.3%)	32 (38.6%)	58 (36.0%)
Neurologic	17 (21.8%)	21 (25.3%)	38 (23.6%)
Endocrine/Metabolic	21 (26.9%)	25 (30.1%)	46 (28.6%)
Musculoskeletal	1 (1.3%)	5 (6.0%)	6 (3.7%)
Dermatologic	9 (11.5%)	11 (13.3%)	20 (12.4%)
Infectious Disease	10 (12.8%)	11 (13.3%)	21 (13.0%)
Other	34 (43.6%)	38 (45.8%)	72 (44.7%)

Clinical Study Report of SMOF-018-CP3, Table 14.1.4.3 . (study-rpt-smof-cp3.pdf).

Table 7. Patients Classified with MedDRA Term: Hepatic

	MedDRA: SOC/Dictionary-Derived Term/Reported Term	
	Intralipid N=78	SMOFlipid N=83
(b) (6)	Hepatobiliary disorders/ Hyperbilirubinemia/ Conjugated hyperbilirubinemia	
	Investigations/ Blood alkaline phosphatase increased/ Elevated alkaline phosphatase activity level	
		Hepatobiliary disorders/ Hyperbilirubinemia neonatal/ hyperbilirubinemia of prematurity
		Hepatobiliary disorders/ Hyperbilirubinemia/

		Hyperbilirubinemia

Listing 16.2.4.2, Medical History by Patient (ITT Analysis Set)

None of the patients listed in Table 8 went on to develop PNAC.

Important Prior and Concomitant Medications

Overall, 78.9% of patients received prior medications, (SMOFlipid 67%; Intralipid 76.9%). Antimicrobials were the most commonly prescribed, (SMOFlipid 45.8%; Intralipid 44.9%), followed by analgesics, (SMOFlipid 41.0%; Intralipid 38.5%), and blood substitutes and perfusion solutions, (SMOFlipid 36.1%; Intralipid 41.0%).The proportion of patients was similar between both study arms for all prior medications. (Sourced from table 14.1.4.2)[26].

All patients were taking at least one concomitant medication at baseline.[27] The percentage of patients in each treatment arm had similar use patterns of all medication classifications that were reported in ≥ 20% of patients. The most frequently reported concomitant baseline medication was blood substitutes and perfusion solutions, (SMOFlipid 98.8%; Intralipid 98.7%), followed by mineral supplements (SMOFlipid 85.5%; Intralipid 87.2%) and analgesics (SMOFlipid 80.7%; Intralipid 80.8%) . The largest discrepancy was in vaccines (SMOFlipid 42.2% and Intralipid 33.3%).(Table 14.1.4.1).

Throughout the study, patients were permitted to take concomitant medications or treatments that were necessary to provide supportive care, unless they could potentially influence outcome measures. The following medications were excluded:

- Beta-carotene, lutein, lycopene, selenium, Vitamins A, C, and E, as sole additives
- Any lipid emulsion other than study medication
- Enteral administration of fish oil

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study was conducted in hospitalized patients, and the investigational product was administered intravenously, therefore, compliance was not a concern. Any interruption of the study drug infusion for longer than 4 hours required an explanation. Any other deviations from the planned infusions were documented in case report forms.

[26] Study-rpt-smof-018-cp3.pdf. (sourced from table 14.1.4.2)
[27] Table 10-5.Study-rpt-smof-018-cp3.pdf. (sourced from table 14.1.4.1)

Efficacy Results/Growth and Development Endpoint

All efficacy endpoints were secondary endpoints. Efficacy was determined by evaluating EFAD by using the Holman Index, growth and development through body measurements, the time to partial or full enteral feeds, length of stay, and completing PN without lipid minimalization.

Fatty Acids in Plasma and Red Blood Cell Membranes

The mean baseline concentrations of fatty acids were similar between groups. The main findings for fatty acids in plasma were the notable increase in mean concentrations of eicosapentaenoic acid and docosahexaenoic acid following administration of SMOFlipid, but no change was seen following administration of Intralipid. Conversely, with the administration of the Intralipid, the change from baseline findings were consistent with the administration of the fully soy-based formula. Alpha-linolenic acid and linoleic acid levels increased following the administration of Intralipid but decreased with SMOFlipid.

The Holman Index is used to diagnose biochemical EFAD. It is determined by calculating the ratio of triene (i.e., Mead acid) to tetraene (i.e., Arachidonic acid ratio (T:T) ratio in plasma. A T:T ratio of > 0.2 is considered biochemical EFAD. Signs and symptoms of EFAD, which can be severe and can cause permanent developmental disability in the pediatric population, are detected at ratios of > 0.4.[28,29]

Changes were made after the database lock to further describe patients with EFAD. Additional Holman Index Categories were added: Normal: < 0.05, suspected EFAD: ≥ 0.05 to < 2.0, moderate EFAD: ≥ 0.20 to < 0.40, severe EFAD: ≥ 0.40.

In the SMOFlipid group, at baseline, five (6%) patients met the criteria for suspected, and one (1.2%), for moderate EFAD. By end of the initial treatment phase (EOT), two (2.4%) patients had suspected EFAD. For the remainder of the study, one case of suspected EFAD was reported on day-29 and in the end of treatment (EOT) phase. Moderate EFAD was detected only at baseline, in one patient, and no severe EFAD was reported in any patient in the SMOFlipid arm.

In the Intralipid group, suspected EFAD was present in nine (11.5%) patients at baseline, two (2.6%) on day-29, three (3.8%) on day-85, and one (1.3%) at EOT. No moderate or severe EFAD was detected in any Intralipid patient.

In both the SMOFlipid and Intralipid arms, the few EFA abnormalities were classified as suspected and were detected at baseline. Only one case of moderately severe EFAD, which was detected prior to exposure to either study drug, was observed. Although few cases of EFAD

[28] Holman RT. The ratio of trienoic: tetraenoic acids in tissue lipids as a measure of essential fatty acid requirement. J Nutr. 1960;70:405–10.
[29] Gura KM, Parsons SK, Bechard LJ, Henderson T, Dorsey M, Phipatanakul W, et al. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. Clin Nutr. 2005;24:839–47. doi: 10.1016/j.clnu.2005.05.020.

were identified in the second and third months of the study, only 33 (41.0%) of SMOFlipid and 33 (42.3%) of Intralipid patients completed the initial phase; therefore, fewer than half of the remaining patients were exposed to the study drugs for more than 4 weeks.

Table 8. Categorization of EFAD According to Holman Index – Post hoc (ITT Set)

	Combined		Total
	Intralipid (N = 78)	Smoflipid (N = 83)	(N = 161)
Baseline			
< 0.05	61 (78.2)	72 (86.7)	133 (82.6)
≥ 0.05 - < 0.20 (suspected EFAD)	9 (11.5)	5 (6.0)	14 (8.7)
≥ 0.20 - < 0.40 (moderate EFAD)	0	1 (1.2)	1 (0.6)
≥ 0.40 (severe EFAD)	0	0	0
EOT Initial treatment phase			
< 0.05	62 (79.5)	69 (83.1)	131 (81.4)
≥ 0.05 - < 0.20 (suspected EFAD)	2 (2.6)	2 (2.4)	4 (2.5)
≥ 0.20 - < 0.40 (moderate EFAD)	0	0	0
≥ 0.40 (severe EFAD)	0	0	0
Day 29			
< 0.05	27 (34.6)	27 (32.5)	54 (33.5)
≥ 0.05 - < 0.20 (suspected EFAD)	1 (1.3)	1 (1.2)	2 (1.2)
≥ 0.20 - < 0.40 (moderate EFAD)	0	0	0
≥ 0.40 (severe EFAD)	0	0	0
Day 57			
< 0.05	6 (7.7)	7 (8.4)	13 (8.1)
≥ 0.05 - < 0.20 (suspected EFAD)	0	0	0
≥ 0.20 - < 0.40 (moderate EFAD)	0	0	0
≥ 0.40 (severe EFAD)	0	0	0
Day 85			
< 0.05	3 (3.8)	3 (3.6)	6 (3.7)
≥ 0.05 - < 0.20 (suspected EFAD)	0	0	0
≥ 0.20 - < 0.40 (moderate EFAD)	0	0	0
≥ 0.40 (severe EFAD)	0	0	0
EOT Extension treatment phase			
< 0.05	10 (12.8)	11 (13.3)	21 (13.0)
≥ 0.05 - < 0.20 (suspected EFAD)	1 (1.3)	1 (1.2)	2 (1.2)
≥ 0.20 - < 0.40 (moderate EFAD)	0	0	0
≥ 0.40 (severe EFAD)	0	0	0

N = number of patients in the analysis set.
Source: Table 14.2.2.3.11

Body Measurements:

The growth and development of patients were evaluated by assessing the parameters body weight, body length/height, and head circumference. Mean and median values increased over time for all measured parameters in both treatment groups.

Body Weight
Baseline measurements of body weight demonstrate that 62 (74.7%) of SMOFlipid patients and 62 (79.5%) of Intralipid patients had normal body weight at baseline. The SMOFlipid arm had a higher prevalence of low body weight patients at baseline (20, 24.1%) than the Intralipid arm (12, 15.4%). By day 29, the study arms were more closely aligned with normal body weight in 24 (28.9%) SMOFlipid patients, and 25 (32.1%) Intralipid patients, and low body weight in 9 (10.8%) SMOFlipid patients and 6 (7.7%) Intralipid patients.

Body Length
Baseline measurements of body length demonstrated that (53,63.9%) of SMOFlipid patients and 60 (76.9%) of Intralipid patients had normal body length at baseline. Patients in the SMOFlipid arm had a higher prevalence of low body length patients at baseline (25, 30.1%) than the Intralipid arm (12, 15.4%). By day 29, the study arms were more closely aligned with normal body length in (20,24.1%) SMOFlipid patients and 27 (34.6%) Intralipid patients. Low body length remained in 13 (15.7%)of SMOFlipid patients and 6 (7.7%) Intralipid patients.

Head Circumference
In baseline measurements of head circumference, SMOFlipid patients had a lower prevalence of normal (57, 68.7%) and high (1, 1.2%) measurements, and a higher rate of low measurement (20, 24.1%), compared to Intralipid patients, with 62 (79.5%) normal, 2 (2.6%) high, and 9 (11.5%) low. By Day 29, no patient in either treatment arm had a high head circumference; normal head circumference in SMOFlipid was 25 (30.1%) and Intralipid 30 (38.5%), while low had decreased to 8 (9.6%) and 3 (3.8%).

Table 9. Categorization of Age-standardized Body Weight, Body Length, and Head Circumference (ITT Set)

	Number (%) of Patients		
	Combined		Total
	Intralipid (N = 78)	Smoflipid (N = 83)	(N = 161)
Parameter	n (%)	n (%)	n (%)
Body weight			
Baseline, n	74	82	156
Low	12 (15.4)	20 (24.1)	32 (19.9)
Normal	62 (79.5)	62 (74.7)	124 (77.0)
High	0	0	0
Day 29	31	33	64
Low	6 (7.7)	9 (10.8)	15 (9.3)
Normal	25 (32.1)	24 (28.9)	49 (30.4)
High	0	0	0
Body Length			
Baseline	72	78	150
Low	12 (15.4)	25 (30.1)	37 (23.0)
Normal	60 (76.9)	53 (63.9)	113 (70.2)
High	0	0	0
Day 29	33	33	66
Low	6 (7.7)	13 (15.7)	19 (11.8)
Normal	27 (34.6)	20 (24.1)	47 (29.2)
High	0	0	0
Head circumference			
Baseline	73	78	151
Low	9 (11.5)	20 (24.1)	29 (18.0)
Normal	62 (79.5)	57 (68.7)	119 (73.9)
High	2 (2.6)	1 (1.2)	3 (1.9)
Day 29	33	33	66
Low	3 (3.8)	8 (9.6)	11 (6.8)
Normal	30 (38.5)	25 (30.1)	55 (34.2)
High	0	0	0

N = number of patients in the analysis set; n = number of patients with non-missing values; n (%) = number (percentage) of patients with event.
Source: Table 14.2.2.2.1 (body weight), Table 14.2.2.2.3 (body length), Table 14.2.2.2.5 (head circumference)

Time to Full Enteral or Oral Feeds (i.e., PN weaning)

The median time until full enteral and oral feeds was 21.95 days for Intralipid and 23.29 days for SMOFlipid. The hazard ratio of 1.034 (95% CI: 0.725, 1.476) indicated that the rate of patients attaining full enteral and oral feeds was similar between groups at any time point during the study.

Table 10. Summary of Time to Enteral or Oral Feeds (Intention-to-Treat Analysis Set)

Table 14.2.2.3.1
Summary of Time to Full Enteral or Oral Feeds (Intention-to-Treat Analysis Set)

Parameter	Intralipid (N=78)		Smoflipid (N=83)
Number of subjects with event	58		58
Number of subjects died (Competing Risk Event)	1		0
Number of subjects censored	19		25
Median time (days) to event [1]			
Combined (both strata)	21.95		23.29
NEC	NC		13.50
No NEC	21.43		26.04
Fine and Gray Competing Risk Model			
Combined (both strata) [2]			
Hazard Ratio		1.034	
95% CI of HR		0.725, 1.476	
NEC [3]			
Hazard Ratio		5.603	
95% CI of HR		1.062, 29.570	
No NEC [3]			
Hazard Ratio		0.901	
95% CI of HR		0.621, 1.308	

Notes: HR=Hazard Ratio (Smoflipid/Intralipid), NC=Not Calculable, CI=confidence interval, N=Number of patients in the analysis set. Summaries are by planned treatment for the intention-to-treat analysis set, and by actual treatment for the per protocol set and safety analysis set.
[1] Median time to event estimated from the cumulative incidence function (Aalen estimator).
[2] Proportional hazard modelled with treatment and underlying disease.
[3] Proportional hazard modelled with treatment, underlying disease and interaction term.
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Data Quality and Integrity

The study was monitored regularly by a clinical research associate (CRA) from Clinpace, the contract research organization. CRAs were to ensure patient protection, study procedures, laboratory practices, study intervention administration, and the implementation of data collection processes. The goal was to assure accurate, consistent, complete, and reliable data in compliance with International Council of Harmonization of Technical Requirements for Pharmaceuticals for human use (ICH) E6, Good Clinical Practice, and applicable regulatory guidance and guidelines.

5.1.3. Assessment of Efficacy Across Trials

The three pediatric studies conducted by the sponsor and submitted with the original NDA are described in section 3.2. All of the studies were randomized, double-blind, active control studies which evaluated the safety and tolerability or efficacy of SMOFlipid compared to

Intralipid. The studies ranged from 7 days to 4 weeks in duration, and enrolled patients that ranged in age from preterm infants to children. A total of 172 patients were treated, with 87 in the SMOFlipid and 85 in the Intralipid groups (ITT). The short duration of the studies, which was a maximum of 28 days, provided limited information about the efficacy endpoints.

Study SMOF-CP3-018 enrolled at total of 161 patients, 83 of whom received SMOFlipid, and 78 of whom received Intralipid. The primary (safety) endpoint was evaluated at 28 days; however, the patients continued treatment up to 84 days.

Efficacy Endpoints

The efficacy endpoints were secondary endpoints which:

- Compared the efficacy of SMOFlipid 20% to Intralipid 20% in neonates and infants reflected by specific nutritional parameters that were related to growth, such as head circumference and metabolic findings such as fatty acids in plasma.
- Evaluated overall safety of SMOFlipid 20% in neonates by aspects of hospital course, such as length of stay and time to full enteral feeding

Summary findings across four company-sponsored studies.

FK conducted four studies to assess the efficacy of SMOFlipid compared to a soy-based ILE. The trials were not powered to show statistically significant differences in clinical outcomes, but instead used descriptive statistics to analyze the data. In three of the four studies, 00-SMOF-002, 00-SMOF-004, and 03-SMOF-005, the primary efficacy variable was weight, and sometimes other anthropometric measures including length and head circumference. Secondary variables included nutritional status (determined by measuring lipid and albumin levels), sepsis, respiratory support/mechanical ventilation, and triglyceride levels. In the most recent trial, SMOF-CP3-018, the efficacy endpoints were secondary endpoints and included anthropometric measures as well nutritional parameters such as fatty acid levels and time to enteral/oral feedings. In all four studies, the anthropometric comparisons, the nutritional parameters, and the incidence of hospitalization-related events, such mechanical ventilation, between the SMOFlipid and Intralipid groups were comparable. However, the change in anthropometric measures which have been evaluated over two to four week periods of time are not likely to be as meaningful as studies of longer duration. Although SMOF-CP3-018 was planned for 84 days, the dropout rate by 28 days was around 60%, reducing the quantity of data to be analyzed.

Fatty acid profiles were analyzed to detect EFAD as a secondary variable in each of the studies. In 00-SMOF-002, the sponsor noted an increase in ω-3 fatty acids in the SMOFlipid arm, a finding which was consistent because the ω-3 fatty acid content of SMOFlipid is greater than that of Intralipid. In 00-SMOF-004, the preterm infants in the SMOFlipid group also had fatty acid levels in plasma that reflected a higher omega-3 fatty acid and alpha-tocopherol profile than the Intralipid group, likely due to the fatty acid composition of SMOFlipid. In 03-SMOF-005, no patient had an increase in the Holman Index, however, one patient in the SMOFlipid arm started with an elevated T:T ratio of 0.29 but ended with an improved level of 0.21. One patient in the Intralipid group had a small increase (0.02 to 0.03) in the Holman index. In Smof-

CP3-018, the SMOFlipid group was found to have increases in mean concentrations of EPA and DHA, while the Intralipid group was found to have increased levels of linoleic acid; findings which reflect with the compositions of the respective ILEs. In Smof-018-CP3, there were no clinically meaningful cases of EFAD.

The sponsor-conducted studies measured pertinent efficacy endpoints and enrolled the appropriate population. However, it is necessary to point out that the relatively short duration of the four trials limited the ability to detect important safety outcomes that may take longer than 28 days to develop (i.e., EFAD)

Subpopulations

Efficacy analyses were performed in the subgroups of patients with and without necrotizing enterocolitis (NEC). In the ITT population, nine patients in the SMOFlipid group had NEC and six in the Intralipid population had NEC. The small study size and small number of patients with NEC do not allow for meaningful interpretation of this subgroup analysis.

5.2. Review of Safety

5.2.1. Safety Review Approach

The primary basis of the safety review was to demonstrate superiority of SMOFlipid over Intralipid, as determined by the number of patients who developed PNAC within the first 28 days of the study which was the primary endpoint. PNAC was diagnosed by measuring conjugated bilirubin routinely. Levels of > 2 mg/dL, which were detected within the first 28 days of study treatment, confirmed by a second sample collected 7 days after the first sample, were diagnostic of PNAC.

Secondary safety endpoints included laboratory values such as fatty acid and transaminase levels, and adverse event data to compare SMOFlipid to Intralipid. Special endpoints, which were adverse events common in extremely preterm infants, such as intraventricular hemorrhage and necrotizing enterocolitis, were also used for comparison.

Deaths, SAEs, TEAEs, and study drug discontinuations were documented as part of the overall safety review.

5.2.2. Review of the Safety Database

Overall Exposure

The sponsor submitted results from its four sponsored pediatric studies and literature references. In company sponsored trials, 170 patients were exposed to SMOFlipid. The studies were well controlled, enrolled patients with appropriate pathology, and evaluated meaningful endpoints. The trials ranged from 7 to 84 days and compared SMOFlipid to the same soybean-based lipid emulsion, Intralipid.

A large number of literature references were included in the submission and findings for over 3000 patients exposed to SMOFlipid were provided. To further evaluate the literature review, the Division consulted colleagues in DEPI to determine if the scope and content of the review was comprehensive. DEPI concluded that the literature search conducted by the Sponsor was complete and truthful; additionally, the DEPI reviewer identified more articles describing other relevant trials.

The DEPI postmarket evaluation identified additional clinical studies that were not included in FK's literature review. Additional pediatric patient exposure to Smoflipid has been confirmed, a finding which is consistent its considerable off-label use.

Table 11. Overview of Patients Exposed to SMOFlipid

Duration of Treatment	Origin	Total Number of Pediatric Patients	Breakdown in Age Categories
≤1 month	Company-sponsored studies	87	72 neonates 7 infants 8 children
	Published studies	2920	2905 neonates 15 from multiple age groups
≤2 months	Published studies	180	180 neonates
≤12 weeks	Company-sponsored studies	83[a]	77 neonates 6 infants
	Published studies	11	11 infants
≤12 months	Published studies	173	25 infants and children 148 of multiple age groups
1.5 years	Published studies	20	20 from multiple age groups
0.5-8.7 years	Published studies	23	23 from multiple age groups
N.S.	Published studies	354	354 neonates

N.S. = not specified
a. Total of 33 patients in Smoflipid group completed 28 days, a total of 25 patients in Smoflipid group received treatment between 28 and 84 days, and a total of 3 patients in Smoflipid group completed 84 days

(Source: 2.7.3)

Adequacy of the safety database:

The three previous sponsor-conducted randomized, controlled pediatric trials were of short duration, lasting from seven to 14 days. Including the findings from the most recently conducted pediatric study, most patients had 28 days or less of exposure to SMOFlipid. Although none of the studies were powered to reach statistical significance, meaningful data was obtained, and safety results demonstrated that triglyceride levels, as well as other safety findings, were similar in the SMOFlipid and Intralipid groups.

The clinical review team consulted the Office of Surveillance and Epidemiology- Division of Epidemiology (OSE-DEPI) and requested a review of the methodology and approach in literature reviewed by the sponsor. DEPI cited limitations as excluding non-English reports, case reports, meeting abstracts and reports from studies conducted by FK. DEPI concluded that the literature review in the submission was complete and truthful. However, due to the weakness

of the evidence presented in published reports, DEPI recommended that for labeling purposes, the review team should "ignore information in reports from studies of SMOFlipid treatment in infants, children, and adolescents (non-neonatal pediatric population)."

5.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission included a declaration of Data Quality Assurance. The sponsor utilized a contract research organization (CRO) (b) (4)) to provide site monitoring, ensure GCP of laboratory practices, and facilitate adherence to regulatory guidelines.

The submission quality was acceptable.

Categorization of Adverse Events

I have reviewed the mapping of verbatim terms to preferred terms for the dataset. I did not identify any irregularities.

Routine Clinical Tests

With the exception of the primary endpoint, safety assessments were categorized as secondary endpoints in the study protocol. Routine serology was performed, according to the schedule described in the study protocol, to assess some safety endpoints including liver and renal function, and hematologic/coagulation studies. Other safety endpoints such as the incidence of the retinopathy of prematurity and late onset sepsis, categorized as adverse events of special interest, were determined by clinical assessment. Additional assessments were performed as needed.

Table 12. Schedule of Assessments in Protocol SMOF-018-CP3.

Daily procedures and assessments during treatment (starting on Day 1): Study drug administration, study drug administered, dextrose administered, amino acids administered, enteral nutrition and oral food administered, Body Weight, AEs, Concomitant Medication

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

d = day

[a] EOT visit to be performed on the following day after receiving the last dose of study drug.

[b] If conjugated bilirubin exceeded 1.5 mg /dL it had to be assessed weekly, also after Day 29

[c] If conjugated bilirubin was > 1.5 mg/dL at the EOT visit a blood sample for the assessment of conjugated bilirubin had to be drawn at the Follow-up Visit

[d] Additional blood samples for assessment of triglycerides and blood glucose needed to be drawn during ramp up of lipid dose. Should triglycerides exceed 250 mg/dL at any time, lipids were withheld until analysis of triglycerides in another blood sample the following morning.

[e] Special analyses: Fatty acids, sterols, α-Tocopherol.

(Study Report Smof-018-CP3.)

5.2.4. Safety Results

Deaths

Two patients had a fatal TEAE, one in each arm of the study. In the Intralipid group, the patient's cause of death was cardiogenic shock. In the SMOFlipid group, the cause of death was sepsis. The sponsor did not consider either death to be related to the study drug.

Patient (b) (6) was a 10-day old Asian female in the Intralipid group. Cause of death: cardiogenic shock. No NEC. Cardiovascular history: congenital atrial septal defect, patent ductus arteriosus, ventricular septal defect. Other conditions: bilateral superior vena cava syndrome, (suspected) duodenal atresia, thrombocytopenia, extremely low birth weight, pulmonary hypertension. She expired on day 42. Her medical problems presented numerous confounding factors so her death could not be attributed to parenteral nutrition.

Patient (b) (6) was 2-day old white male with sepsis who received SMOFlipid. Cause of death: sepsis. His medical history was significant for gastroschisis, recurrent hypotension, and chylothorax. He developed sepsis, with positive blood cultures for enterococcus faecalis & Staphylococcus epidermidis. He expired on day 49. His severe pathology was confounding and his death could not be attributed to parenteral nutrition.

Serious Adverse Events

Serious TEAEs were of similar proportion in both treatment arms and were documented in 9.6% [8/81] of patients in the SMOFlipid group and 6.4% [5/78] of patients in the Intralipid group. The TEAE reported most frequently by system organ class (SOC) was infections and infestations (SMOFlipid 4.8%; Intralipid 1.3%). Sepsis, pulmonary hypertension, meningitis, and accidental overdose were reported in single patients, with the exception of necrotizing colitis (2 patients). (Listing 14.3.2.1a).

D**ropouts and/or Discontinuations Due to Adverse Effects**

SMOF-018-CP3: The reasons for early discontinuations are summarized in Table 19. Approximately 60% of patients in both study arms discontinued the study early, i.e., PN was stopped. The most frequently reported reason for discontinuation of a patient's participation in both groups was that the patient weaned off of the study product earlier than Day 28. In both study groups, subjects had early weaning at similar proportions (44/53% in SMOFlipid; 43/55% in Intralipid). Further reasons for early discontinuation in the SMOFlipid group included adverse event and withdrawal of consent in 2 (2.4%) patients, and in 1 (1.2%) for investigator decision and elevated conjugated bilirubin levels. No reasons were provided for the additional 2 (2.6%) subjects of the Intralipid group. One patient was discontinued due to COVID-19 restrictions (reason: other; Listing 16.2.1.2).

Table 13. Summary of Early Discontinuation – Combined Stages (all enrolled patients)

Discontinuation Reason	Number (%) of Patients		
	Combined		
	Intralipid N = 78	Smoflipid N = 83	Total N = 161
Early Discontinuation	45 (57.7)	50 (60.2)	95
Reason for discontinuation			
Patient weaned off study product earlier than Day 28	43 (55.1)	44 (53.0)	87
Adverse event	0	2 (2.4)	2 (1.2)
Other	2 (2.6)	0	2 (1.2)
Parent/legal guardian withdrawal of Consent	0	2 (2.4)	2 (1.2)
Investigator decision	0	1 (1.2)	1 (0.6)
Withdrawn due to elevated bilirubin levels	0	1 (1.2)	1 (0.6)

N = number of patients in the analysis set.
Note: Denominators for percentages are based on the number of randomized patients in the treatment group. More than one reason for early discontinuations may be reported for each patient.
(stdy-rpt-SMOF-018-CP3.pdf)

Significant Adverse Events

Two (1.2%) of patients died during the study. The incidence of TEAEs and SAEs were comparable between the two study groups. One patient died in each study group.

Table 14. Overall Summary of Adverse Events (safety analysis set)

Category	Combined				Total	
	Intralipid (N = 78)		Smoflipid (N = 83)		(N = 161)	
	n (%)	m	n (%)	m	n (%)	m
Any AE	57 (73.1)	361	59 (71.1)	334	116 (72.0)	695
Any TEAE	55 (70.5)	357	59 (71.1)	328	114 (70.8)	685
Any SAE	5 (6.4)	9	8 (9.6)	8	13 (8.1)	17
Any AE resulting in study discontinuation[1]	3 (3.8)	3	6 (7.2)	6	9 (5.6)	9
Any deaths	1 (1.3)	1	1 (1.2)	1	2 (1.2)	2

m = number of adverse events; N = number of patients in the analysis set; n (%) = number (percentage) of patients with at least one AE in the respective assessment.

Note: Denominators for percentages are based on the number of patients in the underlying disease group and treatment group.

[1] One patient in Smoflipid was weaned off study prior to AE onset and was erroneously recorded as discontinuing study due to an AEs (see Section 12.4.1.3).

Source: Table 14.3.1.1

Study report-SMOF-018-CP3 (table 12-2).

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs occurred in 59 (71.1%) of the SMOFlipid group and 55 (70.5%) of the Intralipid group. Gastrointestinal disorders were the most common in both groups, and incidences were similar, and, in SMOFlipid (27, 32.5%) and Intralipid (31, 39.7), with vomiting being the most frequently reported TEAE. Next, also with similar incidences, were Investigations, in which elevated gamma-glutamyl transferase occurred most frequently, followed by blood and lymphatic system disorders in which neonatal anemia was most frequent.

TEAEs leading to discontinuation

The most frequently reported TEAE leading to discontinuation was cholestasis: SMOFlipid (3, 3.6%), Intralipid (2, 2.6%). Of the 3 patients in the SMOFlipid group who discontinued the study due to the event of cholestasis, only 1 had DBil levels >2 mg/dL from samples tested by the central laboratory. All other TEAEs leading to discontinuation were events that occurred in only one patient each, including hematochezia, sepsis, and hypertriglyceridemia in the SMOFlipid group, and parenteral nutrition-associated liver disease in the Intralipid group. There was no significance difference in the rate and types of TEAEs between the two groups. (table 14.3.1.4a)

Adverse events of special interest (AESIs)
For PREA PMR 3002-1, the Agency required that the efficacy evaluation should include measures and endpoints that are major neonatal morbidities and consequently of special interest in neonates. These adverse events of special interest (AESIs) include: BPD (bronchopulmonary dysplasia), ROP (retinopathy of prematurity), IVH (intraventricular hemorrhage), PVL (periventricular leukomalacia), NEC (necrotizing enterocolitis), and late-onset sepsis.

AESIs were reported in 12.4% of patients generally with comparable frequencies between groups for all AESIs (SMOFlipid: 12%; Intralipid 12.8%).The most frequent events were late-onset sepsis in low birth weight and premature neonates (Intralipid: 6.4%; SMOFlipid: 7.2%), necrotizing enterocolitis (Intralipid: 2.6%; SMOFlipid: 3.6%), and bronchopulmonary dysplasia (Intralipid: 2.6%; SMOFlipid: 1.2%).

Laboratory Findings

Liver function parameters, AST, ALT, GGT, and Triglyceride changed throughout the study, see Table XX. In the SMOFlipid and Intralipid groups, AST and ALT levels decreased from baseline to EOT of the initial phase but increased by EOT of the extension phase. GGT levels increased from baseline, peaked on day-15, remained elevated but declined by EOT of the extension phase. Triglyceride levels increased and decreased in both groups throughout the study but were elevated at EOT of the extension phase. All liver parameters were increased by the end of the study; however, the changes were not considered to be clinically relevant.

Differences between the groups at the end of the initial treatment phase for hematologic parameters: leukocytes, hemoglobin, neutrophils, platelet and lymphocyte values were seen for shifts to abnormal but most were not considered clinically significant.

Table 15. Changes in Liver Parameters (ITT Set)

	Combined			
	Intralipid (N = 78)		Smoflipid (N = 83)	
Parameter	n	Mean (SD)	n	Mean (SD)
AST (U/L)				
Baseline	58	59.0 (52.47)	63	47.6 (35.81)
Change from baseline to				
Day 8	55	-22.1 (55.24)	58	-12.7 (35.23)
Day 15	44	-15.5 (59.45)	42	-12.9 (47.41)
Day 22	29	-23.5 (41.42)	36	-8.0 (46.31)
Day 29	21	-14.2 (33.62)	23	-22.2 (41.35)
EOT initial phase	48	-12.2 (53.42)	52	-8.3 (42.51)
EOT extension phase	15	81.7 (110.81)	12	172.4 (660.92)
ALT (U/L)				
Baseline	58	36.8 (79.17)	66	21.3 (14.19)
Change from baseline to				
Day 8	55	-16.3 (81.43)	61	-1.8 (15.74)
Day 15	46	-13.7 (1.90)	44	4.4 (20.85)
Day 22	29	1.9 (35.13)	37	11.1 (29.26)
Day 29	21	14.4 (24.12)	24	4.9 (24.13)
EOT initial phase	48	-4.7 (91.12)	54	7.3 (22.93)
EOT extension phase	15	120.4 (136.12)	12	64.3 (120.71)
GGT (U/L)				
Baseline	49	115.1 (73.80)	60	100.7 (73.10)
Change from baseline to				
Day 8	47	34.6 (98.92)	53	76.7 (132.45)
Day 15	40	82.9 (132.47)	41	112.8 (168.82)
Day 22	24	73.5 (137.15)	34	80.0 (173.50)
Day 29	20	47.6 (103.85)	21	59.4 (100.73)
EOT initial phase	45	82.2 (111.89)	48	86.5 (153.22)
EOT extension phase	13	35.1 (140.54)	11	39.1 (95.07)
Triglycerides (mg/dL)				
Baseline	70	80.8 (41.73)	73	77.1 (29.95)
Change from baseline to				
Day 8	54	-10.0 (37.64)	58	12.9 (56.05)
Day 15	50	-7.3 (37.99)	46	4.7 (71.99)
Day 22	29	12.7 (59.02)	38	-10.7 (41.84)
Day 29	24	9.3 (69.25)	22	-18.1 (32.15)
EOT initial phase	51	-0.9 (59.81)	51	-6.2 (39.07)
EOT extension phase	14	41.9 (57.17)	12	4.6 (59.13)

N = number of patients in the analysis set; n = number of patients with non-missing values.
Source: Table 14.3.4.5 (baseline values); Table 14.3.4.6 (changes from baseline)

Vital Signs

No trends or clinically relevant changes were observed in **vital signs** during the study. Only a few clinically significant **physical examination** findings were observed.

5.2.5. Analysis of Submission-Specific Safety Issues

PNAC/PNALD

The basis for NDA 207648, PMR 3002-1, Study SMOF-018-CP3, was that all patients receiving parenteral nutrition, including SMOFlipid, are potentially at risk for developing parenteral nutrition-associated cholestasis (PNAC), as described in sections 2.1 and 2.2.

According to FK, five patients met the criteria for the primary endpoint, three from the Intralipid arm, two from the SMOFlipid arm.

Table 16. Conjugated Bilirubin levels for PNALD Patients during the first 28 days of Treatment

Patient ID	Treatment arm	Study Day first qualifying elevation	Direct bilirubin level	Study day second qualifying elevation	Direct bilirubin level
(b) (6)	IL	28	5.4	35	**10.4**
	IL	30	2.1	36	2.6
	IL	25	3.2	28	4.7
	SL	4	2.7	11	4.5
	SL	14	3.7	21	2.3

(adapted from table 16.2.9.1)

We reviewed the data provided by the sponsor in Listing 16.2.9.1, "Conjugated Bilirubin levels for PNALD Patients during the first 28 days of Treatment," and Listing 16.2.9.2, "Conjugated Bilirubin levels > 2.0 mg/dL." The table below shows the Division of Hepatology and Nutrition's (DHN) adjudication of the parenteral nutrition-associated cholestasis (PNAC) cases that occurred in SMOF-018-03 (refer to listing 16.2.9.2 "Conjugated Bilirubin levels > 2.0 mg/dl"). The "carrot" symbol indicates cases that DHN concluded met the case definition that were not counted by the Applicant. Intralipid-treated patients (b) (6) and (b) (6) had a second qualifying direct bilirubin elevation measured more than seven days after the initial measurement, 21 days and 14 days later, respectively. To DHN, the measurement of elevated direct bilirubin greater than 7 days later strengthens the likelihood of these patients having PNAC rather than diminishing the likelihood.

DHN does not consider Smoflipid-treated patient (b) (6) to have a case of PNAC. Patients must be treated with parenteral nutrition for at least 14 days to qualify as having PNAC. Patient (b) (6) was diagnosed on day 4 of treatment. Finally, Smoflipid-treated patient (b) (6) had a direct bilirubin measured at 2.2 on day 15, and the level measured 6 days later was 2. DHN is counting this as a case.

Table 17. Cases of PNAC in Study SMOF-018-03

Patient ID	Treatment arm	DHN adjudication of PNAC cases	FK PNAC cases	Study Day 1st qualifying elevation/ Direct bilirubin level (mg/dL)	Study day 2nd qualifying elev/ Direct bilirubin level (mg/dL)
(b) (6)	IL	*	*	25/3.2	28/4.7 39/3.2
	IL	*	*	28/5.4	35/10.4
	IL	*	*	30/2.1	36/2.6
	IL	^		34/4.3	55/5.9
	IL	X	X	44/4.4	46/3.1 50/4.3
	IL	X	X	49/3.5	53/2.5
	IL	X	X	49/2.4	55/2 62/2 76/2.2
	IL	^		64/2.7	78/2.1
	IL	X	X	69/3.2	77/3.1
	SL	Not a case	*	4/2.7	11/4.5
	SL	*	*	14/3.7	21/2.3
	SL	^		15/2.2	21/2

*cases counted in first 28 days; X cases counted in 29-84 days; ^DHN additional cases

(adapted from Listing 16.2.9.2)

Overall, it is clear that more patients in the Intralipid arm developed a direct bilirubin level of > 2mg/dL, than in the SMOFlipid arm. Additionally, Intralipid patients developed elevated direct bilirubin levels with cumulative exposure. Only two SMOFlipid patients developed increased direct bilirubin levels after two weeks of SMOFlipid exposure, and one of those patients died, which raises concerns of an intercurrent illness contributing to the cholestasis. The Intralipid arm shows a consistent trend of patients developing cholestasis in all three months of the study. The results of the study indicate that cumulative exposure to Intralipid leads to more cholestasis than cumulative exposure to SMOFlipid does.

Literature Review

To investigate post-market findings of PNAC associated with SMOFlipid, FK conducted and submitted the findings of a literature review. The review was evaluated thoroughly by the

Division of Epidemiology (DEPI) who conducted a literature search and identified additional articles.

Neonates

The literature findings of FK's and DEPI literature search that included neonates were evaluated by the Office of Pediatric Therapeutics (OPT). The OPT medical officer concluded that in the identified 15 RCTs of neonates receiving SMOFlipid vs. Intralipid, a similar incidence of PNAC was reported in most (9/15) trials. In the remaining six trials SMOFlipid-treated patients had slightly decreased (3/15) or decreased (3/15) PNAC compared to Intralipid-treated patients. No trial reported Intralipid as having less PNAC than SMOFlipid.

Twelve observational studies were identified comparing SMOFlipid to Intralipid. A lower incidence of PNAC in SMOFlipid-treated patients compared to Intralipid-treated patients was reported in 8/12 studies. There was no difference in 3/12, and in 1/12, the Intralipid group had a lower incidence of PNAC. The literature most often supports that in neonates SMOFlipid is less likely to cause PNAC than Intralipid.

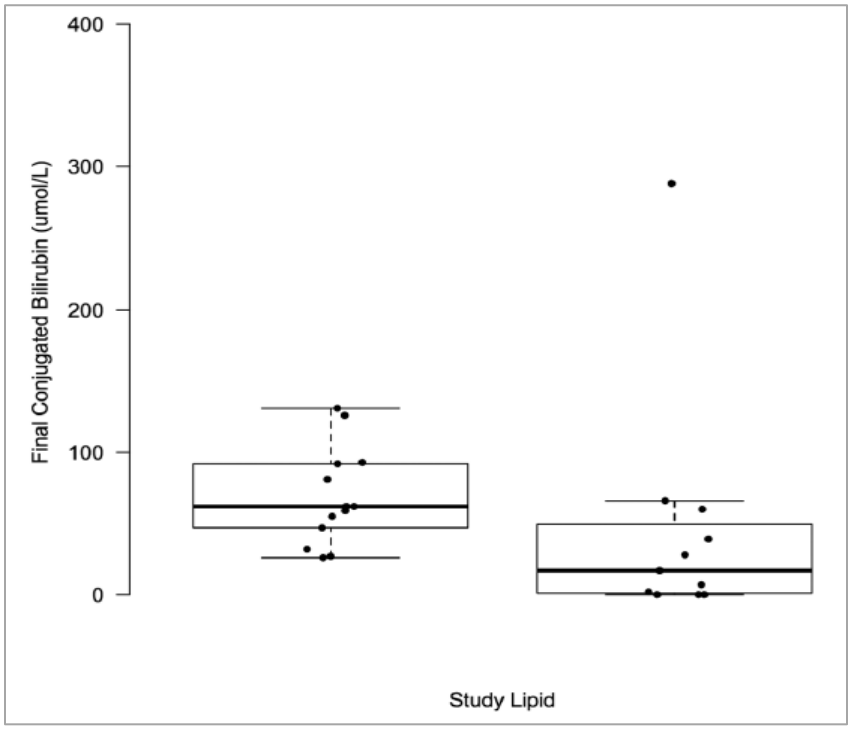
Older children

In a search for published studies involving literature reports in in patients older and other than neonates, FK identified 9 reports, DEPI identified an additional three. Two studies that provided more robust data are summarized below.

Diamond 2017[30], was a 12-week randomized clinical trial performed in Canada. It was a small, 12-weeek that enrolled 26 PN-dependent children who were less than 24 months old and had with early hepatic dysfunction. Thirteen patients received were receiving SMOFlipid, and 13 received Intralipid. Diamond followed 11 SMOFlipid patients (ages 4.3-8.7 months and mean 5.5 weeks on PN before entry) and 13 Intralipid patients (ages 3.5-7.2 months and mean 4.4 weeks on PN before entry) for up to 12 weeks (follow-up discontinued on full enteral tolerance or progression of liver disease). Follow-up through end of study (EOS) showed conjugated bilirubin values lower in the SMOFlipid-treated patients as compared to the than Intralipid-treated patients.

[30] Diamond IR, Grant RC, Pencharz PB, et al. Preventing the progression of intestinal failure-associated liver disease in infants using a composite lipid emulsion: a pilot randomized controlled trial of SMOFlipid. JPEN J Parenter Enteral Nutr. 2017;41(5):866-877

Figure 3. Diamond 2017: Conjugated bilirubin levels in soybean oil vs SMOFlipid-treated patients.

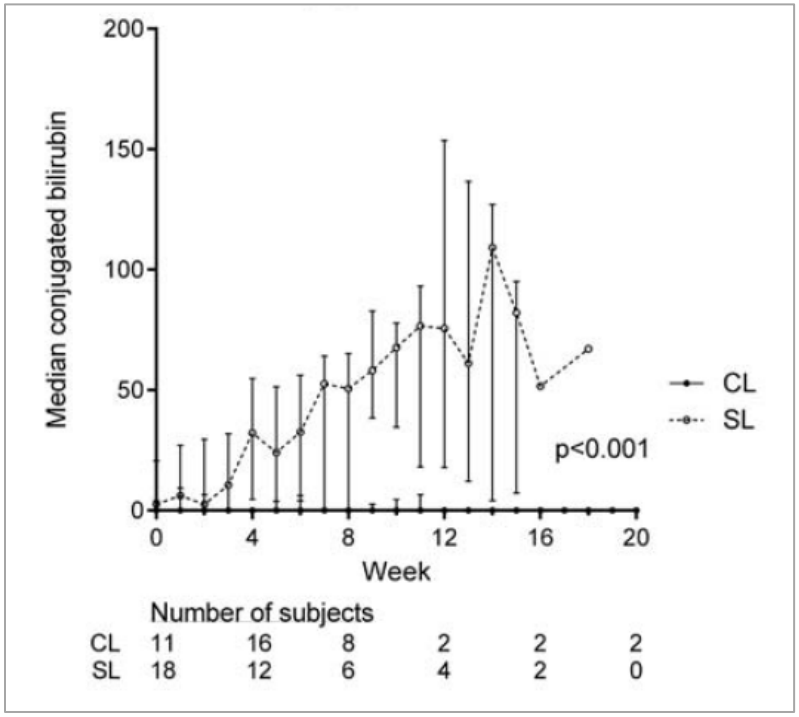


Source: Figure 3 in Diamond 2017.
Conjugated bilirubin values (µmol/L) in 13 Intralipid patients (left-hand box plot) and 11 SMOFlipid patients (right-hand box plot).

Lam 2018[31] prospectively enrolled and followed 20 pediatric patients, with a median age of 0.6 months, interquartile range, IQR, 0.1-28 months) at The Hospital for Sick Children in Toronto, Canada, for 20 weeks. The enrollment criteria included treatment with SMOFlipid for ≥4 weeks. For comparison, Lam 2018 used patient charts to retrospectively identify an historical cohort (2000-2013) that included 20 age- and primary-diagnosis-matched children exposed to SL [soy-lipid] emulsion for a similar duration of time." Figure 4 shows the median conjugated bilirubin over time in each of the two treatment arms. The dotted line represents patients on soybean oil- (SO) based ILE (Intralipid [SL]),), which shows elevations throughout all quartiles of the study. In contrast, SMOFlipid patients (CL), represented by the solid line, showed fewer incidences of elevated bilirubin elevation.

[31] Lam CKL, Church PC, Haliburton B, et al. Long-term exposure of children to a mixed lipid emulsion is less hepatotoxic than soybean-based lipid emulsion. J Pediatr Gastroenterol Nutr. 2018;66(3):501-504.

Figure 4. Lam 2018: Conjugated bilirubin levels in SMOFlipid vs. Intralipid Patients



Conjugated bilirubin (µmol/L), medians and interquartile ranges, in pediatric patients on SMOFlipid (CL) or Intralipid (SL)
SOURCE: Figure 4 in Lam 2018.

These two clinical trials provided some additional evidence supporting final lower conjugated bilirubin levels in SMOFlipid-treated patients than Intralipid-treated patients.

EFAD
EFAD can occur in patients receiving PN when inadequate levels of fatty acids are provided. As described in section 2.1, EFAs must be acquired from sources of nutrition, and deficiency can lead to impaired neurocognitive development with permanent sequelae in neonates and children. Because essential fatty acids are a critical component of nutrition, EFAD can be categorized as an efficacy as well as a safety issue. For the purposes of this review, we have categorized EFAD as an efficacy concern. (Refer to section 5.1.2.)

5.2.6. Specific Safety Studies/Clinical Trials

In the pooled analysis of all four pediatric trials, the incidence of adverse events was similar between treatment groups. Safety was measured by obtaining routine blood panels, including complete blood count, liver function studies, C-reactive protein, and serum triglyceride levels, and on the basis of SAES and TEAES. In the three original pediatric trials, AES, TEAEs, and hematologic evaluations were similar.

Table 18. Overview of Adverse Events in the Pooled Analysis-All Pediatric Patients

Category	Smoflipid (N=87), n (%)	Intralipid (N=85), n (%)
Any adverse event	46 (52.9)	48 (56.5)
Any treatment-emergent adverse event	38 (43.7)	42 (49.4)
Any related treatment-emergent adverse event	6 (6.9)	9 (10.6)
Any serious adverse event	6 (6.9)	5 (5.9)
Any serious treatment-emergent adverse event	4 (4.6)	4 (4.7)
Any related serious treatment-emergent adverse event	0	1 (1.2)
Any treatment-emergent adverse event leading to temporary discontinuation of study treatment	3 (3.4)	5 (5.9)
Any treatment-emergent adverse event leading to study withdrawal	4 (4.6)	2 (2.4)
Death	2 (2.3)	2 (2.4)

The pooled analyses included Studies 00-SMOF-004, 03-SMOF-005, and 00-SMOF-002.
Source: ISS TABLE 66

The primary endpoint of SMOF-018-CP3, a safety endpoint, was conjugated bilirubin > 2 mg/dL (PNAC) during the first 28 days of study treatment. In the SMOFlipid arm, a total of 2/83 (2.4%) and 3/78 (3.8%) of SMOFlipid and Intralipid patients, respectively, reached the primary endpoint. Of particular interest, only two patients in the SMOFlipid group developed PNAC, and both did so within the first 28 days of the trial. In the Intralipid group, six patients, in addition to the three in the first month of the trial, developed PNAC.

TEAEs were equivalent in both treatment arms. Hematologic investigations were the most common, in 29 (45%) and 29 (37%) of SMOFlipid and Intralipid patients, respectively, with an increase in gamma-glutamyl transferase increased being the most reported in both groups. Gastrointestinal disorders were reported in 27 (33%) and 31 (40%) of SMOFlipid vs Intralipid patients, with vomiting being the most common in both groups. Two patients died during the study, neither death was attributable to the study drug.

Table 19. Summary of Common Treatment-Emergent Adverse Events Reported in Study SMOF-018-CP3- Safety Analysis Population

MedDRA System Organ Class Preferred Term	Smoflipid (N = 83)		Intralipid (N = 78)	
	n (%)	Events	n (%)	Events
Any Treatment-Emergent Adverse Event	59 (71.1)	328	55 (70.5)	357
Blood and Lymphatic System Disorders	19 (22.9)	22	26 (33.3)	39
Anaemia	4 (4.8)	5	8 (10.3)	11
Anaemia neonatal	15 (18.1)	16	17 (21.8)	20
Cardiac Disorders	5 (6.0)	6	6 (7.7)	8
Tachycardia	3 (3.6)	3	4 (5.1)	6
Gastrointestinal Disorders	27 (32.5)	81	31 (39.7)	77
Abdominal distension	7 (8.4)	8	3 (3.8)	3
Abdominal pain	4 (4.8)	4	5 (6.4)	6
Constipation	7 (8.4)	9	7 (9.0)	7
Diarrhoea	3 (3.6)	4	4 (5.1)	8
Gastrooesophageal reflux disease	5 (6.0)	5	7 (9.0)	7
Vomiting	15 (18.1)	27	16 (20.5)	25
Hepatobiliary Disorders	9 (10.8)	9	11 (14.1)	11
Cholestasis	7 (8.4)	7	9 (11.5)	9
Investigations	29 (34.9)	59	29 (37.2)	87
Bilirubin conjugated increased	3 (3.6)	3	7 (9.0)	8
Blood alkaline phosphatase increased	1 (1.2)	1	6 (7.7)	7
C-reactive protein increased	6 (7.2)	8	7 (9.0)	7
Cardiac murmur	1 (1.2)	1	4 (5.1)	4
Gamma-glutamyltransferase increased	10 (12.0)	10	11 (14.1)	12
Hematocrit decreased	2 (2.4)	2	5 (6.4)	6
Metabolism and Nutrition Disorders	17 (20.5)	31	12 (15.4)	23
Hyperkalaemia	5 (6.0)	7	2 (2.6)	2
Hyponatraemia	7 (8.4)	8	1 (1.3)	1
Respiratory, Thoracic and Mediastinal Disorders	12 (14.5)	26	11 (14.1)	21
Tachypnoea	6 (7.2)	7	2 (2.6)	2

MedDRA = Medical Dictionary for Regulatory Activities (version 23.0)
Common treatment-emergent adverse events were those events reported ≥5 patients in either treatment group.
Since a patient may have experienced more than one event within a system organ class, the sum of the patients for the individual preferred terms may exceed the total for the system organ class.
A system organ class was included only if at least one preferred term within the system organ class was reported in ≥5 patients in either treatment group.
Source: STUDY SMOF-018-CP3 CSR TABLE 14.3.1.3a

5.2.7. Additional Safety Explorations

Leachables/Extractables

The pharmacology/toxicology (pharm/tox) team determined that the leachable/extractable studies done for the original SMOFlipid NDA were actually conducted (b) (4)

Concerns about the leachable/extractable profile of SMOFlipid arose (b) (4)

On September 30, 2021 DHN requested the results of all of the available leachables data for the finished marketed SMOFlipid product in the (b) (4) container. Upon receipt of the requested data, DHN determined that the submission represented a major amendment. On October 27, 2021, DHN issued a letter to FK notifying them that the review clock was extended by three months (new PDUFA date: March 22, 2022).

The estimated maximum exposure to (b) (4) from SMOFlipid 20% in adult and pediatric patients markedly exceeds the currently accepted permitted daily exposure.[32] Based on the evaluation and recommendations of the pharmacology/toxicology team, we have issued PMR 4240-3 for a 3-month intravenous toxicology study in rats to assess the safety and potential exposure to (b) (4) in SMOFlipid 20%. In addition, we have issued PMR 4240-2 for a twenty-eight-day intravenous dose-range finding toxicity study of (b) (4) (leachable) in rats to provide a rationale for dose selection for the three-month rat toxicity study (PMR 4240-3).

Pediatrics and Assessment of Effects on Growth

See section 5.1.3. Assessment of Efficacy Across Trials.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

A 55-day old patient had an accidental overdose on day-15 which occurred as a result of a mechanical infusion pump error. The event was of moderate intensity. On the same day the patient was diagnosed with blood triglycerides increased, irritability, rash erythematous, acidosis, and tachycardia which were all considered to be related to the study treatment. The patient was treated with intravenous saline, the remedial therapy of accidental overdose. The study treatment was interrupted due to this event. The event resolved on the same day.

[32] David Joseph, PhD. NDA 207648/S-005, pharmacology/toxicology review. March 18, 2022.

5.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

DHN requested assistance in assessing the postmarket experience with SMOFlipid by consulting:

1. The Division of Epidemiology 1 (DEPI): The DEPI reviewer assessed the systematic literature review presented in the submission and identified literature from the pediatric setting that was not specific to the neonatal period. The DEPI reviewer identified four additional RCTs, two of which enrolled neonates, and eight additional observational studies (five of which appear to have been published possibly after FK conducted its search), two of which enrolled neonates. The DEPI reviewer concluded that the sponsor (a) submitted a complete and truthful literature presentation which compared SMOFlipid with another ILE; and (b) the evidence from published studies of SMOFlipid use in infants, children, and adolescents (non-neonatal population) summary is not robust enough to support it being added to labeling.

2. The Office of Pediatric Therapeutics (OPT), OCPP/OC: The OPT medical officer reviewed FK's literature review and the additional studies identified by DEPI. The reviewer described DEPI's literature search as being more expansive but materially consistent with the FK's review of neonatal studies. In the opinion of the reviewing medical officer, SMOFlipid was associated with similar or slightly less PNAC than other LEs. Neonates receiving SMOFlipid fared similarly to those receiving other LEs with regard to mortality and growth parameters, but SMOFlipid may have a had slightly better effect on growth.

3. The Division of Pharmacovigilance (DPV): Because the published literature had limited information about EFAD in pediatric patients treated with SMOFlipid, DHN requested that DPV search the FDA Adverse Events Reporting System for cases of EFAD. The DPV reviewer searched the FAERS database and the medical literature and identified 10 cases of EFAD, eight of which occurred in pediatric patients. Six of the ten cases (60%) met Tier 1 diagnostic criteria , i.e., physical findings of EFAD such as skin manifestations, a Holman Index of > 2, or both. The median time-to-onset among the eight cases reporting this information was 38 days, ranging from 14 to 420 days. Of the 10 cases, 6 received the age-appropriate doses of SMOFlipid, 3 were underdosed, and 1 did not report the dose. Based on this evidence, prescribers and patients receiving SMOFlipid should be aware of the associated risk of EFAD.

Fresenius Kabi Review of Postmarket Safety

As part of the pediatric efficacy supplement submission, FK summarized the postmarket safety of SMOFlipid in the Summary of Clinical Safety. Since first registration of the product in February 2004, approximately 46.2 million patient days were calculated for Smoflipid (based on an estimate of 500 mL/day).

FK provided the following summary:

From first launch in 2004 through 28 February 2021, a total of 395 adverse drug reactions (ADRs) in 200 pediatric patients were reported from spontaneous/authority reports or from literature. Of these ADRs, a total of 119 in 77 pediatric patients were reported to be serious (both listed and unlisted).

The most common SOCs included the following:

- Injury, Poisoning and Procedural Complications (131 ADRs in 105 patients),
- General Disorders and Administration Site Conditions (55 ADRs in 52 patients),
- Investigations (52 ADRs in 38 patients),
- Infections and Infestations (39 ADRs in 28 patients), and
- Metabolism and Nutrition Disorders (38 ADRs in 33 patients).

The most common preferred terms to which ADR terms were assigned (excluding no adverse event and off label use including drug use in unapproved populations) included the following:

- Blood triglycerides increased (including the preferred terms blood triglycerides increased and hypertriglyceridemia; 17),
- Sepsis (including the preferred terms bacterial sepsis, device related sepsis, Klebsiella sepsis, sepsis neonatal, sepsis, septic shock, and pseudomonal sepsis; 17),
- Essential fatty acid deficiency (11),
- Bilirubin conjugated increased (including the preferred terms blood bilirubin increased and bilirubin conjugated increased; 11),
- Rash (including the preferred terms rash and rash maculo-papular; 10),
- Cholestasis (including the preferred terms cholestasis and neonatal cholestasis; 9), and
- Hypersensitivity (including the preferred terms drug hypersensitivity and hypersensitivity; 8).”

The information provided by FK about the postmarket safety experience of SMOFlipid does not identify any AEs that are unexpected based on the review of the FK-sponsored clinical trials and the published literature.

Expectations on Safety in the Postmarket Setting

SMOFlipid has been used off-label in pediatric patients since it was approved in adults in 2016. Additional safety data in pediatric patients about EFAD and PNAC, particularly with long-term exposure, will be of benefit to prescribers and patients.

5.2.9. Integrated Assessment of Safety

The FK-sponsored studies of SMOFlipid were of short duration, with most data being collected on patients with 28 days or less of exposure. The three pediatric studies submitted with the original SMOFlipid NDA, of 1-4 weeks duration, showed that SMOFlipid's safety profile was equivalent to that of Intralipid. Study SMOF-018-CP3, which lasted for 84 days, demonstrated that patients with longer term exposure to SMOFlipid had less PNAC than those exposed to Intralipid, especially in the 29-84 day period.

The findings of the literature review, submitted by FK and evaluated by Dr. Joel Weissfeld of DEPI and Dr. Gerri Baer of OPT, are consistent with that of the clinical trials. The postmarket information evaluated by the review team indicates that SMOFlipid has similar efficacy to soy-based ILE in premature infants but is less likely to cause PNAC. EFAD has been observed in pediatric and adult patients receiving SMOFlipid; however, the short duration of previously conducted studies could not assess the risk of EFAD with prolonged SMOFlipid exposure.

5.3. Conclusions and Recommendations

SMOFlipid has been used extensively off-label in the pediatric population since being approved for adult use in July 2016 which has generated meaningful postmarket information. Based on the results of company-sponsored studies, published studies, and postmarket safety assessment, SMOFlipid does not pose safety risks in the pediatric population which are greater than those observed with soybean-based ILEs that are approved for pediatric use. Measured safety parameters such as AESI and rates of sepsis are similar between SMOFlipid and 100% soybean-based ILEs.

PNALD occurs in ≥ 85% of neonates receiving prolonged parenteral nutrition.[33] Based on the totality of evidence, SMOFlipid is less likely to cause PNAC in neonates than 100% soy-based ILEs. EFAD, also a concern with prolonged ILE use, is not associated with SMOFlipid more than with other soybean-based ILEs, based on clinical trials of short duration. However, routine screening for PNAC and EFAD, along with other measures of safety, should be performed.

[33] Huff, K.A., Breckler, F., Cruse, W., Szeszycki, E. and Vanderpool, C. (2021), Pediatric Smoflipid Therapy: Patient Response and Safety Concerns. Journal of Parenteral and Enteral Nutrition, 45: 792-799. https://doi.org/10.1002/jpen.1929

Although there remains a potential safety concern about the toxicity of (b) (4) an impurity identified in leachable/extractable studies, the benefits of SMOFlipid in the pediatric population due to the documented lower risk of PNAC compared to the 100% soy-based ILEs outweigh the potential risk of toxicity from (b) (4) Postmarket requirements will be issued to assess the toxicological risk of this impurity. (See section 8).

6 Pediatrics

This is a pediatric efficacy study. Refer to the review.

7 Labeling Recommendations

7.1. Prescription Drug Labeling

The Applicant submitted draft Prescribing Information (PI) for SMOFlipid. During the review cycle the PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

The following table summarizes the main revisions to the SMOFlipid labeling based on DHN's review of the pediatric efficacy supplement.

Table 20. FDA Revisions to the Prescribing Information

Section	Section Title	FDA Recommendations and Rationale
	(b) (4)	• Removed (b) (4) for "Death in Preterm (b) (4)," because this risk occurred in patients treated with 100% soybean oil-based lipid emulsions at an infusion rate higher than what is recommended for SMOFlipid • Maintained in Warnings and Precautions
1	Indications and Usage	• Added the pediatric population to the indication • Removed (b) (4)
2	Dosage and Administration	• Reorganized important administration instructions (2.1) and preparation instructions (2.2) • Added dosage regimens for pediatric patients (2.3)
3	Dosage Forms and Strengths	• Aligned format with the "How Supplied" section of the PI

5	Warnings and Precautions	• Updated information about parenteral nutrition-associated liver disease (PNALD) to align with findings from the mostly recently conducted clinical study, post-market reporting, and literature findings (5.1) • Combined the W/P sections for PNALD and hepatobiliary disorders because the concepts are related and to decrease redundancy (5.1) • Changed monitoring "(b) (4)" to "liver tests" to be more encompassing of the types of tests that may be conducted to assess signs of liver injury (5.1) • Revised Section (5.2), it is now "Death in Preterm Neonates" and advises monitoring patients for pleural and pericardial effusion. Monitoring for pleural and pericardial effusion was included in the Omegaven labeling (100% fish oil-based ILE), and SMOFlipid has 15% fish oil • Added contraindication to SMOFlipid use in patients with known hypersensitivity to the ingredients of SMOFlipid (5.3) • Changed (b) (4) Infections" to "Infections" (5.4) • Clarified that lipid emulsions are an independent risk factor for catheter-related infections and removed reference to (b) (4) (5.4) • Included hypertriglyceridemia and parameters for contraindication, comorbidities of concern, parameters for monitoring and dose adjustment (5.7) • Updated information about essential fatty acid deficiency (EFAD) to align with findings from the most recently conducted clinical study, postmarket reporting, and literature findings (5.9)
6	Adverse Reactions	• Included pediatric study data about parenteral nutrition-associated cholestasis (PNAC) and EFAD from the most recent sponsor-conducted study in pediatric patients (6.1) • Added a Kaplan-Meier curve reflecting the time

		frame of cases of PNAC that occurred during SMOF-018-CP3 (6.1) • Added a common AE table for the pediatric age group (6.1)
7	Drug Interactions	• Changed concomitant use of [redacted] (b) (4) to warfarin as a reason for increased monitoring for anticoagulant activity.
8	Use in Specific Populations	• Updated "Risk Summary," stating that the use of the recommended dose of SMOFlipid is not expected to cause adverse maternal or fetal outcomes (8.1) • Updated "Risk Summary," citing that literature findings support that the recommended dose of SMOFlipid is not expected to cause harm to a breastfed infant (8.2) • Referenced findings from three pediatric studies that support the use of Smoflipid in neonates (8.4) • Included a statement that the use of Smoflipid in older pediatric patients is supported by evidence from a short-term study in pediatric patients and additional evidence from studies in adults. (8.4) • Recommended monitoring pediatric patients for laboratory evidence of EFAD because they may be particularly vulnerable to neurologic complications. (8.4)
10	Overdosage	• [redacted] (b) (4) " Information moved to section 5.7.
11	Description	• Clarified mean concentrations of essential fatty acids
12	Mechanism of Action	• Added pharmacodynamics subsection to meet the requirements of 21 CFR 201.57(c)(13)(i)(B). (12.2)
14	Clinical Studies	• Added Pediatric Clinical Studies subsection (14.2)
15	References	• Deleted section, considered extraneous
17	Patient Counseling Information	• Revised format to conform to that recommended in *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2014).

8 Postmarketing Requirements and Commitment

1. Fulfill PREA PMR 3002-1.
2. Release PREA PMR 3002-2 because the randomized controlled trial (RCT) comparing SMOFlipid to Intralipid was impracticable based on FK's inability to sign up centers to participate in the trial and enroll patients in the centers that did sign up to participate.
3. Release FDAAA PMR 3002-8 required with the original SMOFlipid approval to study EFAD and PNALD in adults. Although the final protocol submission is not due until July 2022, we anticipate similar difficulties enrolling this RCT as were observed with 3002-2.
4. Require as a new FDAAA PMR, a single-arm open-label safety study of SMOFlipid in patients anticipated to need 8 weeks or longer of PN treatment to monitor for EFAD and PNAC. This trial will include pediatric patients older than one month (equal numbers 1 month-2 years; 2-11 years; 11-17 years) and adults
5. Require nonclinical toxicology studies to characterize the potential safety risks of (b) (4)
    a. Dose ranging study- 28-day IV tox study in rats
    b. 3-month IV tox study in rats

9 Deputy Director for Safety Comments

Fresenius Kabi submitted a pediatric efficacy supplement for SMOFlipid on June 22, 2021. The data upon which the assessment of benefit and risk of SMOFlipid use in pediatric patients included four pediatric trials and a review of published trials of SMOFlipid use in the pediatric population. Three of the four trials (two in neonates, one in older children; all 1-4 weeks duration) were included with the original NDA submission. SMOFlipid was not approved for the pediatric population with the original NDA because the Division felt there was inadequate data to support the efficacy and safety in this age group. The new trial (SMOF-018-CP3) that was submitted with this efficacy supplement was conducted to address PREA PMR 3002-1, intended to study PNAC in the neonatal population, as well as measure anthropometric endpoints and assess for EFAD (see 3.1 for full text of the PMR).

As described in section 5.2.5 above, the incidence of PNAC in SMOF-018-CP3 in the SMOFlipid arm was substantially lower than the Intralipid arm. There were no PNAC cases in SMOFlipid-treated patients after day 15, whereas the earliest PNAC case with Intralipid was at day 25, and several cases occurred subsequent to that time point. These later occurring cases comport with the understanding of PNAC as increasing in incidence with longer duration of PN treatment. Figure 1 below that is being added to Section 6.1 of the SMOFlipid labeling displays the cumulative incidence curves of time to PNAC for the SMOFlipid and Intralipid (Soybean Oil) treatment arms. There is increasing uncertainty in the estimate of the cumulative incidence as

fewer patients are at risk later in the trial, and we have requested that FK add standard error bars at 20-day intervals.

Figure 5: Cumulative Incidence Curve of Time to Parenteral Nutrition-Associated Cholestasis (PNAC)

EFAD was monitored for in, and there were no treatment-emergent clinically meaningful cases in the first 28 days of the trial. No clinically meaningful cases were observed subsequent to that (29-84 days), but relatively few patients continued in the trial so there was little opportunity to observe EFAD. A DPV review of EFAD cases in the FDA Adverse Event Reporting System showed a median time to event for EFAD of 38 days in the eight cases that reported a time to event, so it may just be that there were not enough patients followed for long enough to observe EFAD if it was going to happen.

When SMOFlipid was approved for adults in July 2016, a second PREA PMR (3002-2) was issued to focus on measuring PNAC and EFAD in children older than 3 months who were expected to need 90 days of PN (see 3.1 for full text of the PMR). This trial was not able to enroll patients for a variety of reasons, but most significantly because patients were able to get SMOFlipid off-label, and families did not want their child randomized and risk getting Intralipid. There were also some logistical difficulties because many patients were getting home PN. In February 2021, FK submitted a meeting request to discuss changing the trial to a single arm, open label safety

study of SMOFlipid in the same population. PeRC recommended that FK get a deferral extension for that trial so that FDA could have time to review the pediatric efficacy supplement, including SMOF-018-CP3.

Based on the review of the supplement, including the limited data on EFAD in patients treated longer than 28 days, the Division has determined that a PMR is still needed to assess EFAD and PNAC in pediatric patients older than 1 month who receive a longer duration of PN (at least 8 weeks). However, we recognize that the RCT required in PREA PMR 3002-2 is impracticable. Additionally, at the time SMOFlipid was approved, a FDAAA (FDA Amendments Act of 2007) PMR was issued to assess EFAD and PNALD in adults as follows:

3002-8 Randomized clinical trial comparing SMOFLIPID (lipid injectable emulsion) to another standard-of-care IV lipid emulsion, evaluating long-term risk of developing essential fatty acid deficiency (EFAD) and parenteral nutrition associated liver disease (PNALD) in adult patients receiving chronically-administered total parenteral nutrition (TPN). Plasma phytosterol levels should be assessed in patients using validated analytical assay methods developed under PMR 3002-5.

With the following milestone schedule:

Final Protocol Submission: 07/2022
Study Completion: 01/2025
Final Report Submission: 01/2026

Given the experience with PREA PMR 3002-2, DHN anticipates that FK will run into the same enrollment problems with the adults as they did with the children.

Therefore, at the time of approval of the SMOFlipid pediatric efficacy supplement, DHN will release PREA PMR 3002-2 and FDAAA PMR 3002-8. In place of these trials we will require as a new FDAAA PMR, a single-arm open-label safety study of SMOFlipid in patients anticipated to need 8 weeks or longer of PN treatment to monitor for EFAD and PNAC. This trial will include pediatric patients older than one month (equal numbers in the following age groups: 1 month-2 years; 2-11 years; 11-17 years) and adults.

As noted in section 5.2.7, in the safety assessment of the organic leachables (or impurities) and the elemental impurities detected in the migration studies for SMOFlipid, the pharmacology/toxicology identified a single deficiency that needs to be addressed. Specifically, FK has not provided sufficient data or relevant information to support a safety assessment of (b) (4) which FK proposes to be a degradant of lipids. Therefore, a 3-month intravenous toxicology study of (b) (4) in rats is needed. Because DHN has determined that the benefits of SMOFlipid use in pediatric patients outweighs the risks, including this potential risk of toxicity from (b) (4), we will issue a PMR for a 3-month intravenous toxicology study of (b) (4) in rats to characterize its potential safety risks. In addition, to assure that

appropriate dose selection is used for the 3-month toxicity study in rats, we will also issue a PMR for a 28-day intravenous dose-ranging study in rats.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARI N BLACKBURN
03/21/2022 04:17:16 PM

JUDITH A RACOOSIN
03/21/2022 04:23:40 PM
I concur, as summarized in the Deputy Director for Safety Comments (Section 9).