# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | NDA 207648/S-005 (IND 102137) |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA207648\0089 |
| **Submission Date** | 6/22/2021 |
| **PDUFA goal date** | 3/22/2022 (with a 3-month extension) |
| **Submission Type** | Efficacy Supplement |
| **Brand Name** | Smoflipid 20% |
| **Generic Name** | A mixture of soybean oil (6%), median chain triglycerides (MCTs) (6%), olive oil (5%) and fish oil (3%) |
| **Dosage Form and Strength** | Lipid Injectable Emulsion |
| **Route of Administration** | Intravenous Infusion |
| **Proposed Indication** | A source of calories and essential fatty acids for parenteral nutrition (PN) used in pediatric population when oral or enteral nutrition is not possible, insufficient, or contraindicated |
| **Proposed Dosing Regimen** | Neonates and Infants (b) (4)<br>0.5 to 1 g/kg/day followed by successive increase of 0.5 to 1 g/kg/day up to 3 g/kg/day<br><br>Children (2 to <12 years of age):<br>1 to 2 g/kg/day followed by successive increases of 0.5 to 1 g/kg/day up to 3 g/kg/day<br><br>Adolescents (12 to <17 years of age):<br>1 to 2 g/kg/day and should not exceed 2.5 g/kg/day |
| **Applicant** | Fresenius Kabi |
| **OCP Division** | DIIP |
| **OND Division** | DHN |
| **OCP Reviewer** | Qianni Wu, PharmD |
| **OCP Team Leader** | Insook Kim, PhD |

# 1. EXECUTIVE SUMMARY

Smoflipid 20% (NDA 207648/Original 1) was initially approved under 505(b)(1) pathway on July 13, 2016, for use 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. The Applicant submitted this efficacy supplement with a clinical study report (SMOF-018-CP3) on hospitalized neonates/infants to support expanding the indication, dosing and labeling in pediatric population for age groups from birth to 17 years old. The Applicant proposed to fulfill Pediatric Research Equity Act (PREA) Post Marketing Requirement (PMR) 3002-1.

The Clinical Pharmacology review of this supplement focused on evaluating the adequacy of the bioanalytical methods and in-study analysis of PK data (i.e., fatty acids in plasma and phytosterols in plasma) to support the evaluation of essential fatty acid profiles and phytosterol levels from Study SMOF-018-CP3 to address PREA PMR 3002-1.

In Study SMOF-018-CP3, the Applicant measured plasma fatty acids: linoleic acid (LA), α-linolenic acid (ALA), mead acid (MA), eicosapentaenoic acid (EPA), arachidonic acid (ARA), and docosahexaenoic acid (DHA) at baseline and after 28 days of treatment using adequately validated bioanalytical assay methods. After 28-day treatment with Smoflipid 20%, the mean plasma concentrations of EPA and DHA increased from baseline by 205% and 83% respectively, while the mean plasma concentrations of ARA, LA and ALA decreased from baseline by 42%, 21% and 13%, respectively. The Holman Index, also known as triene:tetraene (T:T) ratio, was calculated as a ratio between MA and ARA and did not show a significant change from baseline following 28-day treatment with Smoflipid (mean T:T ratios at baseline and at the end of initial treatment Phase were 0.033 and 0.024, respectively). Refer to the Clinical Review for the clinical meaning of the T:T ratio.

The Applicant also measured plasma phytosterols: sitosterol, desmosterol, brassicasterol, lanosterol, ergosterol, campesterol, stigmasterol, sitostanol, lathosterol, and cholesterol, at baseline and during the treatment. Following treatment of Smoflipid 20%, phytosterol concentrations either decreased from baseline or did not change significantly. No increase in concentrations was observed for any of phytosterols measured. The bioanalytical assay method was previously reviewed and found acceptable. Refer to the review by Dr. Anand Balakrishnan in DARRTS (Reference ID:4641372).

## 1.1 Recommendations

The Office of Clinical Pharmacology found the clinical pharmacology information in this supplement acceptable provided the mutual agreement on the labeling language has been reached.

OCP determined that the assessment of plasma phytosterol levels "in patients using validated analytical assay methods developed under PMR 3002-5" required under PREA PMR 3002-1 has been fulfilled from a clinical pharmacology standpoint.

The overall decision on the fulfillment of PREA-PMR 3002-1 is deferred to the DHN.

## 1.2 Labeling Recommendation

The Applicant proposed to include the metabolism of ALA and LA worded as "alpha-linolenic acid and linoleic acid are metabolized within a common biochemical pathway through a series of desaturation and elongation steps. Downstream products of alpha-linolenic acid are EPA and DHA, and linoleic acid is

converted to arachidonic acid" in Section (b) (4). We recommend moving this content to Section 12.3 instead. Refer to approved labeling for final language.

OCP determined that plasma fatty acids concentrations were measured by adequately validated assay methods and acceptable for labeling if deemed to be included in the label.

## 2. Background

Smoflipid 20% (NDA 207648/Original 1) was initially approved under 505(b)(1) pathway on July 13, 2016 for use 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. At the same time, a Complete Response (CR) Letter was issued to NDA 207648/Original 2 for pediatric indication, in which FDA indicated that insufficient evidence in the application to determine whether Smoflipid is safe and effective in pediatric patients from birth to 16 years of age.

Two PREA PMRs 3002-1 and 3002-2 for pediatric studies were issued upon approval of the original NDA (the approval letter for NDA 207648/Original 1 dated July 13, 2016), requiring two prospective, randomized, controlled trials on hospitalized neonates/infants and pediatric patients 3 months or older, respectively. In addition, PMR 3002-5 requires a development of bioanalytical assays to assess plasma phytosterol levels in patients. The three PMRs and relevant regulatory history are listed as follows:

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**

Final Protocol Submission: 08/2015
Study Completion: 10/2018
Final Report Submission: 10/2019

- Based on the previous communications regarding PREA PMR 3002-1, the Agency agreed that the Applicant completed the Study SMOF-018-CP3 with patients enrolled

up to April 2020 and submitted the study report due to the challenge in patient recruitment and unexpected delay, based on a Type C Meeting Preliminary Comments under IND 102137 dated April 16, 2020. In addition, the Agency also agreed that genetic polymorphism in fatty acid desaturase genes FADS1 and FADS2 can be studied only in older pediatric patients in Study for PREA PMR 3002-2 based on the same meeting comments.

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 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.

Final Protocol Submission: 05/2017
Study Completion: 11/2020
Final Report Submission: 11/2021

- On February 5, 2021, the Applicant requested a release of PREA PMR 3002-2 and reissuance of a new PREA PMR containing a modified trial design to an open-label study. The Agency granted a deferral extension to May 2022 in lieu of a release and reissuance of this PREA PMR dated March 10, 2021.

3002-5 Develop and validate an appropriate analytical method for measuring phytosterol levels in plasma.

Final Report Submission: 02/2018

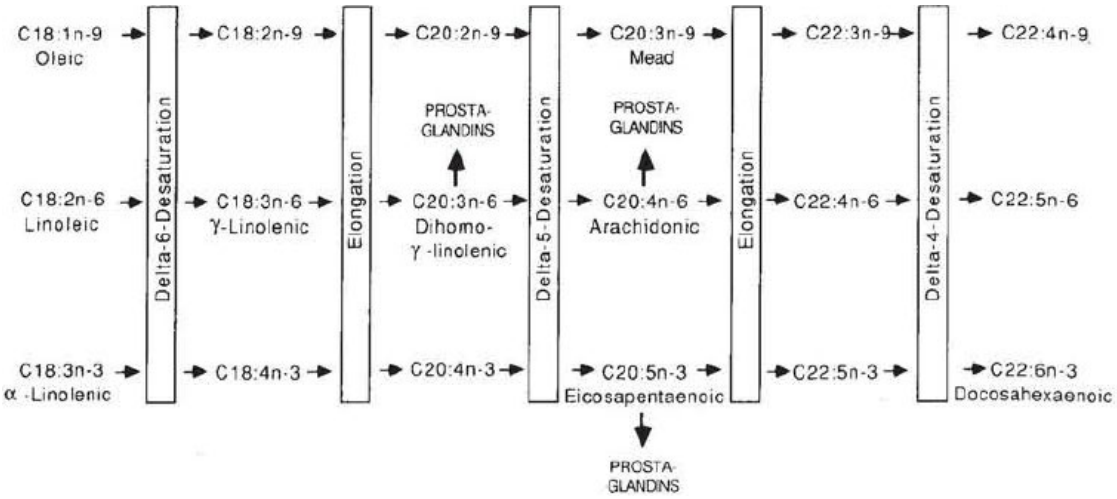
- The Applicant submitted analytical method and the associated validation reports for measurement of plasma phytosterol levels to fulfill the PMR 3002-5 dated February 28, 2018 under NDA 207648 (SDN 73). The reports were reviewed by Dr. Anand Balakrishnan dated July 15, 2020 (DARRTS Reference ID:4641372) and determined that this PMR was fulfilled, and a Fulfillment of Postmarketing Requirement Letter was sent dated Sep. 10, 2020.

## 3. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

**Smoflipid 20%**

Smoflipid 20% comprises a mixture of soybean oil (6%), medium-chain triglyceride (MCT) (6%), olive oil (5%) and fish oil (3%). Smoflipid provides a biologically utilizable source of calories and essential fatty acids. Intravenous lipid emulsions are metabolized in a similar manner as naturally occurring chylomicrons, which results in an increase of plasma triglyceride level. Triglycerides are then hydrolyzed by lipoprotein lipase in peripheral tissues to release free fatty acids ready to be taken up by cells. Fatty acids serve as an important substrate for energy production, majorly via fatty acid metabolism through beta oxidation.

The two essential fatty acids LA (omega-6 fatty acid) and ALA (omega-3 fatty acid) compete with each other and with oleic acid (OA, omega-9 fatty acid), a non-essential fatty acid, for binding to a microsomal enzyme system to allow further metabolism via desaturation and chain elongation. ALA can be metabolized into EPA and DHA. LA can be metabolized to ARA. OA can be metabolized to MA. The binding affinity to the microsomal enzyme system from highest to lowest is ALA, LA, and OA. Therefore, little OA is expected to be metabolized when ALA and LA are available.[1] See Figure 1 for metabolic pathways of these three types of fatty acids.




Source: NDA 207648/S-5 Module 2.5 Clinical Overview, pg. 7[1]

**Figure 1.** Simplified Metabolic Pathway for LA, ALA and OA.

The mean (range) essential fatty acid concentrations in Smoflipid 20% are 35 mg/mL (28 to 50 mg/mL) and 4.5 mg/mL (3 to 7 mg/mL) for linoleic acid and alpha-linoleic acid, respectively. It also contains other fatty acids including EPA (1% to 3.5%) and DHA (1% to 3.5%), both of which are equivalent to 2

[1] Koletzko B. Fats for brains. Eur J Clin Nutr. 1992;46(Suppl 1):S51-62.

to 7 mg/mL if concentrations are calculated using the total lipid concentration (i.e., 200 mg/mL) times reported fraction of each fatty acid.

**Comparison with injectable lipid emulsion products approved for pediatric patients**

Two parenteral lipid emulsion products (i.e., Intralipid (NDA 018449) and Omegaven (NDA 210589)) are approved for pediatrics. Compared to those, the essential fatty acids contents (i.e., LA and ALA) in Smoflipid 20% were around (b)(4) fold lower than those in Intralipid 20%, a soy-bean oil lipid emulsion, while at least (b)(4) fold higher than those in Omegaven, a fish oil lipid emulsion. It was also noted that both Smoflipid 20% and Omegaven contain EPA and DHA, while Intralipid does not. The contents of EPA and DHA are at least (b)(4) fold higher in Omegaven than in Smoflipid 20%.

The lower contents of LA and ALA in Smoflipid were noted during the Clinical Review for the Original Pediatric NDA application by Dr. Karyn Berry dated Dec. 24. 2015 and Dr. Berry concerned that preterm neonates who do not receive steadily increasing doses up to 3 g/kg/day may not receive adequate amount of essential fatty acids to prevent EFAD (DARRTS Reference ID: 3865529). Of note, Omegaven, the fish oil lipid emulsion that contains LA and ALA contents lower than Smoflipid, was approved in 2018 for pediatric patients down to preterm neonates with PNAC.

**Proposed dosage regimen for pediatric patients**

The proposed daily dose of Smoflipid 20% in pediatric patients is shown in Table 1.

**Table 1.** Applicant's Proposed Smoflipid 20% Dosage Recommendation For Pediatric Patients

| **Pediatric Age Groups** | **Initiation (g/kg/day)** | **Advance (g/kg/day)** | **Goal (g/kg/day)** | **Duration (hours)** |
|---|---|---|---|---|
| Preterm and term neonates and infants (birth to < 2 years old) | 0.5 to 1 | Increase by 0.5 to 1 | 3 (Max: 3) | 12-24 * |
| Children (2 to <12 years old) | 1 to 2 | Increase by 0.5 to 1 | 3 (Max: 3) | 12-24 |
| Adolescents (12 to < 17 years old) | 1 to 2 | --- | 1 to 2 (Max: 2.5) | 12-24 |

Source: adapted from Module 2.5 Clinical Overview Table 6. Max: maximum dose that should not be exceeded.
*For preterm and term neonates, infusion duration is 20 to 24 hours.

The proposed duration for infusion depends on the clinical situation. The proposed dosing is a weight-based dosing scheme consistent with total parenteral nutrition dosing rationale. The proposed lipid dosage by age is based on clinical practice, which accounts for individual baseline expenditure, activity level, energy deposition, patient's ability to eliminate the infused lipid as well as essential fatty acids requirement at different age. There is no clinical pharmacology specific information to inform the dose. We defer the acceptability of the proposed dosing regimen to the clinical review.

**Determination of Genetic polymorphisms in the fatty acid desaturase genes (FADS)**

In the PREA PMR 3002-1 and 3002-2, the genetic polymorphisms in the FADS1 and FADS2 genes were required to be assessed in a subset of population. FADS1 and FADS2 genes encode enzymes delta-5 and delta-6 desaturases, which are responsible for metabolizing LA and ALA into desaturation and elongation metabolite products, including ARA, EPA and DHA. Plasma levels of these fatty acids are modulated by endogenous metabolism and dietary intake. In the Clinolipid 20% (Olive oil 80% and Soybean oil 20%)

Clinical Review dated September 20, 2013 (NDA 204508, DARRTS Reference ID: 3375416), Dr. Klaus Gottlieb noted a highly significant association between FADS gene cluster polymorphism and fatty acids levels in serum phospholipids based on published literature and recommended that genetic polymorphism in FADS1 and FADS2 genes should be determined in an exploratory analysis to uncover possible subpopulation with altered FA metabolism and increased EFA requirements.[2]

The review team decided to re-evaluate the need of assessing genetic polymorphism in FADS1 and FADS2 genes in the future pediatric study. This reviewer performed a literature research to see if the knowledge regarding genetic polymorphisms in FADS1 and FADS2 genes has been updated since 2013. There are numerous single nucleotide polymorphisms (SNPs) identified in the human FADS gene cluster in human chromosome 11.[3] Although a large effect size of FADS gene variations on polyunsaturated fatty acids (PUFA) metabolism continues being marked, there seems no consensus reached regarding which SNP or sets of SNPs are more relevant to the altered fatty acids metabolism, as the selection of SNPs and haplotype constructions varies among different studies.[3 4 5 6 7] In addition, the distribution of genotype predicting active and inactive PUFA conversion affected by desaturase activity and/or expression level are different among various populations.[8] With a lack of consensus on the selection of SNPs and haplotype construction in addition to a possible inter-population variability in genotype frequencies, the genetic polymorphism study remains to be experimental and needs to be evaluated with an adequate sample size. This reviewer will defer to DHN regarding the decision on whether or not continuing to require such exploratory genetic polymorphism analysis on FADS1 and FADS2 genes in future clinical studies.

**Individual Study Review: Study SMF-018-CP3**

**Study design:** Study SMOF-018-CP3 was a randomized, controlled, double-blind, parallel group study on hospitalized neonates and infants who are expected to require parenteral nutrition (PN) for 28 days to compare the efficacy and safety between Smoflipid 20% and the current standard of care with Intralipid

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[2] Lattka E, Illig T, Koletzko B, Heinrich J. Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. Curr Opin Lipidol. 2010;21(1):64-69. doi:10.1097/MOL.0b013e3283327ca8.

[3] Koletzko B, Reischl E, Tanjung C, et al. FADS1 and FADS2 Polymorphisms Modulate Fatty Acid Metabolism and Dietary Impact on Health. Annu Rev Nutr. 2019;39:21-44. doi:10.1146/annurev-nutr-082018-124250

[4] Schaeffer L, Gohlke H, Müller M, et al. Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet. 2006;15(11):1745-1756. doi:10.1093/hmg/ddl117

[5] Tanaka T, Shen J, Abecasis GR, et al. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. PLoS Genet. 2009;5(1):e1000338. doi:10.1371/journal.pgen.1000338

[6] Salas Lorenzo I, Chisaguano Tonato AM, de la Garza Puentes A, et al. The Effect of an Infant Formula Supplemented with AA and DHA on Fatty Acid Levels of Infants with Different FADS Genotypes: The COGNIS Study. Nutrients. 2019;11(3):602. Published 2019 Mar 12. doi:10.3390/nu11030602

[7] Meldrum SJ, Li Y, Zhang G, et al. Can polymorphisms in the fatty acid desaturase (FADS) gene cluster alter the effects of fish oil supplementation on plasma and erythrocyte fatty acid profiles? An exploratory study. Eur J Nutr. 2018;57(7):2583-2594. doi:10.1007/s00394-017-1529-5

[8] Ameur A, Enroth S, Johansson A, et al. Genetic adaptation of fatty-acid metabolism: a human-specific haplotype increasing the biosynthesis of long-chain omega-3 and omega-6 fatty acids. Am J Hum Genet. 2012;90(5):809-820. doi:10.1016/j.ajhg.2012.03.014

20%. Patients who were eligible for this study should have at least 80% of nutritional needs met with PN at baseline.

A total of 152 neonates and 9 infants were randomized and received at least one dose in the study. The mean (SD) chronological age was 9.9 (17.67) days. The study comprised two treatment phases: the Initial Treatment Phase up to 28 days followed by the Extension Treatment Phase up to 84 days. Patients who still required injectable lipid emulsion after 28-day treatment continued into Extension Treatment Phase. The primary endpoint was the number of patients in each treatment group with conjugated bilirubin levels > 2 mg/dL during the first 28 days of study treatment, confirmed by a second sample collected 7 days after the first sample.

Initially, 83 and 78 patients were randomized to Smoflipid and Intralipid treatment groups, respectively, and received at least one dose of treatment, which are defined as the Intent-to-Treat (ITT) population by the Applicant. Only 33 patients in each group completed 28-day treatment. There were 22 and 25 patients from Smoflipid and Intralipid group, respectively, proceeded in the Extension Treatment Phase beyond 28 days. Only seven patients (3 patients in Smoflipid group and 4 patients in Intralipid group) completed 84-day treatment. The median (range) daily doses for patients in Intralipid and Smoflipid groups were 2.77 (1.7, 3.3) g/kg/day and 2.79 (0.9, 3.2) g/kg/day, respectively.

Oral and enteral feeds were allowed during the study. Patients were weaned off the study drug upon receiving 100 mL/kg/day oral/enteral feeds for at least 3 days. The median time until full enteral and oral feed was 21.95 days for Intralipid and 23.29 days for Smoflipid. During the Initial Treatment Phase, 19 patients (10 in Intralipid group and 9 in Smoflipid group) were solely on PN throughout 28-day treatment with 100% daily calories provided by PN (including study drugs).

**Plasma fatty acids and phytosterols concentrations**: The plasma fatty acids and phytosterol levels were measured at baseline and on Day 29 (or the following day of last dose if discontinued early) during the Initial Treatment Phase, and on Day 57 and Day 85 (or the following day of last dose if discontinued early) during the Extension Treatment Phase. The concentrations of fatty acids LA, ALA, ARA, EPA, DHA and MA were measured in the plasma. Although ARA and MA are not major components of fatty acids of Smoflipid (the approved PI), they are metabolites of LA and OA, respectively. The values were used to derive Holman Index, also known as triene:tetraene (T:T) ratio, which is a ratio of MA and ARA, to evaluate the potential of EFAD. This reviewer defers to the Clinical's assessment of the clinical relevance of Holman Index (i.e., T:T ratio).

A total of 70 and 78 patients from Intralipid and Smoflipid groups, respectively, reported baseline values of the plasma fatty acids concentrations. The number of patients with reported plasma fatty acids values at baseline was smaller than the ITT population. A total of 64 and 71 patients from Intralipid and Smoflipid groups, respectively, reported plasma fatty acids concentrations during the Initial Treatment Phase. Only 11 and 12 patients from Intralipid and Smoflipid groups, respectively, reported plasma fatty acids concentrations during the Extension Treatment Phase. The reporting rates of plasma fatty acid values among patients received at least one dose during Initial Treatment Phase were 86% (71 out of 83 patients) in Smoflipid group and 82% (64 out of 78 patients) in Intralipid group, while the reporting rates among patients who received treatment beyond 28 days during Extension Treatment Phase were 55% (12 out 22

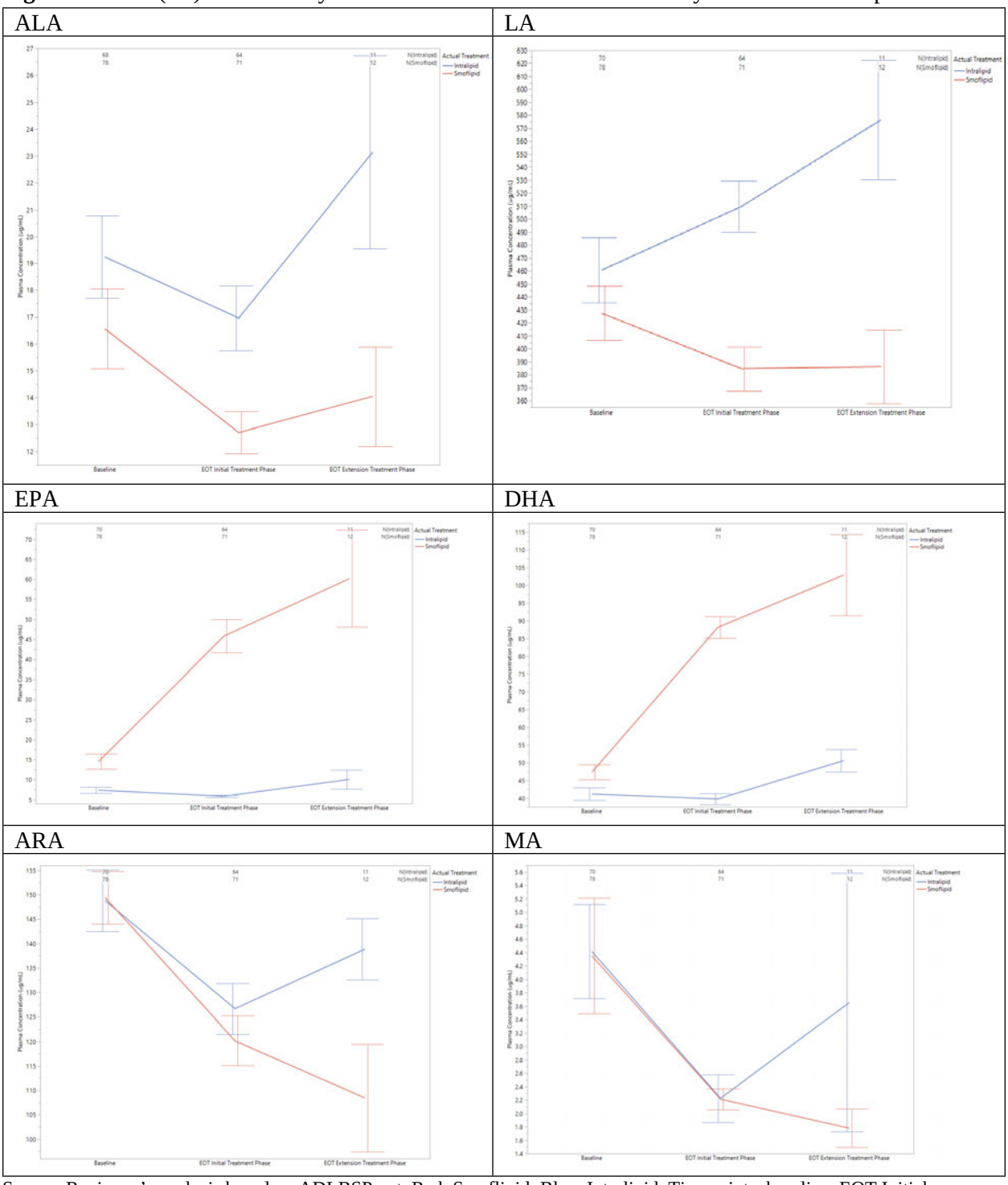
patients) in Smoflipid group and 44% (11 out 25 patients) in Intralipid group. The missing values during the Extension Phase was high, which limits the interpretation of the result.

Nine patients (4 in Smoflipid group and 5 in Intralipid group) received at least one dose of treatment but did not have any plasma fatty acids values reported at any timepoint. The reasons for not assessing plasma fatty acids and phytosterols was documented for 5 patients only at certain timepoints as "Physician Decision". The reason of no values reported for the other 4 patients and other timepoints for the 5 patients was not clear. Among those, three patients (all from Smoflipid) completed the Initial Treatment Phase and one of them proceeded to Extension Treatment Phase and was weaned off the study products before the end of the Extension Treatment Phase. Six patients (1 from Smoflipid group and 5 from Intralipid group) discontinued the treatment early during Initial Treatment Phase due to weaning off the study products. In the Applicant's Clinical Information Amendment dated Oct. 18, 2021, the Applicant pointed out that the total volume of blood that could be taken from a single patient in a week or month was limited by (1) the small total blood volume of those young neonates; (2) their poor medical condition; (3) the difficult handling of neonates that are connected to multiple tubes and sensor cables, which resulted in many laboratory assessments that were required per protocol were not performed.

The mean plasma fatty acids concentrations were compared between Smoflipid (red line) and Intralipid groups (blue line) at baseline and throughout both Initial Treatment Phase and Extension Treatment Phase, as shown in Figure 2. Smoflipid treatment group experienced 215% and 86% increase from baseline in mean plasma concentrations of EPA and DHA, respectively, as well as 20%, 23% and 10% decrease from baseline in mean plasma concentrations of ARA, ALA and LA, respectively, during the Initial Treatment Phase. It was noted that the direction of change from baseline for the mean plasma concentrations of EPA, DHA, and LA were opposite in the Intralipid group during the Initial Treatment Phase. The mean plasma concentrations of ARA, MA and ALA decreased from baseline in both treatment

groups and concentrations were comparable between two treatment groups at the end of the Initial Treatment Phase.

**Figure 2**. Mean (SE) Plasma Fatty Acids Concentrations Over Both Study Phases In ITT Population




Source: Reviewer's analysis based on ADLBSP xpt. Red: Smoflipid; Blue: Intralipid. Timepoints: baseline, EOT Initial Treatment Phase and EOT Extension Treatment Phase.

Note: EOT Initial Treatment Phase include values collected on Day 29 or earlier if treatment was discontinued early; EOT Extension Treatment Phase include values collected on Day 84 or earlier if treatment was discontinued early.

The fatty acid profiles were also reported in the Applicant's previously conducted trials on premature neonates (Study 03-SMOF-005 and 00-SMOF-004) as well as in the published randomized controlled studies on neonate population.[9] [10] [11] A similar trend in change from baseline for EPA and ARA measured in plasma lipoprotein and/or red blood cell (RBC) phospholipids were observed in clinical trials (03-SMOF-005 and 00-SMOF-004) on premature neonates treated with Smoflipid up to 14 days compared to study results from SMOF-018-CP3. The mean concentration of EPA showed a greater increase while the mean concentration of ARA showed a greater or comparable decrease in Smoflipid group compared to Intralipid group.

In addition, the Neonatal-Perinatal Medical Consultation for this supplement by Dr. Gerri Baer (DARRTS Reference ID: 4888505) reviewed the relevant literature for Smoflipid product and noted that increasing EPA and DHA but decreasing ARA from baseline following the use of Smoflipid for 2-3 weeks were generally reported in randomized controlled studies on neonate population, which is similar to what was observed in study SMOF-018-CP3, although the biologic matrices used in the literature may be different. It was noted that LA and ALA were reported increasing from baseline after treatment of Smoflipid in both Sponsor's previous trials and published reported literature on neonates, whereas LA and ALA decreased in Smoflipid group in Study SMOF-18-CP3. The different biologic matrices, different analytical methods and different treatment durations may contribute to the observed difference.

This reviewer also noted that the DHA and EPA increased from baseline, while LA, ALA and ARA decreased from baseline in neonate patients using Omegaven Infusion over 10 weeks based on the Clinical Pharmacology Review for Omegaven Original NDA application by Dr. Elizabeth Shang (NDA 210589, DARRTS Reference ID: 4298339). The overall trend in fatty acids (DHA, EPA, LA, ALA and ARA) change from baseline was similar compared to what was observed with Smoflipid during the Initial Treatment Phase. Of note, Omegaven, which comprises only fish oil, also has noticeably lower contents of LA and ALA and higher contents of EPA and DHA compared to Intralipid. The similar change in plasma fatty acid profiles were found between neonates treated with Omegaven and Smoflipid 20%. Both products had similar fatty acids composition regarding LA, ALA, EPA, and DHA.

In Applicant's previously submitted clinical trial (00-SMOF-002) in infants age 1 month to < 2 years old (n=13) and children age up to <12 years old (n=15) for a treatment duration of 4 weeks, the mean concentrations of ALA, LA and ARA slightly decreased or unchanged from baseline, while the mean concentrations of EPA+DHA increased from baseline in both infants and children treated with Smoflipid,

[9] Deshpande G, et al. Fish Oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates. J Pediatr Gastroenterol Nutr. 2014;58(2):177-182. doi:10.1097/MPG.0000000000000174

[10] Najm S, et al. Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial. Clin Nutr ESPEN. 2017;20:17-23. doi:10.1016/j.clnesp.2017.04.004

[11] Papandreou P, et al. Administration of an Intravenous Fat Emulsion Enriched with Medium-Chain Triglyceride/ω-3 Fatty Acids is Beneficial Towards Anti-Inflammatory Related Fatty Acid Profile in Preterm Neonates: A Randomized, Double-Blind Clinical Trial. Nutrients. 2020;12(11):3526. Published 2020 Nov 16. doi:10.3390/nu12113526

which may suggest that the impact of Smoflipid on the trend of plasma fatty acids change from baseline may be similar across all pediatric age groups up to 12 years old. However, the Study 00-SMOF-002 was completed in 2006 with no bioanalytical assay report available. The reported values may only be used for descriptive purpose.

The Applicant defined a T:T ratio < 0.05 as normal. The mean T:T ratio at different timepoints in Intralipid and Smoflipid groups were shown in Table 2. There was no significant difference observed between two treatment groups in both Initial Treatment Phase and Extension Treatment Phase. However, an up to 18% and an up to 56% missing value rate in Initial Treatment Phase and Extension Treatment Phase, respectively, may limit the interpretation of the results for a longer treatment, especially beyond 28 days of treatment. The clinical relevance of T:T ratio will be deferred to clinical evaluation.

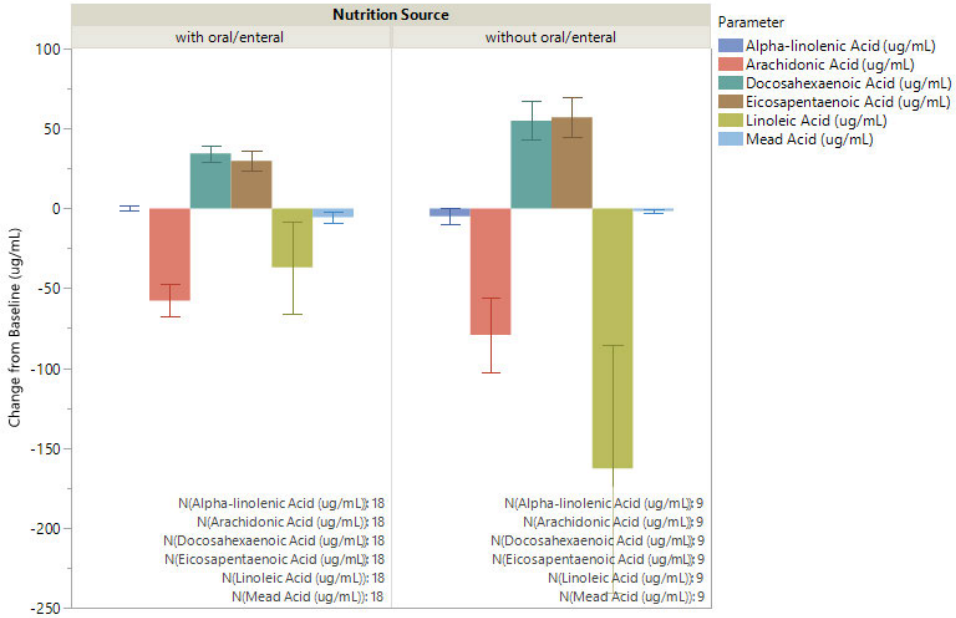
**Table 2.** Mean (SD) T:T Ratio in ITT Population

| | Intralipid | Smoflipid |
|---|---|---|
| **Baseline** | 0.027 (0.031) (n=70) | 0.026 (0.031) (n=78) |
| **EOT Initial Treatment** | 0.017 (0.020) (n=64) | 0.020 (0.011) (n=71) |
| **EOT Extension Treatment** | 0.026 (0.044) (n=11) | 0.019 (0.015) (n=12) |

Source: Reviewer's analysis based on ADLBSP xpt.
Note: EOT Initial Treatment: EOT Initial Treatment Phase include values collected on Day 29 or earlier if treatment was discontinued early; EOT Extension Treatment Phase include values collected on Day 84 or earlier if treatment was discontinued early.

This reviewer conducted a sub-group analysis on patients in Smoflipid group who completed the Initial Treatment Phase (28-day treatment). The mean plasma concentrations of fatty acids change from baseline on Day 29 were compared between patients who are exclusively on PN with Smoflipid and those who concurrently received oral/enteral nutrition at some point during the 28-day treatment, which is present in Figure 3.

**Figure 3.** Mean (SE) Plasma Concentrations of LA, ALA, ARA, EPA, DHA and MA Change From Baseline On Day 29 Among Patients Who Completed 28-Day Treatment With Smoflipid




Source: Reviewer's analysis based on ADCAL xpt and ADLBSP xpt. From left to right: dark blue: ALA; red: ARA; green: DHA; brown: EPA; mustard: LA; light blue: MA.

Note:

(1) Patients who were considered exclusively on Smoflipid (i.e., Without Oral/Enteral) were those with 100% daily calories provided by PN with Smoflipid on Day 1-7, Day 8-14, Day 15-21 and Day 22-28 in ADCAL.xpt.

(2) Six subjects who completed 28-day treatment of Smoflipid did not have reported change form baseline for fatty acids in ADLBSP xpt. All of them also received oral/enteral nutrition concurrently (i.e., With Oral/Enteral). Two subjects ( (b) (6) and (b) (6) only had baseline values reported. Three subjects ( (b) (6) did not have any fatty acids values reported in the dataset ADLBSP.xpt nor in bioanalytical assay report. The reason of why no values were reported for these three subjects was not clear. One subject ( (b) (6) ) did not have reported timing for the sample collected at the end of Initial Treatment Phase. Values from (b) (6) and (b) (6) and (b) (6) were excluded from the analysis.

Among the 27 patients shown in Figure 3 who completed 28-day treatment regardless of their oral/enteral intake status and had both baseline and end of Initial Treatment Phase (i.e., Day 29) values reported, the mean plasma concentrations of EPA and DHA increased from baseline by 205% and 83% respectively, while the mean plasma concentrations of ARA, LA and ALA decreased from baseline by 42%, 21% and 13%, respectively, after 28-day treatment with Smoflipid. The overall trend in change from baseline for the mean plasma fatty acids concentrations following treatment of Smoflipid was comparable between the ITT population (Figure 2) and patients who completed 28-day treatment and had both baseline and end of Initial Treatment Phase values reported (Figure 3), which increased the confidence that the missing data may have limited impact on qualitatively describing the trend of fatty acids profiles over Initial Treatment Phase in Study SMOF-018-CP3.

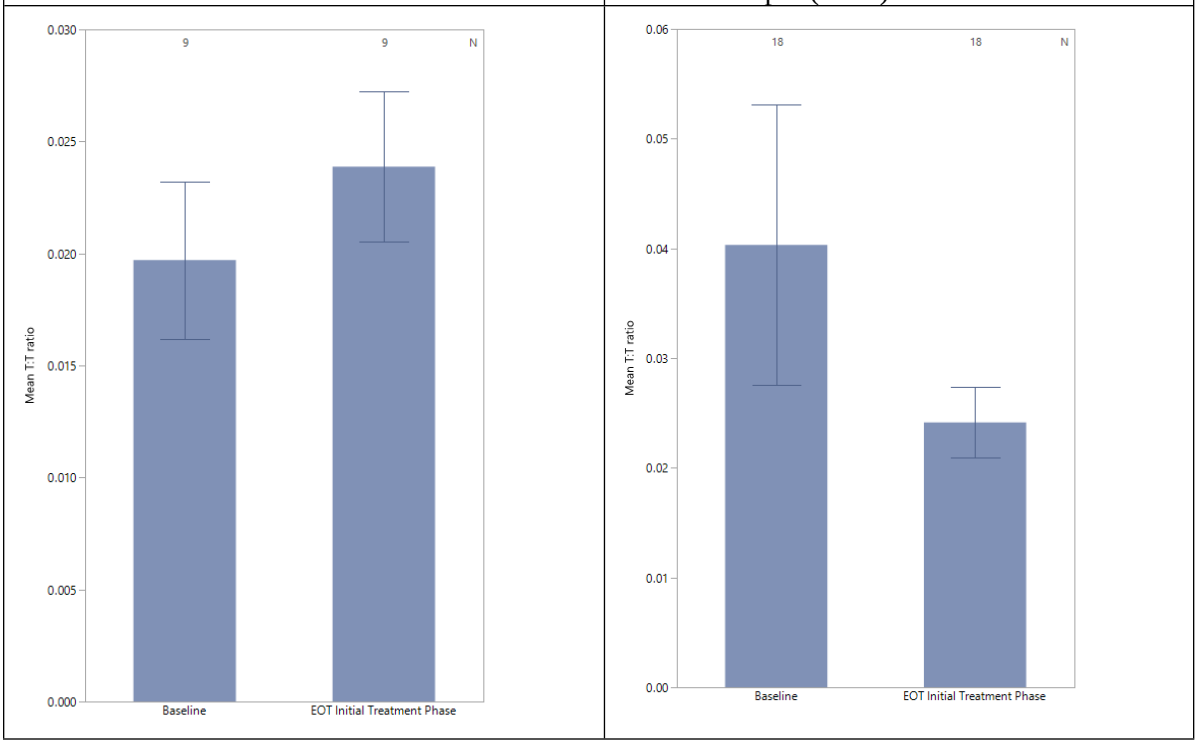
When comparing the overall trend of plasma fatty acids change from baseline between patients who completed 28-day treatment exclusively with Smoflipid and those who also concurrently took oral/enteral nutrition during the Initial Treatment Phase, the overall trend for plasma fatty acids change from baseline was similar between these two types of patients. It was noted that the mean decrease from baseline for LA was around 4-fold greater and the mean increases from baseline for EPA and DHA were around 2-fold greater in patients exclusively on Smoflipid than patients who concurrently received oral/enteral nutrition.

No significant difference in change from baseline were noted for other fatty acids. However, given a small sample size, the interpretation of the result may be limited.

Among the 27 patients in Smoflipid group who completed 28-day treatment and had both baseline and end of Initial Treatment Phase values reported, the mean change of T:T ratio from baseline was -0.009. The mean T: T ratio at baseline and at the end of Initial Treatment Phase were 0.033 and 0.024, respectively. The change in T:T ratio was also compared between patients who were exclusively on Smoflipid and patients who concurrently received oral/enteral nutrition at some point during the 28-day treatment, as shown in Figure 4. Patients who concurrently received oral/enteral nutrition during the Initial Treatment Phase had a slightly higher mean T:T ratio at baseline than patients who were exclusively on PN throughout the Initial Treatment Phase (0.04 vs. 0.02). The mean T:T ratio decreased by around 2-fold at the end of Initial Treatment Phase from baseline in patients who concurrently taking oral/enteral nutrition with Smoflipid, while the mean T:T ratio did not change much in patients who exclusively received Smoflipid. Again, given a small sample size, the interpretation of the result can be limited.

**Figure 4**. Mean (SE) T:T Ratio At Baseline And On Day 29 Among Patients Who Completed 28-Day Treatment With Smoflipid

| Exclusive on PN with Smoflipid (n=9)ł | Concurrently Taking Oral/Enteral Nutrition With Smoflipid (n=18)* |
|---|---|




Source: Reviewer's analysis based on ADCAL xpt and ADLBSP xpt.

ł Patients who were considered exclusively on Smoflipid were those with 100% daily calories were provided by PN with Smoflipid on Day 1-7, Day 8-14, Day 15-21 and Day 22-28 in ADCAL xpt

*Six subjects who completed 28-day treatment of Smoflipid and concurrently takes oral and enteral nutrition did not have plasma samples collected at all timepoints for measuring fatty acids. Two subjects ( (b) (6) ) only had baseline values reported. Three subjects ( (b) (6) ) did not have any fatty acids values reported in the dataset ADLBSP xpt nor in bioanalytical assay report. The reason of why no values were reported for these three subjects was not clear.

One subject (b) (6) ) did not have reported timing for the sample collected at the end of Initial Treatment Phase. Values from (b) (6) and (b) (6) and (b) (6) were excluded from the analysis.

The Applicant evaluated the plasma phytosterols levels in Study SMOF-018-CP3, which included phytosterols, sitosterol, desmosterol, brassicasterol, lanosterol, ergosterol, campesterol, stigmasterol, sitostanol, lathosterol, cholesterol, at baseline, on Day 29 (or the following day of last dose if discontinued early) during the Initial Treatment Phase, on Day 57, and Day 85 (or the following day of last dose if discontinued early) during the Extension Treatment Phase, as shown in Table 3. All phytosterols decreased or remained the same from baseline following treatment of Smoflipid in both treatment Phases, whereas three phytosterols (sitosterol, campesterol and stigmasterol) increased from baseline in Intralipid group following treatment with Intralipid in both treatment Phases. As the in-study bioanalytical assays did not meet the requirement, the result can be viewed for descriptive purpose. See Bioanalytical Assays Section of this review for more details.

**Table 3**. Change in Plasma Phytosterols in ITT Population

| | | Intralipid | | Smoflipid | | | Intralipid | | Smoflipid |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean Concentration (SD) (µg/mL) | n | Mean Concentration (SD) (µg/mL) | | n | Mean Concentration (SD) (µg/mL) | n | Mean Concentration (SD) (µg/mL) |
| **Sitosterol** | | | | | **Brassicasterol** | | | | |
| Baseline | 70 | 45.076 (28.8620) | 78 | 41.900 (28.7879) | Baseline | 53 | 0.146 (0.2255) | 55 | 0.129 (0.2033) |
| Change to EOT Initial Phase | 59 | 39.854 (38.5996) | 69 | -6.357 (22.4175) | Change to EOT Initial Phase | 44 | 0.018 (0.2163) | 35 | -0.037 (0.2263) |
| Change to EOT Extension Phase | 10 | 129.938 (52.8942) | 12 | -14.247 (46.0845) | Change to EOT Extension Phase | 6 | 0.134 (0.0931) | 6 | -0.169 (0.2486) |
| **Campesterol** | | | | | **Ergosterol** | | | | |
| Baseline | 70 | 12.396 (10.1990) | 77 | 11.628 (10.4005) | Baseline | 40 | 0.028 (0.0210) | 40 | 0.025 (0.0215) |
| Change to EOT Initial Phase | 60 | 15.385 (21.4772) | 69 | -3.079 (9.6125) | Change to EOT Initial Phase | 35 | -0.007 (0.0183) | 38 | 0.001 (0.0214) |
| Change to EOT Extension Phase | 10 | 56.681 (34.4784) | 12 | -8.159 (22.0449) | Change to EOT Extension Phase | 8 | 0.002 (0.0038) | 8 | -0.010 (0.0267) |
| **Stigmasterol** | | | | | **Lathosterol** | | | | |
| Baseline | 66 | 7.649 (4.0597) | 72 | 6.473 (3.5595) | Baseline | 65 | 2.411 (0.9417) | 75 | 2.215 (1.0751) |
| Change to EOT Initial Phase | 54 | 4.830 (5.6464) | 63 | -2.658 (3.2875) | Change to EOT Initial Phase | 56 | -0.366 (1.1811) | 62 | -0.279 (1.1651) |
| Change to EOT Extension Phase | 8 | 17.862 (3.0202) | 11 | -2.422 (5.1974) | Change to EOT Extension Phase | 10 | -0.801 (0.8797) | 12 | -0.956 (2.2253) |
| **Sitostanol** | | | | | **Lanosterol** | | | | |
| Baseline | 70 | 0.838 (0.5692) | 78 | 0.710 (0.4423) | Baseline | 65 | 1.281 (0.8046) | 73 | 1.135 (0.5630) |
| Change to EOT Initial Phase | 60 | 0.945 (0.9989) | 69 | -0.238 (0.4344) | Change to EOT Initial Phase | 56 | 0.273 (1.0466) | 60 | -0.385 (0.5471) |
| Change to EOT Extension Phase | 9 | 3.433 (1.1015) | 12 | -0.328 (0.8131) | Change to EOT Extension Phase | 10 | 1.039 (0.9342) | 12 | -0.548 (0.7836) |
| **Desmosterol** | | | | | **Cholesterol** | | | | |
| Baseline | 64 | 1.396 (1.8371) | 70 | 1.196 (1.0923) | Baseline | 69 | 1159.638 (293.2282) | 78 | 1163.654 (334.7942) |
| Change to EOT Initial Phase | 53 | -0.508 (2.0678) | 59 | -0.014 (1.3948) | Change to EOT Initial Phase | 60 | -129.433 (295.6223) | 69 | -23.072 (358.8932) |
| Change to EOT Extension Phase | 9 | -2.337 (4.2890) | 11 | -0.562 (1.6695) | Change to EOT Extension Phase | 10 | 145.100 (243.1133) | 12 | -232.250 (621.2414) |

Source: Adapted from SMOF-018-CP3 CSR Table 12-11. n= number of patients with non-missing values

Note: EOT Initial Treatment: EOT Initial Treatment Phase includes values collected on Day 29 or earlier if treatment was discontinued early; EOT Extension Treatment Phase includes values collected on Day 84 or earlier if treatment was discontinued early.

## Bioanalytical Assays

The fatty acids concentrations were quantified in plasma using a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. The validation summary for the bioanalytical method is presented in Table 4.

**Table 4.** Validation Summary of Bioanalytical Method For Plasma Fatty Acids

| | | | |
|---|---|---|---|
| Analyte | eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), α-linolenic acid (ALA), linoleic acid (LA), and mead acid (MA) in human plasma | | |
| Matrix | Human plasma (K2EDTA as anticoagulant) | | |
| Internal Standard | Eicosapentaenoic Acid-$d_5$<br>Docosahexaenoic Acid-$d_5$<br>Arachidonic Acid-$d_8$<br>α-linolenic Acid-$d_5$<br>Linoleic Acid-$d_{11}$<br>5(Z),8(Z),11(Z)-Eicosatrienoic Acid-$d_6$ | | |
| Injection Volume | 50 µL of plasma | | |
| Analytical Method/Detection | Reverse LC-MS/MS | | |
| Calibration model | Linear regression | | |
| Calibration range* | 1.00 – 100 µg/mL for EPA<br>2.00 – 200 µg/mL for DHA<br>5.00 – 500 µg/mL for AA<br>1.00 – 100 µg/mL for ALA<br>20.0 – 2000 µg/mL for LA<br>0.500 – 50.0 µg/mL for MA | | |
| Weighting factor | 1/concentration$^2$ | | |
| Quantification method | Peak area ratio (analyte/internal standard) vs. nominal concentrations of calibration standard | | |
| Sensitivity (LLOQ) | EPA: 10.3 µg/mL (in human plasma); 1 µg/mL (BSA)<br>DHA: 27.6 µg/mL (in human plasma); 2 µg/mL (BSA)<br>AA: 189 µg/mL (in human plasma); 5 µg/mL (BSA)<br>ALA: 12.9 µg/mL (in human plasma); 1 µg/mL (BSA)<br>LA: 553 µg/mL (in human plasma); 20 µg/mL (BSA)<br>MA: 2.79 µg/mL (in human plasma); 0.5 µg/mL (BSA) | | |
| Intra-day (Run) precision and accuracy | Analyte | Precision (%CV) (at plasma LLOQ) | Accuracy (% RE) (at plasma LLOQ) |
| | EPA | 0.9% to 5.7% | 1.9% to 4.4% |
| | DHA | 2.4% to 3.0% | -5.1% to -1.8% |
| | AA | 2.1% to 2.9% | -1.1% to 0.5% |
| | ALA | 3.2% to 4.1% | -2.3% to 0.8% |
| | LA | 2.1% to 4.8% | -4.2% to 5.2% |
| | MA | 4.3% to 8% | -0.4% to 4.7% |
| Inter-day (Run) precision and accuracy | Analyte | Precision (%CV) | Accuracy (% RE) |
| | EPA | 4% | -2.9% |
| | DHA | 2.9% | -3.3% |
| | AA | 2.5% | -0.5% |

| | | | |
|---|---|---|---|
| | ALA | 3.6% | -0.8% |
| | LA | 4.8% | 0.0% |
| | MA | 6% | 2.2% |
| Carryover | No significant carryover observed | | |
| Stability | Bench top stability: up to 20 hours at room temperature in human plasma<br><br>Freeze/thaw stability: 3 cycles in human plasma at ~-20 °C and ~-70 °C<br><br>Extract storage stability: up to 73 hours stored at ~4 °C<br>Autosampler stability: Up to 39 hours at room temperature (Addendum 1: 122 hours at ambient temperature)<br><br>Frozen sample long term storage stability: 16 days at ~-20 °C and ~-70 °C (Addendum 1: 441 days at -70°C for MA and 614 days at -70°C for rest of fatty acids) | | |

Source: Reviewer's summary based on
*Calibration standards are prepared in surrogate matrix made by 40 mg/mL bovine serum albumin (BSA) dissolved in HPLC water

Method Validation (Report Number: RPT17343), its addendum (Report Number: RPT17343-AD1-1.0) and sample analysis supporting Study SMOF-018-CP3 (Report Number: RPT18329-SA1-1.0) were in-line with the Agency's recommendation outlined in the Guidance For Industry Bioanalytical Method Validation (May 2018) except that a total of 96 (44 collected at baseline and 52 collected at other timepoints) out of 321 samples (30%) were outside the stability range established in the addendum of the validation report (RPT 17343-AD1-1.0). Most of samples were more than 30 days out of the established storage stability window. This reviewer compared the mean baseline concentrations of all samples with the mean of samples analyzed within the stability range and found the values were overall comparable, as shown in Table 4. It was noted that the mean concentration of MA was slightly lower in samples within stability range. The impact of sample stability in evaluating plasma fatty acids profile is expected to be minimal.

**Table 4.** Mean Plasma Fatty Acids Concentrations At Baseline Comparison Between All Samples And Samples Within Stability Range

| | **Intralipid All Samples Mean (SD)* (n=70)** | **Intralipid Within Stability Range Mean (SD) (n=46)** | **Modified Cohen's d** | **Smoflipid All Samples Mean (SD)* (n=78)** | **Smoflipid Within Stability Range Mean (SD) (n=58)** | **Modified Cohen's d** |
|---|---|---|---|---|---|---|
| EPA | 7.36 (6.545) | 8.07 (7.685) | -0.09 | 14.52 (16.480) | 14.26 (15.067) | 0.02 |
| DHA | 41.14 (14.724) | 42.02 (14.272) | -0.06 | 47.31 (18.484 ) | 47.44 (18.038) | -0.01 |
| ARA | 148.80 (52.531) | 146.27 (29.339) | 0.05 | 149.42 (47.438) | 143.39 (41.965) | 0.14 |
| ALA | 19.24 (12.675) | 20.55 (14.196) | -0.09 | 16.57 (13.081) | 16.10 (11.722) | 0.04 |
| LA | 460.62 (211.354) | 493.04 (225.44) | -0.14 | 427.44 (185.206) | 419.97 (168.635) | 0.04 |
| MA | 4.42 (5.88) | 3.80 (4.750) | 0.13 | 4.35 (7.620) | 3.47 (3.247) | 0.27 |

Source: Reviewer's analysis based on Report RPT18329-SA1-1.0
*From SMOF-018-CP3 CSR Table 11-2
Note: Modified Cohen's d= [Mean (stable samples)- Mean (all samples)] / SD (stable samples)

Plasma phytosterols and fatty acids in RBC were measured in Study SMOF-018-CP3. The same method and validation for assessing plasma phytosterols was used as what was reviewed for the fulfilment of PMR 3002-5. However, regarding the in-study performance, no incurred sample reanalysis was performed for plasma phytosterols due to insufficient sample volume and runs with failed Quality Control (QC) samples were accepted also due to insufficient sample volume for re-analysis. The bioanalytical assay for plasma phytosterols in Study SMOF-018-CP3 deems not acceptable. Similar issues occurred in the sample analyses for fatty acid in RBC, during which incurred sample reanalysis failed due to insufficient sample volume and long storage durations.

## Conclusion

Despite up to 18% missing values for plasma fatty acids in the Initial Treatment Phase, the reported values are adequate to qualitatively describe the trend of plasma fatty acids change from baseline following the use of Smoflipid over 28 days.

Patients who completed the 28-day treatment exclusively on Smoflipid had a comparable plasma fatty acids profile compared to those who completed 28-day treatment concurrently with oral/enteral nutrition. No significant change in T:T ratio from baseline was observed in patients who were exclusively on Smoflipid for 28 days. The mean plasma concentrations of EPA and DHA increased from baseline by 205% and 83% respectively, while the mean plasma concentrations of ARA, LA and ALA decreased from baseline by 42%, 21% and 13%, respectively, after 28-day treatment with Smoflipid regardless of their oral/enteral intake status. However, the small sample size may limit the conclusion drawn from these analyses.

Overall, the plasma fatty acids concentrations measured in Study SMOF-018-CP3 are adequate to qualitatively describe the plasma fatty acid profile over a treatment duration of 28 days from a clinical pharmacology perspective. The Clinical Pharmacology will defer to the Clinical's evaluation of the clinical meaning of the results and the inclusion of the data in the label.

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