



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report
for
Soya oil, Medium chain triglycerides, Olive oil,
Fish oil

Proprietary Product Name: SMOFlipid
Submission No: PM-2008-03674-3-1
Sponsor: Fresenius Kabi Australia Pty Ltd



June 2010

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I. Introduction to Product Submission

Product Details

<i>Type of Submission</i>	New Combination
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	15 March 2010
<i>Active ingredient(s):</i>	Soya oil, Medium chain triglycerides, Olive oil, Fish oil
<i>Product Name(s):</i>	SMOFlipid
<i>Sponsor's Name and Address:</i>	Fresenius Kabi Australia Pty Ltd 964 Pacific Highway Pymble NSW 2073
<i>Dose form(s):</i>	Emulsion for intravenous infusion
<i>Strength(s):</i>	Soya oil 6%, Medium chain triglycerides 6%, Olive oil 5%, Fish oil 3%
<i>Container(s):</i>	Plastic infusion bag
<i>Pack size(s):</i>	100, 250 and 500 mL
<i>Approved Therapeutic use:</i>	Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated.
<i>Route(s) of administration:</i>	Intravenous
<i>Dosage:</i>	Adults The standard dose is 1.0 – 2.0 g fat/kg body weight (bw)/day, corresponding to 5 – 10 mL/kg bw/day. The recommended infusion rate is 0.125 g fat/kg bw/hour, corresponding to 0.63 mL SMOFlipid/kg bw/hour, and should not exceed 0.15 g fat/kg bw/hour, corresponding to 0.75 mL SMOFlipid/kg bw/hour. Children It is recommended not to exceed a daily dose of 2g fat/kg bw/day, corresponding to 10 mL SMOFlipid/kg bw/day. With increased requirements in the youngest children a dose up to a maximum of 3g fat/kg bw/day can be considered. Neonates and infants The initial dose should be 0.5 – 1.0 g fat/kg bw/day followed by a successive increase by 0.5 – 1.0 g fat/kg bw/day up to 3.0 g fat/kg bw/day. It is recommended not to exceed a daily dose of 3g fat/kg bw/day, corresponding to 15 mL SMOFlipid/kg bw/day. The rate of infusion should not exceed 0.125 g fat/kg bw/hour. In premature and low birth weight neonates, SMOFlipid should be infused continuously over around 24 hours.
<i>ARTG Number:</i>	156359

Product Background

The two principal sources of energy are carbohydrate and lipid.

Glucose is the carbohydrate of choice. It is a physiological substrate required by the brain and metabolised by all body tissues, besides being a prerequisite of protein anabolism. Concentrated solutions of glucose must be given to satisfy the caloric requirements. Most patients increase their endogenous insulin secretion to allow the blood glucose to remain within physiological limits. Diabetics will require added insulin. When insulin production is reduced as in the early posttraumatic and septic state, infusion of excessive glucose results in lipogenesis with a marked increase in carbon dioxide (CO₂) production. If hyperglycaemia occurs, consideration should be given to reducing the glucose infusion rate, rather than adding insulin.

Lipid provides more energy per unit volume than carbohydrate, and also avoids the complications of excess glucose administration.¹

The development of this formulation follows on from the emergence of side effects as each new innovation was produced to counter side effects of existing preparations. In the original technique of Total Parenteral Nutrition (TPN) glucose ± ethyl alcohol was used as the energy source. While there were the obvious problems of hyperglycaemia² and hypertonicity, the recognition of essential fatty acid deficiency led to the use of lipid as an energy source, which also diminished the other problems.

Intravenous fat emulsions consist of triglycerides dispersed in water together with emulsifiers to stabilize the system. A number of vegetable oils, many of which caused side effects, were studied before the first formulation of a fat emulsion for infusion was established. In 1961, a soybean oil emulsion stabilized with egg phospholipids as an emulsifier intended for intravenous administration was found to be well tolerated under clinical conditions (Schuberth and Wretling 1961).³ Such emulsions have been commercially available under the trade name Intralipid for approximately 45 years.

Intralipid contains long-chain triglycerides (LCTs) from soybean oil, which contains the 2 essential fatty acids alpha (α)-linolenic acid and linoleic acid. One of the possible disadvantages with the existing LCTs is their relatively high content of polyunsaturated fatty acids (PUFA), in particular linoleic acid.

Medium chain triglycerides (MCTs) were then added to the LCTs. The claimed benefits from the MCTs include not only a diminution by dilution of these effects, but also there appeared to be nutritional benefit in faster utilisation and more peripheral utilisation by muscle rather than storage as adipose tissue, plus entry into the mitochondria independent of carnitine which was often depleted in these patients. MCTs however lack the essential fatty acids and, if used at >50% alone, produced a risk of hyperlactacidaemia, hyperketonaemia and central nervous system (CNS) toxicity.

The addition of olive oil, which is rich in monounsaturated fatty acids (ω-9), decreases the proportion of PUFA.

The effect on inflammatory response it is believed relates to the ratio of α-linolenic acid (ω-3) to linoleic acid (ω-6), with an excess of the latter (as in soya lipid) being pro inflammatory. Thus fish

¹ Intensive Care Manual, Fourth Edition, TE Oh (ed), Oxford Butterworth-Heinemann 1997. Chapter 84, Parenteral Nutrition, page 725.

² Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. J Parenter Enteral Nutr. 2006; 30:351-67.

³ Acta Chirurgica Scandinavica Supplementum 278. Stockholm 1961, page 3.

oils, which are rich in very long chain ω -3 fatty acids especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been added with the intention of further diminishing this effect.

SMOFlipid 20% is comprised of the lipid components Soybean oil, Medium chain triglycerides, Olive oil, and Fish oil.

This composition of the different oils was chosen to:

- Provide sufficient amounts of essential fatty acids
- Decrease the load of ω -6 polyunsaturated fatty acids, especially linoleic acid
- Provide the very long chain ω -3 fatty acids EPA and DHA and thereby
- Decrease the ω -6: ω -3 fatty acid ratio
- Replace part of the polyunsaturated fatty acids by monounsaturated fatty acids (oleic acid)
- Include medium chain triglycerides to provide additional rapidly available energy

The indication sought is for:

Supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated.

The proposed dosage is:

The patient's ability to eliminate the fat infused should govern the dosage and infusion rate.

Adults

The standard dose is 1.0 - 2.0 g fat/kg/day, corresponding to 5 – 10 mL/kg/day.

The recommended infusion rate is 0.125 g fat/kg/h, corresponding to 0.63 mL SMOFlipid/kg/h, and should not exceed 0.15 g fat/kg/h, corresponding to 0.75 mL SMOFlipid/kg/h.

Children

It is recommended not to exceed a daily dose of 3 g fat/kg/day, corresponding to 15 mL SMOFlipid/kg/day. The daily dose should be increased gradually during the first week of administration. The infusion rate should not exceed 0.15 g fat/kg/h.

Neonates and infants

The initial dose should be 0.5 - 1.0 g fat/kg/day followed by a successive increase by 0.5 - 1.0 g fat/kg/day up to 3.0 g fat/kg/day.

It is recommended not to exceed a daily dose of 3 g fat/kg/day, corresponding to 15 mL SMOFlipid/kg/day. The rate of infusion should not exceed 0.15 g fat/kg/h.

In premature and low birth weight neonates, SMOFlipid should be infused continuously over around 24 hours.

The route of administration is intravenous infusion into a peripheral or central vein.

Regulatory Status

The proposed formulation contains:

1. Soya bean oil - extracts of this have been registered in Australia for nutritional intravenous (IV) use including some of the sponsors own products – Intralipid, Kabiven and Lipovenos.
2. Medium Chain Triglycerides (MCTs) – there is no MCT product on the Australian Register of Therapeutic Goods (ARTG) (including nutritional IV use). MCTs are marketed in Australia as oral food supplements, for example Caprilon, Liquigen, and MCT Duocal from Scientific Hospital Supplies and MCT Oil from Mead Johnson and in enteral nutrition products, for example Osmolite from Abbott.

3. Olive oil – the only product registered for IV nutrition use containing olive oil is Clinoleic, a product Baxter registered in February 2004.
4. Fish oil – there is no fish oil registered for nutritional IV use; there are multiple oral preparations listed.

The sponsor has currently marketed overseas an IV MCT preparation Structolipid, and an IV fish oil preparation Omegaven.

SMOFlipid was approved in the European Union (EU) between 2004 and 2007. In addition to the EU, the product is registered in Switzerland and in Argentina, Croatia, Egypt, Iceland, Malaysia, Mexico, Norway, Philippines, Russia, Singapore, South Africa, Taiwan, Turkey and Uruguay.

The common indication approved in these countries except for Italy is:

Supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated.

The indication in Italy is as follows:

Supply of lipids, including essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substances (active ingredients)

Soya oil has been used in registered “Intralipid” Soya Oil Emulsion Injection products by the current sponsor which have been approved by the TGA (AUST R 14471, 14472, 48245, 48246, 53538, 53539, 53540 and 53541). Olive oil is present in injections marketed by other companies. Medium chain triglyceride (MCT) is present in a number of prescription medicine products but it has not been used in injections. Fish oil is not present in any prescription medicine products.

Fresenius Kabi Australia Pty Ltd applied to register a new combination SMOFlipid 20% composed of four oils, namely soya-bean oil 6%, medium chain triglycerides (MCT) 6%, olive oil 5% and fish oil 3% emulsion for intravenous infusion with the trade name SMOFlipid for the treatment of supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated. The recommended daily doses are 1.0 – 2.0 g fat/kg body weight per day, corresponding to 5 – 10 mL/kg body weight per day for adults.

Drug Product

The formulation and method of manufacture of SMOFlipid are based on the registered Intralipid products, which contain egg lecithin as emulsifier and glycerol for tonicity adjustment. However, it was found that a co-emulsifier, sodium oleate, was required in SMOFlipid in order to form a stable emulsion. In addition, SMOFlipid includes dl- α -tocopherol as antioxidant and sodium hydroxide to adjust to pH 8.

The packaging of SMOFlipid is identical to Intralipid. It consists of a three-layer inner plastic bag, known as ‘Excel’ film, to which a plastic port system is attached, and an oxygen- and water-impermeable outer bag. In between the two bags there is an oxygen-absorber sachet and an ‘Oxalert’ oxygen integrity indicator. The filled bags are terminally sterilised at $\geq 121^{\circ}\text{C}$.

The specifications applied to SMOFlipid are satisfactory. Adequate stability data have been provided to support the proposed shelf life of 2 years below 25°C (do not freeze).

Quality Summary and Conclusions

There is no objection on chemistry and quality control grounds to registration of SMOFlipid.

This application was considered by the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) at its 128th meeting on 21 September 2009. The subcommittee raised a number of pharmacokinetic and labelling issues for consideration by the Delegate. In particular, the subcommittee recommended that more prominence be given in the Consumer Medicines Information (CMI) document to the warning regarding allergies to fish, egg or soy products. It was suggested that an appropriate warning also be included on the product labels. A warning statement regarding allergies to fish, egg or soy products was included in the final approved CMI.

The PSC noted that the droplet size limits applied to SMOFlipid differ from those applied to Intralipid. Furthermore the laser diffraction test method proposed for use in measuring droplet size for SMOFlipid is different to the method approved for use with Intralipid. Although the PSC agreed that the laser diffraction test method proposed for use with SMOFlipid appears to be an appropriate method, data from a direct comparison of the droplet size of SMOFlipid and Intralipid using the same methodology would be informative for setting appropriate droplet size specifications for SMOFlipid especially considering the extensive clinical experience with Intralipid.

The PSC considered the pharmacokinetic summary inadequate to allow the Committee to make any recommendations with respect to the pharmacokinetics of SMOFlipid. The Committee therefore recommended the clinical evaluator undertake a detailed evaluation of the pharmacokinetics of this product, particularly with respect to the claim made in the Product Information (PI) that SMOFlipid has different pharmacokinetics to Intralipid. Alternative PK text later suggested by the Delegate was included in the final approved PI.

Subject to consideration of the PSC recommendations by the Delegate, there were no objections with regard to chemistry, manufacturing and controls to registration of this product.

III. Nonclinical Findings

Introduction

SMOFlipid is a combination of four different parenteral nutrition (PN) oils (soybean oil, MCT, olive oil and fish oil) already used in parenteral nutrition and registered as follows: Intralipid (soybean oil emulsion) registered by Pharmatel Fresenius Kabi Pty Ltd, Lipovenos MCT (including medium-chain triglycerides (MCT)) and Omegaven (fish oil emulsion) both registered by Fresenius Kabi, and a olive oil/soybean oil emulsion (Clinoleic, a Baxter Healthcare Pty Ltd product)

The maximum dose of SMOFlipid is 3 g/kg/day, which would result in daily MCT, soya and olive oil exposures less than those from currently-registered parenteral products. There are no PN agents containing fish oil registered in Australia, however there are multiple listed oral products.

The nonclinical submission comprised studies performed with SMOFlipid as well as those performed with the individual fat components. Full study reports and the English translation of a submitted paper were supplied in response to a request. Submitted nonclinical studies using the proposed clinical formulation included an acute toxicity study in rats, 2 repeat-dose studies in dogs (up to 3 months duration), a full set of genotoxicity studies and local tolerance studies. Studies with Omegaven were amongst the submitted supporting studies. This is considered acceptable to support an application for a fixed combination containing one or more new active substances according to the TGA-adopted EU guideline (*EMEA/CHMP/SWP/258498/2005: Guideline on the nonclinical development of fixed combinations of medicinal products*).

Pharmacology

Primary pharmacodynamics

SMOFlipid is essentially similar to Intralipid with the addition of MCTs and fish oil. MCTs are predominantly catabolised, rather than stored as adipose tissue and are therefore added to SMOFlipid as an immediate source of energy. The polyunsaturated fats in fish oil are precursors for the synthesis of eicosanoids (prostaglandins, thromboxanes, leukotrienes and other lipid mediators).

Secondary pharmacodynamics and safety pharmacology

No safety pharmacology studies using SMOFlipid were submitted. This is considered acceptable based on the amount of information on the individual components already submitted to the TGA. MCTs are hydrolysed at a faster rate than the other triglyceride components in SMOFlipid. Medium chain fatty acids (MCFAs) bind weakly to albumin and as a result they readily cross the blood-brain barrier. CNS effects from MCFAs have been observed in multiple species at plasma concentrations of 3-8 $\mu\text{mol/mL}$ (432-1152 $\mu\text{g/mL}$) (reviewed in Johnson and Cotter, 1986).⁴ At high infusion rates (about 10-fold that expected with SMOFlipid), mortalities were observed in mice, rats, rabbits and dogs with perimortem clinical signs of marked coordination disturbance, abnormalities of behaviour and posture, tremors and apathy. The plasma concentration of MCFAs will be important and can be regulated by both dose and infusion rate. This effect is an added risk associated with SMOFlipid not seen with Intralipid but should be adequately controlled with the proposed infusion rate.

Pharmacokinetics

The pharmacokinetics of soya oil and olive oil (LCTs) have been reviewed in previous evaluations and will not be discussed here. In capillaries, both MCTs and LCTs are hydrolysed by lipoprotein lipase to glycerol and free fatty acids, and MCFAs and long chain fatty acids (LCFAs), respectively. MCTs are hydrolysed at a faster rate than LCTs and therefore have a faster elimination rate. Free MCFAs then readily enter the liver, kidney, heart and other peripheral organs where they are oxidised by β -oxidation and the citric acid cycle to carbon dioxide and water. Alternatively, they lead to the formation of the ketone bodies, acetoacetate and β -hydroxybutyrate. In contrast, albumin-bound LCFAs do not readily enter peripheral organs and are predominantly metabolised by the liver with a preference for re-esterification to phospholipids or triglycerides and therefore potentially fat storage. MCFAs are subjected to a lower re-esterification rate than LCFAs with a reduced tendency to fat storage than LCTs.

The inclusion of MCTs in the PN agent could lead to increased plasma levels of medium chain dicarboxylic acids, 3-hydroxy fatty acids and ketone bodies. Hyperketonaemia was observed in repeat-dose toxicity studies with SMOFlipid. If excess MCTs are administered, the capacity of extrahepatic tissues to use ketone bodies is saturated and this may be of particular concern in some diabetes patients. The increased level of ketone bodies aggravates metabolic acidosis and accelerates the breakdown of homeostatic mechanisms (Bach & Babayan, 1982).⁵

The polyunsaturated fatty acids from fish oil (C22:6 and C22:5) are predominantly distributed to phospholipid, particularly in the liver. These fatty acids were undetectable in adipose triglycerides from beagles that had received fish oil, either alone, in combination with LCTs or in combination with MCTs/LCTs. Based on the lower LCT content in SMOFlipid compared with Intralipid, there is likely to be less fat storage from this parenteral agent compared with currently-registered parenteral agents.

⁴ Johnson RC, Cotter R. Metabolism of medium-chain triglyceride lipid emulsion. *Nutr Internat* 1986; 2: 150-158.

⁵ Bach AC, Babayan VK. Medium-chain triglycerides: an update. *Am J Clin Nutr* 1982; 36: 950-962.

Toxicology

General toxicity

Submitted toxicity studies included studies with soya oil and MCFA-containing lipids. As the toxicity of these lipids has been evaluated previously they are not discussed here. The toxicity of parenteral fish oil products has not been previously evaluated by the TGA. Submitted studies with intravenously (IV)-administered Omegaven 10% included two single dose studies in mice and rats, and two repeat-dose studies (with soya oil). A number of rats that had received the maximum single dose of Omegaven had loose faeces but no other treatment-related effects were observed. There were no toxicities observed in the repeat-dose studies that could be attributed to the fish oil at the maximum tested doses. In rats and dogs, these were equivalent to 2 and 7 times, respectively, the clinical dose of fish oil on a body surface area (BSA) basis from the maximum dose of SMOFlipid.

Studies using the clinical formulation of SMOFlipid included a single dose toxicity study in rats and repeat-dose studies up to 13 weeks duration in dogs. Doses used in the toxicity studies were low based on relative exposures (Table 1), but are typical for nonclinical studies with PN agents. Of note, though, infusion rates were considerably higher than that proposed clinically (≥ 5 -times on a BSA basis). This is considered adequate, as some of the toxicities (particularly neurotoxicity with MCTs) will depend largely on peak plasma concentrations achieved, rather than total time-weighted systemic exposure.

In a single dose toxicity study, no clinical signs or gross necropsy findings were observed in rats at ≤ 18 g/kg (approximately equivalent to the clinical dose based on BSA). All ten animals treated with 36 g/kg (ER (exposure ratio) =2, based on BSA) died in the 24 hours following infusion. Prior to death, animals had reduced motility, ataxia, catalepsy, reduced muscular tonus and dyspnoea. Mortality rates and peri-mortem clinical signs were similar with those observed in rats treated with similar doses (and infusion rates) of Intralipid or Lipovenös.

Table 1: Relative dose of SMOFlipid used in toxicity studies

Species (Strain)	Study; duration	Dose (g/kg/day)	Relative dose (based on g/kg)	Dose (g/m ² /day) ^a	Relative dose (based on g/m ²)	Infusion rate (g/kg/h)	Relative infusion rate (based on g/m ²)
Rat (SD)	9356/95 single dose	0, 9, 18, 36	0, 3, 6, 12	0, 18, 108, 216	0, 0.2, 1, 2	6	7
Dog (Beagle)	9358/1/95 4 weeks	0, 9	0, 3	0, 180	0, 2	1.5	6
Dog (Beagle)	10825/97 13 weeks	0, 3, 6	0, 1, 2	0, 60, 120	0, 0.7, 1.2	1	4
Human	–	3	–	99	–	0.15	–

^aUsing a g/kg to g/m² conversion factor of 6, 20 and 33 for rats, dogs and humans.

In dogs, the toxicity profile of SMOFlipid in toxicity studies up to 13 weeks was as expected for each of its individual components: soft or loose faeces (fish oil), hyperketonaemia (MCTs), mild thrombocytopenia (olive and soya oils), granulomatous pneumonia associated with fatty deposits in the lungs (soya oil) and lipophilic deposits in the liver (soya oil, olive oil and MCTs). Fatty changes in the liver had not completely reversed after a 4 week treatment-free period. The No Observable Adverse Effect Level (NOAEL) for toxicity was 6 g/kg/day (ER=1.2 based on BSA). As toxicities noted in SMOFlipid -treated animals did not appear to occur with greater incidence or severity than in animals that had received identical doses of the individual lipid components, there are no toxicological concerns with SMOFlipid that are in addition to those with currently-registered PN agents.

Genotoxicity

A standard battery of genotoxicity studies was conducted with the clinical formulation. As expected for this type of product, SMOFlipid was apparently not genotoxic. No carcinogenicity studies with SMOFlipid were submitted. Carcinogenicity studies performed by the National Toxicology Program with tricaprylin (an MCT), safflower oil, which contains polyunsaturated fats, and corn oil, which is a mixture of poly- and mono-unsaturated fats identified significant dose-related increases in the incidence of pancreatic exocrine hyperplasia and adenoma and increased incidences of proliferative lesions of the forestomach in F344/N rats that had received ≥ 4.8 g/kg/day tricaprylin orally for 5 days/week for 2 years. The No Observable Effect Level (NOEL) was 2.4 g/kg/day orally (NTP, 1994).⁶ These neoplastic and hyperplastic formations are likely attributable to the high metabolic load associated with continued administration of large amounts of fat. As these would occur irrespective of the nature of the lipid, there is unlikely to be an increased risk in tumour formation from SMOFlipid compared with currently registered PN agents.

Reproductive toxicity

No studies using SMOFlipid were submitted. Previous reproductive toxicity studies with PN agents indicate that soya oil was not embryotoxic or teratogenic in rats and rabbits up to 9 g/kg. Intralipid (soya oil), the combination of soya and olive oil, and the combination of MCFAs and LCFAs have not been adequately tested in reproductive toxicity studies. No adverse effects were observed in rats that had received (orally) docosahexaenoic acid (C22:6 ω 3)(DHA) and eicosapentaenoic acid (C20:5 ω 3) (EPA), the fatty acids in fish oil (this submission). An increase in resorptions, prolonged gestation duration and increased pup birth and postnatal weights were observed in female rats that had received 1.2 g/kg/day 20% MCT/LCT for 14 days prior to mating (below the clinical dose on a BSA basis). Embryofetal toxicity (resorptions) and skeletal abnormalities were observed in rabbits following infusion of 20% MCT/LCT (3:1) during the period of organogenesis at 4.28 g/kg/day, but not 1 g/kg/day; no adverse effects were seen in rats (Henwood *et al*, 1997).⁷ Similarly, embryotoxicity and an increased incidence of skeletal variations were observed in an embryofetal development study in rabbits that had received a combination of MCFAs and LCFAs. This was attributed to high maternal plasma levels of MCFAs, hyperketonaemia and possibly hypoglycaemia. Due to the presence of MCTs, SMOFlipid may be more embryotoxic than Intralipid or the combination of soya and olive oil and should not be used during pregnancy unless the potential benefit to the mother outweighs the risk to the fetus.

Use in children

No studies have been performed in juvenile animals.

Local tolerance

There were no treatment-related local changes after intra-arterial, paravenous or subcutaneous (SC) administration of SMOFlipid in rabbits. Thrombosis was observed in 1/6 IV-treated animals with more distinct local changes of inflammation and necrosis after intramuscular (IM) administration. These local effects were similar to those seen for Intralipid. These local effects diminished after 14 days. Omegaven 10% was a moderate sensitiser in guinea pigs.

⁶ NTP. Comparative toxicology studies of corn oil, safflower oil and tricaprylin (CAS Nos8001-30-7, 8001-23-8 and 538-23-8) in male F344/N rats as vehicles for gavage. Natl Toxicol Program Tech Rep Ser 1994; 426: 1-314.

⁷ Henwood S, Wilson D, White R, Trimbo S. Developmental toxicity study in rats and rabbits administered an emulsion containing medium chain triglycerides as an alternative caloric source. Fund Appl Toxicol 1997; 40: 185-190.

Impurities

Several potential impurities were identified for SMOFlipid. These included migrants from the plastic containers, phytosterols, the residual solvent, petroleum ether and the degradant, lysophosphatidylcholine. The sponsor provided expert reports discussing the safety of most of these compounds. Toxicological qualification of the migrants relied largely on data following oral administration, rather than the proposed clinical route (IV). As all of these, except one, are orally bioavailable, adequate toxicological assessments could be made for the current application. According to data provided by the sponsor, that particular impurity is not orally bioavailable and therefore assessment of the safety of this compound assumed 0.1% bioavailability. This is not strictly correct and an adequate assessment of this compound has not been supplied. However, as the "Excel" bag is identical to that used in Intralipid products and only slight differences in migration would be expected with differences in lipid composition, the levels of the migrants proposed are considered acceptable. There were no toxicological concerns associated with the levels of the other impurities that would preclude registration of SMOFlipid.

Nonclinical Summary and Conclusions

Fresenius Kabi Australia Pty Ltd applied to register the new chemical entity, SMOFlipid, containing soya, olive and fish oils and medium chain triglycerides (MCTs), as a parenteral nutrition (PN) agent. The maximum proposed dose of MCTs, soy and olive oils from SMOFlipid is less than in currently-registered parenteral agents.

Submitted nonclinical studies using the proposed clinical formulation included an acute toxicity study in rats, 2 repeat-dose toxicity studies of up to 13 weeks duration in dogs, a full set of genotoxicity studies and a number of local tolerance studies.

Toxicity studies with SMOFlipid revealed no novel or exacerbated toxicities compared with currently-registered PN agents.

As with existing PN agents, SMOFlipid was not genotoxic, and an increased risk in tumour formation compared with currently-registered PN agents is considered unlikely.

Reproductive studies with soya oil- and olive oil-containing PN agents have been inadequate. In rats, infusion of 20% MCT/LCT (long chain triglyceride) for 2 weeks prior to mating was associated with increased resorptions, prolonged gestation and increased pup birth and postnatal weights. In rabbits, infusion of 20% MCT/LCT during organogenesis elicited increased resorptions and skeletal abnormalities. SMOFlipid should not be used during pregnancy.

No studies have been performed in juvenile animals.

SMOFlipid was well-tolerated in rabbits after intra-arterial, paravenous, SC and IV administration. Similar to currently-registered PN agents, IM administration of SMOFlipid caused reversible inflammation and necrosis. The fish oil component of SMOFlipid is a moderate sensitiser.

There are no toxicological concerns from several potential impurities in the product.

There are no objections on nonclinical grounds to the registration of SMOFlipid.

IV. Clinical Findings

Introduction

This was described as a hybrid application containing published literature and company sponsored clinical studies, and while this may be true for the nonclinical part of the application, the literature

supplied with the clinical part of the application was described as articles cited and included the Swedish delegate's Executive Summary and Risk Benefit Assessment.

There are no EU guidelines on assessment of lipid emulsions. The reference guidelines in the provided literature include excerpts of the Austrian Society Clinical Nutrition (but not even the complete parenteral nutrition section). While this was dated 2008 it did not appear to be more than a consensus statement protocol without supporting references. The American Society of Enteral and Parenteral Nutrition Guidelines were approved in October 2001 and they were provided in their entirety and contain references. However, not all the constituents related to this submission are registered in the US and the guidelines are thus very limited in content and value. The Guidelines on Paediatric Nutrition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Society for Paediatric Research (ESPR) are more comprehensive, containing references and more importantly the search strategy from 1992 to December 2003.

The submission included:

Pivotal Study of Efficacy

- FE-SM-03-DE: Study of efficacy, safety and tolerance of SMOF 20% vs. Lipovenos 20% during 5 days parenteral nutrition in surgical patients (126 on SMOF).^{8,9}

Non-Pivotal Studies of Efficacy ± Safety in Infants and Children

- 00-SMOF-002: A Study of safety and efficacy of SMOF 20% vs. Intralipid 20% in infants and children (15 on SMOF) requiring long-term parenteral nutrition (4-5 days/week for 4 weeks).
- 00-SMOF-004: A Study of the safety, tolerability and efficacy of SMOF 20% vs. Intralipid 20% (for 7-14 days) in premature infants (30 on SMOF).
- 03-SMOF-005: -A Study of the safety, tolerability and efficacy of SMOF 20% vs. Intralipid 20% (for 7-14 days) in premature infants (42 on SMOF).

Studies Evaluable for Safety Only

- FE-SM-04-CH: Study of safety and tolerance of SMOF 20% vs. Lipovenos 20% in (16 on SMOF) patients requiring long-term parenteral nutrition (for 10-14 days).
- 03-3CB7-001: Study of the safety and tolerance of 3CB SMOF EL compared to Kabiven in post-operative subjects (26 on SMOF) requiring parenteral nutrition (for 5-7 days).
- 03-3CB8-001: Safety and tolerance of 3CB SMOF Peri EL compared to Kabiven Peripheral in 27 patients for 5-7 days.

Pharmacokinetic Studies

- FE-SM-01-BE: Intravascular metabolism of SMOF 20% vs. Lipovenos 20% in healthy subjects.

⁸ The leukotriene findings have been published by Grimm H, Mertes N, Goeters C, Schlotzer E, Mayer K, Grimminger F, Furst P. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* 2006; 45: 55-60.

⁹ Based on patient numbers, authors etc. this appears to have been published as Mertes N, Grimm H, Furst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: A randomized, double-blind, multicentre study. *Ann Nutr Metab* 2006; 50: 253-9.

- FE-SM-02-DE: Clinical study of the safety, tolerability and elimination of SMOF 20%, vs. Lipovenos 20% during and after an IV infusion to healthy male volunteers.

There was no literature review submitted, in particular there was no systematic literature review in relation to efficacy and safety.¹⁰ There was, however, prior agreement between TGA and the sponsor on a non-systematic search for this submission.

The sponsor's non-clinical pharmacokinetic (PK) Written Summary contained considerable information on the digestion, absorption and first pass metabolism of the principal constituents. The formulation used in the PK studies contained less fish oil (20 g/L), and more olive oil (60 g/L). The formulation used in the pivotal studies was that proposed for marketing in Australia.

Pharmacokinetics

The PKs were discussed by the sponsor in its Non-Clinical PK Written Summary: the PKs in the sponsor's Clinical Summary only related to the PK studies submitted. Being given intravenously, only distribution and elimination are relevant.¹¹

Study FE-SM-01-BE

Study FE-SM-01 was an open-label, randomised, 2-treatment, 2-period crossover study to compare the intravascular metabolism of SMOFlipid 20% vs. Lipovenos 20% (soya based) in 10 healthy male volunteers (Table 2).

Table 2: Details of Study FE-SM-01-BE

Design; Study population; PK methods	Subjects; Treatment; Dose, Duration	PK Results	Safety
<p>Open-label, randomized, 2-treatment, 2-period crossover study, to compare the intravascular metabolism of SMOFlipid 20% vs. Lipovenos 20% (soya based) in healthy volunteers.</p> <p>Primary efficacy variables were infusion rate to maintain plasma triglycerides at 3mmol/L and elimination rate after stopping infusion.</p> <p>Secondary variables were concentrations of lipids, apolipoproteins and fatty acid pattern.</p>	<p>10 volunteer Males</p> <p>Age: mean 28y (range 21-36y).</p> <p>Weight: mean 72.4kg (range 61-84kg).</p> <p>All fasted \geq 10h, then 2.5h prior they received concomitantly by peripheral IV infusion glucose 0.25g/kg for first hour, then 0.16g/kg/h and amino acids 0.05g/kg/h to achieve low levels of gluconeogenesis and ketogenesis and fatty acid mobilisation from endogenous stores. These continued throughout for a total of 8-8.3h.</p> <p>One of the two lipid products was given by peripheral IV infusion of 1g of triglycerides/kg/h for 6 min, then approx 0.15g triglycerides/kg/h (to maintain plasma triglycerides at 3mmol/L) for a total of 4h.</p> <p>Approx. 4-week washout between treatment periods.</p>	<p>During last 2h of infusion:</p> <p>SMOF 0.151 \pm 0.039 g/kg/h maintained plasma triglyceride at 3.2mmol/L.</p> <p>Lipovenos 0.138 \pm 0.039g/kg/h maintained plasma triglyceride at 3.0mmol/L.</p> <p>There was no statistical difference.</p> <p>Triglyceride mean T_{1/2} (decay to 50% of the difference before/after infusion) was:</p> <p>SMOF 21.92 minutes</p> <p>Lipovenos 26.96 minutes</p> <p>(There was no statistical difference).</p>	<p>Lipovenos:3 had AE mild headache.</p> <p>SMOF: 4 had AE mild headache, 1 had stinging and itchiness hands (latter felt possibly related to study drug).</p> <p>No clinically relevant abnormal changes in laboratory results.</p> <p>α-tocopherol increased with SMOF but not Lipovenos, γ-tocopherol increased with both preparations.</p>

¹⁰ The literature search is described as non systemic. The actual notes of the pre submission meeting and teleconference use the term non-systematic.

¹¹ pp. 99 - 106 of Rules 1998 (3C) - 3CC3a Pharmacokinetic Studies in Man.

Primary efficacy variables were infusion rate to maintain plasma triglycerides at 3 mmol/L¹² and elimination rate after stopping infusion (Table 3).

Table 3: SM-01. Summary of rate of lipid infusion and decay of plasma triglycerides

	SMOF (N = 10)	Lipovenos (N = 10)	Difference SMOF-Lipovenos (N=10)
Rate of lipid infusion (g TG/kg/h), mean over last 2h			
Mean	0.151	0.138	0.013
Median	0.160	0.142	0.008
SD	0.039	0.039	0.033
Range	0.095 -0.203	0.083 -0.200	-0.044 – 0.063
95% CI ^a			[-0.006; 0.032]
p.value ^a			0.163
Enzymatic triglyceride conc. (mmol/L), mean over last 2hours(3h, 4h)			
Mean	3.213	2.992	0.221
Median	3.236	3.067	0.112
SD	0.260	0.451	0.496
Range	2.644 - 3.621	1.866 – 3.578	-0.358 - 1.262
Half-life (Decay of Plasma triglycerides to 50% of the difference Before/After Infusion) (Minutes)			
Mean	21.92	26.96	-5.04
Median	19.11	24.04	-1.39
SD	8.15	12.69	9.20
Range	13.20 - 37.81	13.52 – 52.41	-18.91 - 5.20
95% CI ^a			[-11.57; 1.49]
p.value ^a			0.113

^a Based on the ANOVA model: Variable = treatment sequence + subject + treatment + visit. CI= confidence intervals

Secondary variables were concentrations of lipids, apolipoproteins and fatty acid pattern. One of the lipid preparations was given by peripheral IV infusion for a total of 4 hours with a 4-week washout before the other lipid was infused for 4 hours. There was no statistical difference in either of the primary variables. Non esterified fatty acids at 1, 2, and 4 hours increased significantly more for SMOF than for Lipovenos (this is presumed due to the greater MCT content from which fatty acids were more rapidly released). There was an increase in triglycerides that occurred mostly in the very low density lipoprotein (VLDL) with SMOF resulting in an ~10% greater rise. There was very little difference or change in the major apolipoproteins in plasma (A-I, A-II, and B), while for most apolipoproteins the component in VLDL doubled by 4 hours then fell for both preparations.

Looking at the fatty acid profiles, the sum of caprylic and capric acids (products of MCTs) rose considerably with SMOF while Lipovenos showed almost no change. Ω -9 levels were maintained with SMOF while they fell with Lipovenos. Ω -6 levels rose with SMOF, but there was a much greater rise with Lipovenos. Of the ω -3 acids; α -linolenic rose more with Lipovenos, while DHA

¹² The reference for this level was given as Carpentier Y A, Kinney JM, Siderova VS, Richelle M, Nishiwaki H, Olivecrona T, Deckelbaum R. Hypertriglyceride clamp: a new model for studying lipid metabolism. Clin Nutr 1990; 9: Spec Suppl; however, this described the technique but used higher plasma triglyceride targets (~6 mmol/L) to show differences between 2 lipids. The reason for choosing 3 mmol/L was not given.

and EPA rose more with SMOF. The individual exposure range was not given but mean exposure could be calculated as ~52 g with a recommended daily exposure of 72-144 g.

Study FE-SM-02-DE

Study FE-SM-02-DE was a double-blind, randomized, active- 2-treatment, 2-period crossover study to compare, the safety, tolerability and elimination of triglycerides, and PK of lipid parameters of SMOFlipid 20% vs. Lipovenos 20% in 12 healthy male volunteers (Table 4).

Table 4: Details of Study FE-SM-02-DE

Design; Study population; PK methods	Subjects; Treatment; Dose, Duration	PK Results				Safety
		Parameter (mean ± SD)	SMOF	Lipovenos	Statistic	
Double-blind, randomized, active- 2-treatment, 2-period crossover study to compare, the safety, tolerability and elimination of triglycerides, and PKs of lipid parameters of SMOFlipid 20% vs. Lipovenos 20%. Primary endpoints: serum triglycerides Tolerability (lab. results, ECG, pulse, BP, temperature & AEs). Secondary endpoints: serum phospholipids, cholesterol, free fatty acids, and free glycerol, local tolerability.	12 volunteer males Age: mean 25.67 (range 18-30)years Weight: mean 72.74 (range 57.8-105.1)kg All fasted ≥ 10h prior and until after the 9h bloods were taken. Infusion of lipid occurred over 6h at 0.125g/kg/h with a washout of ≥ 6days.	AUC _{0-t} ^a [mg*h/dL]	3002 ± 1331	3341 ± 1352		Lipovenos: 1 AE (herpes). SMOF: 2 had AEs of headache (1 thought possibly related), 3 had abnormal sensation hands (thought possibly related), 1 had dizziness. All AEs were mild. 2 subjects showed mild to moderate increases in bilirubin
		C _{max} ^b [mg/dL]	291 ± 144	349 ± 158		
		t _{max} ^c [h]	3.50 ± 0.80	5.44 ± 0.82		
		λ _z ^d [L/h]	2.30 ± 0.88	1.42 ± 0.71	P = 0.003	
		t _{1/2} ^e [h]	0.34 ± 0.11	0.59 ± 0.25	P = 0.0007	

a: AUC_{0-t} = area under the plasma concentration time curve from time zero to time t, b: maximal plasma concentration, c: time to maximal concentration, d: λ_z, e: t_{1/2}: half-life

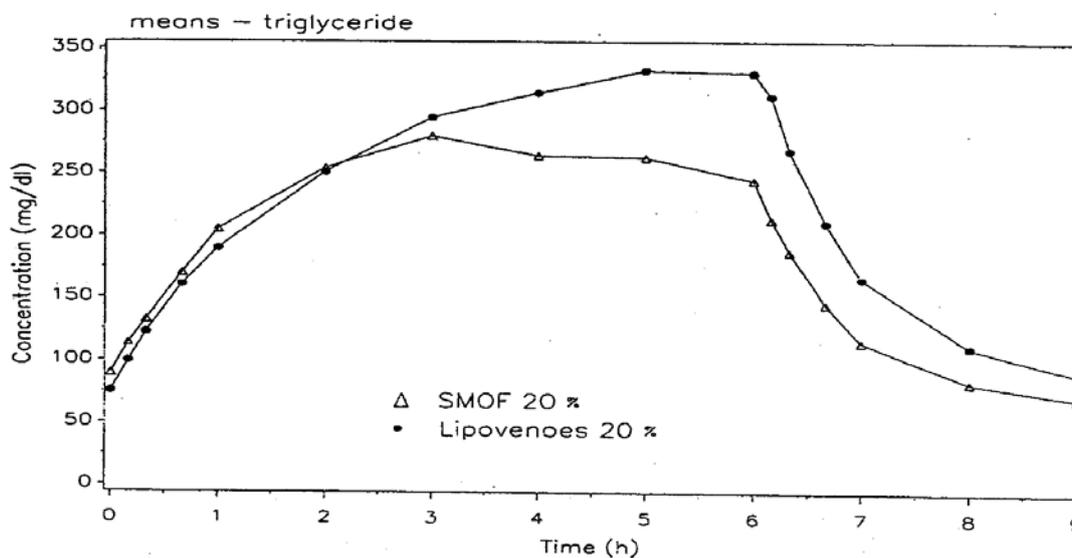
Primary endpoints were serum triglycerides and tolerability (laboratory results, electrocardiogram (ECG), pulse, blood pressure (BP), temperature and adverse effects (AEs). Secondary endpoints were serum phospholipids, cholesterol, free fatty acids, free glycerol, and local tolerance. Infusion of lipid occurred over 6 hours at 0.125g/kg/h with a washout of ≥ 6days. Increase in triglycerides was greater with Lipovenos the difference being statistically significant (p = 0.0325) only at 6 hours (Table 5, Figure 1). Clearance was greater for SMOF (p = 0.003) and t_{1/2} was shorter (p = 0.0007).

Table 5: SM-02.1 PKs of Triglycerides after 6h of SMOF and Lipovenos to Healthy Subjects

Parameter	SMOF 20% mean \pm SD median (range)	Lipovenos 20% mean \pm SD median (range)	Statistic
AUC _{0-t} [mg*h/Dl]	3002 \pm 1331 2598 (1288 - 6164)	3341 \pm 1352 3177 (1844 - 6099)	
C _{max} [mg/dL]	291 \pm 144 260 (100 - 657)	349 \pm 158 348 (137 - 678)	
t _{max} [h]	3.50 \pm 0.80 3.00 (3.00 - 5.00)	5.44 \pm 0.82 6.00 (4.00 - 6.17)	
λ_z [L/h]	2.30 \pm 0.88 1.95 (1.27 - 4.28)	1.42 \pm 0.71 1.17 (0.71 - 2.65)	P = 0.003
t _{1/2} [h]	0.34 \pm 0.11 0.35 (0.16 - 0.54)	0.59 \pm 0.25 0.60 (0.26 - 0.89)	P = 0.0007
C _{4h} [mg/dL]	264 \pm 127 225 (100 - 598)	315 \pm 141 276 (129 - 583)	P = 0.136 ^a
C _{5h} [mg/dL]	263 \pm 144 216 (90 - 657)	333 \pm 150 315 (137 - 647)	P = 0.058 ^a
C _{6h} [mg/dL]	244 \pm 126 198 (88 - 550)	331 \pm 150 348 (114 - 576)	P = 0.0325

^a not significant

Figure 1: SM-02.2 Mean plots of triglyceride concentration following 6h infusions of SMOF and Lipovenos.

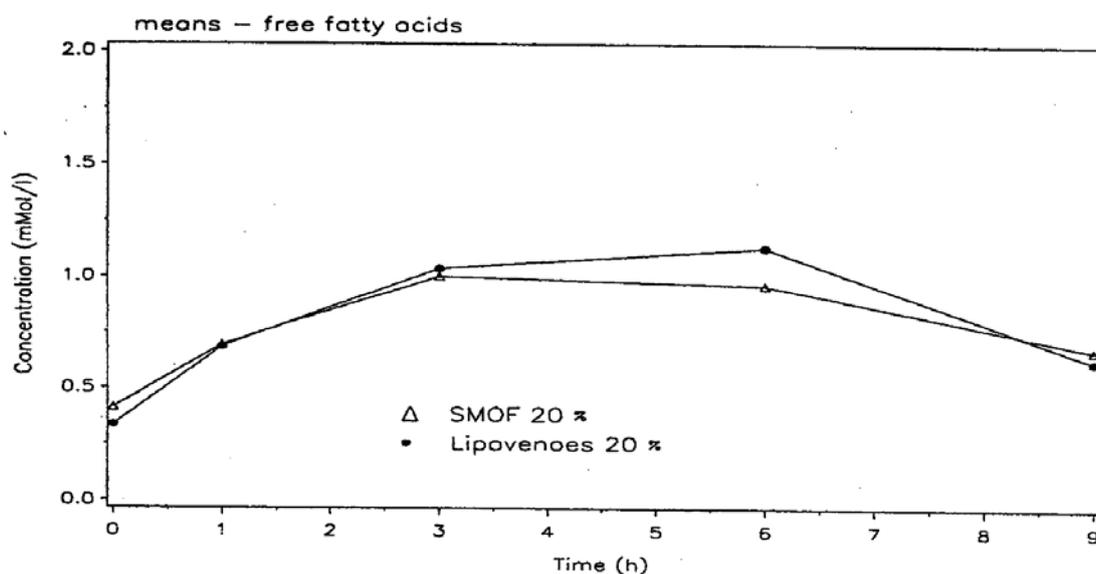


Free fatty acids rose with a time course similar to triglycerides with SMOF slightly lower than Lipovenos (Table 6, Figure 2).

Table 6: SM-02.3 PKs of free fatty acids following administration of SMOF and Lipovenos.

Parameter	SMOF 20% mean ± SD	Lipovenos 20% mean ± SD
	median (range)	median (range)
AUC _{0-t} [mg*h/dL]	15.4 ± 2.81 15.5 (11.2 - 20.9)	15.4 ± 1.88 15.1 (12.3 - 19.2)
C _{max} [mg/dL]	1.04 ± 0.23 0.98 (0.79 - 1.68)	1.16 ± 0.29 1.12 (0.82 - 1.69)
t _{max} [h]	4.25 ± 2.01 3 (3 - 9)	5.75 ± 1.55 6 (3 - 9)

Figure 2: SM-02.4 Mean plots of serum free fatty acid concentration following 6h infusions of SMOF and Lipovenos.

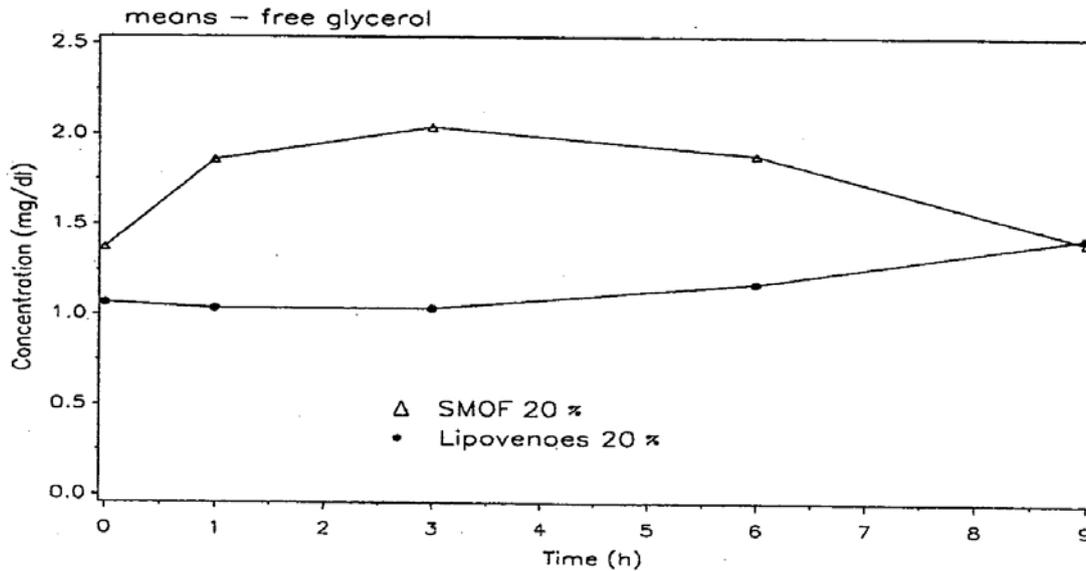


While free glycerol rose somewhat similarly for SMOF, with Lipovenos there was a delayed and lower rise, this was felt to reflect the faster hydrolysis of SMOF (Table 7, Figure 3).

Table 7: SM-02.5 PKs of free glycerol following administration of SMOF and Lipovenos.

Parameter	SMOF 20% mean ± SD	Lipovenos 20% mean ± SD
	median (range)	median (range)
AUC _{0-t} [mg*h/dL]	33.5 ± 20.9 31.1 (5.30 - 83.8)	26.9 ± 11.0 24.3 (10 - 45.6)
C _{max} [mg/dL]	2.52 ± 1.13 2.1 (1.4 - 4.9)	2.08 ± 0.77 1.9 (1.3 - 3.9)
t _{max} [h]	2.83 ± 2.62 3.0 (0 - 9)	7.01 ± 6.56 7.5 (0 - 24)

Figure 3: SM-02.6 Mean plots of free glycerol concentration following 6h infusions of SMOF and Lipovenos.



Total cholesterol did not vary greatly. Phospholipids rose slightly. Total dose infused was 0.75 g/kg, again lower than recommended daily dose.

The evaluator expressed uncertainties about the strength of the findings in the PK studies and did not support the proposed insertion in the PK subsection of the proposed PI. Alternative PK text later suggested by the Delegate was included in the final approved PI.

Drug Interactions

No specific clinical drug-drug interaction studies were carried out but SMOFlipid 20%, as well as the control study medications of Intralipid 20% and Lipovenos 20% have been widely used with no known adverse drug-drug interactions. From marketing experience in other countries, there were no cases of any drug interactions reported. However, the addition of other medications or substances directly to SMOFlipid 20% should generally be avoided unless compatibility is known. Some medicinal products, like insulin, may interfere with the body's lipase system. This kind of interaction seems, however, to be of limited clinical importance.

Heparin given in clinical doses causes a transient release of lipoprotein lipase into the circulation. This may result initially in increased plasma lipolysis followed by a transient decrease in triglyceride clearance.

Soya-bean oil has a natural content of vitamin K₁. However, the concentration in SMOFlipid 20% is so low that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

Pharmacodynamics

There were neither pharmacodynamic (PD) studies nor literature search evidence submitted for the combination or the individual components. It was argued that the individual lipid components had been examined in detail in many years of previous research. As already stated, however, two of the components were new chemical entities (NCEs).

The lipids are in particles similar to chylomicrons in that they have a triglyceride core stabilised by a surface layer of emulsifier (an egg derived phospholipid). Unlike chylomicrons however they contain no lipoprotein, so they acquire circulating lipoprotein. They bind to endothelial lipoprotein lipase (for example, in muscle, adipose tissue) with hydrolysis of triglycerides yielding fatty

acids.^{2,13,14,15} As they give up triglyceride the emulsion particles may take up circulating cholesterol in a process that can lead to hypercholesterolemia. Some similar smaller particles (lioposomes) may form in the emulsion *ex vivo* from excess of emulsifier; these competitively inhibit chylomicron-like particle lipolysis and similarly can uptake cholesterol and bind to albumin and some apoproteins.¹⁶ Hence there are recommendations in the literature concerning intermittent infusion and at limited infusion rate in order to clear these smaller particles, and using a 20% lipid rather than 10% to diminish the relative effect of the excess of emulsifier. The Guidelines on Paediatric Nutrition of ESPGHAN, ESPEN & ESPR however recommends continuous 24 hour infusions in infants, newborn and premature infants.

Fatty acids have four metabolic pathways in the body

- as cell membrane,
- storage in adipose tissue,
- synthesis of eicosanoids, and
- oxidation to provide energy.¹⁷

The soya oil component contains poly unsaturated, long chain triglycerides (LCTs) including the essential fatty acids with an excess (7:1) of linoleic acid (ω -6) over α -linolenic acid (ω -3). These fatty acids are incorporated into the membrane phospholipids of immunologic cells. In the inflammatory immune response they serve as a substrate for eicosanoid synthesis, with linoleic acid (ω -6) forming arachidonic acid, and α -linolenic acid (ω -3) forming eicosapentaenoic acid. There is competition for the same enzymatic path, so that an excess of linoleic acid (ω -6) will result in more arachidonic acid, the products of which are pro inflammatory (including prostaglandin E₂, leukotriene B₄, thromboxane₂, and platelet aggregation factor).^{2,18}

The MCT component is more water soluble (100 x) and medium chain fatty acids have a lower affinity for albumin, they undergo hydrolysis to fatty acids faster and undergo more rapid oxidation (transport of MCTs into the mitochondria is largely independent of carnitine). They are more used for energy generation rather than deposition in the tissues when compared with LCTs.^{2,13}

The olive oil component contains considerable amounts of monounsaturated oleic acid (ω -9) which competes with ω -3 and ω -6 for incorporation into membrane phospholipids. A decrease in synthesis of pro inflammatory eicosanoids is seen.^{19,20} Poly unsaturated fatty acids decrease plasma LDL-cholesterol but also decrease the beneficial HDL-cholesterol, whereas monounsaturated acids reduce LDL-cholesterol whilst having little effect on the beneficial HDL-cholesterol.

¹³ Carpentier YA, Dupont IE. Advances in intravenous lipid emulsions. *World J Surg* 2000; 24: 1493-7.

¹⁴ Driscoll DF. Lipid injectable emulsions. *Nutr Clin Pract* 2006; 21:381-6.

¹⁵ Ulrich H, Pastores SM, Katz DP, Kvetan V. Parenteral use of medium-chain triglycerides: a reappraisal. *Nutrition* 1996; 12: 231-8.

¹⁶ Lai H-S, Lin W-H, Wu H-C, Chang K-J, Chen W-J. Effects of a medium-chain triacylglycerol/long-chain triacylglycerol fat emulsion containing a reduced ratio of phospholipid to triacylglycerol in paediatric surgical patients. *Nutrition* 2005; 21:825-30.

¹⁷ Gentili A, Pigna A, Iannella E, Mondardini MC, Ceccarelli PL, Baccarini E, Baroncini S. Prolonged neonatal parenteral nutrition with a fat emulsion containing medium-chain triglycerides. *Rivista Italiana di Nutrizione Parenterale ed Enterale* 2000; 18:134-42.

¹⁸ Lee S, Gura KM, Kim S, Arsenault DA, Bistrrian BR, Puder M. Current clinical applications of omega-6 and omega-3 fatty acids. *Nutr Clin Pract* 2006; 21:323-41.

¹⁹ G Wanten. An Update on Parenteral Lipids and Immune Function: only smoke or is there fire. *Current Opinion in Clin Nutr Metabol Care* 2006; 9: 79-83.

²⁰ Vahedi K, Atlan P, Joly F, Le Brun A, Evard D, Perennec V, Roux-Haguenau D, Bereziat G, Messing B. A 3-month double-blind randomised study comparing an olive oil- with a soyabean oil-based intravenous lipid emulsion in home parenteral nutrition patients. *Br J Nutr* 2005; 94: 909-16.

The fish oil component, with a predominance of ω -3 LCTs (principally of eicosapentaenoic acid), also alters the ratio of ω -3 to ω -6 in the membrane phospholipids favouring a further decrease in pro-inflammatory eicosanoids. Additionally, there is an improvement in liver function (serum liver enzymes and bilirubin levels).²¹

Peroxidation may occur during manufacture, storage and IV delivery (when TPN is unprotected from light and UV therapy). It may occur *in vivo* in infants and in adults on home TPN, as indicated by the presence of malonic dialdehyde (MDA) in the urine.¹³ Polyunsaturated fatty acids can act as substrates for the formation of lipid hyperoxides (which may in themselves be pro-inflammatory),²² mediated by free radicals. Olive oil, with its lower content of polyunsaturated fatty acids, undergoes less peroxidation *in vivo* and *in vitro*.²³

α -Tocopherol acts as a free radical scavenger both *in vivo* and *in vitro* countering the risk of hyperoxide damage. The content varies with the source of the oils. α -Tocopherol is inserted between phospholipids in cell membranes and lipoprotein surfaces.

The evaluator noted that the pharmacodynamics information came from a review of the literature provided. The evaluator expressed concerns about the selection of references in the absence of a submitted search process (see Conclusion). However, there was a prior agreement with the TGA and the sponsor on a non-systematic search for this submission.

In the primary efficacy study (FM-SM-03-DE) a secondary variable assessed were the eicosanoids LTB₄, LTB₅, TBX₂ & TBX₃. There was a statistical difference shown for LBT₅ between SMOFlipid and Lipovenos, but not for any other parameter or their ratios. Leukocyte phospholipids after treatment showed significant differences in change for EPA, DHA and linoleic acid, while platelet phospholipids had significant differences in change for oleic acid as well as for EPA, DHA and linoleic acid.

Pre-term infants require DHA and AA for rapid body and brain growth. There is no appreciable intrinsic δ -6 desaturase activity to form them from precursors ALA and LA, thus DHA and AA provision is obligatory.

Efficacy

The indications require assessment of efficacy of 3 parameters in patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated, as follows:

- Supply of energy
- Supply of essential fatty acids
- Supply of omega-3 fatty acids

Pivotal Study FM-SM-03-DE

This was a prospective, randomised, parallel group, double-blind, controlled study in patients needing TPN after surgery (Table 8). The study was multicentre in Belgium, France and Germany.

SMOF 20% and Lipovenos 20% were given continuously over 24 hours at 1.5 g fat/kg/day (recommended dose = 1-2 g/day).

Amino acids (~ 1.5 g/kg /d) and glucose (3.0-4.0 g/kg/d) were to be given concurrently.

²¹ G Wanten, P Calder Immune Modulation by Parenteral Lipid Emulsions Am J Clin Nutr 2007; 85: 1171-84.

²² Trebble T, Arden NK, Stroud MA, Wootton SA, Burdge GC, Miles EA Ballinger AB, Thompson RL, Calder PC. Inhibition of tumour necrosis factor-alpha and interleukin 6 production by mononuclear cells following dietary fish-oil supplementation in healthy men and response to antioxidant co-supplementation. Br J Nutr 2003; 90: 405-12.

²³ Pironi L, Guidetti M, Zolezzi C, Fasano MC, Paganelli F, Merli C, Bersani G, Pizzoferrato A, Miglioli M. Peroxidation potential of lipid emulsions after compounding in all-in-one solutions. Nutrition. 2003; 19:784-8.

Table 8: Details of Study FM-SM-03-DE

Design; Population	Treatments; Dose, Duration; Subjects	Efficacy measures/ outcomes	Efficacy results	Safety
<p>Double-blind, randomized, active-controlled, parallel-group study of efficacy, safety, and tolerance of SMOFlipid (SMOF) 20% vs. Lipovenos 20% following major abdominal, thoracic, or urological surgery.</p> <p>249 randomised SMOF: 126 Lipovenos: 123</p>	<p>Continuous infusion over 24h per day for 5days post-op.</p> <p>SMOFlipid 20% or Lipovenos 20%</p> <p>1.5 g fat/kg/d by central IV infusion together with amino acids (~ 1.5 g/kg /d) and glucose (3.0-4.0 g/kg/d). The doses of lipids and glucose could each be optionally reduced by up to 50% on the first post-operative day.</p> <p>SMOF: (ITT = 126, PP = 99)</p> <p>M/F 58(58.6%)/41(41.4%); Age mean 60.5 ± 14.15y (range 23 – 89y); Weight: mean 70.5 ± 11.70kg (range 45-92kg);</p> <p>Lipovenos: (ITT = 123 PP = 100).</p> <p>M/F 65(65%)/35(35%).</p> <p>Age: mean 60.2 ± 13.75y (range 19 – 84y). Weight: mean 71.6 ± 12.81kg (range 39-104.5kg).</p>	<p>Primary: AUC of the difference between baseline serum triglyceride and concentrations at each measurement point up to day 6.</p> <p>Secondary:</p> <ul style="list-style-type: none"> the plasma and cell membrane fatty acid profile and eicosanoid synthesis(at selected study centres). the clinical outcome, mortality and length of stay (LOS) in an ICU and in hospital. other parameters of lipid metabolism (serum total cholesterol and phospholipids). Safety variables including laboratory parameters, vital signs, and AEs), and at selected study centres plasma vitamin E (α-, γ-tocopherols). 	<p>Primary: SMOF lipid infusion as assessed by Serum concentration of triglycerides mean daily AUC (difference from baseline) was non-inferior to Lipovenos infusion.</p> <p>Secondary:</p> <ul style="list-style-type: none"> Plasma fatty acid change for ω3 & ω9 acids reflected the composition of the infusions. Plasma fatty acids in phospholipids and Leukocyte phospholipids showed significant differences in change for EPA, DHA and linoleic acid, as did platelet phospholipids with significant differences in change for oleic acid as well. Mean LOS for the SMOF group was 15.688 days and 17.827 days for the Lipovenos group, LOS in ICU was 4.66 vs. 5.19 days. Mean serum total cholesterol and phospholipids were comparable at all time points across treatment groups. <p>Eicosanoids. There was a statistical difference shown for LBT₅ between SMOFlipid and Lipovenos, but not for LTB₄, TBX₂ or TBX₃.</p>	<p>7 deaths none related to study drug.</p> <p>12 SMOF and 11 Lipovenos patients had 37 possibly or probably treatment-related AEs, including:</p> <p>SMOF; nausea (5), vomiting (4), dysgeusia (2), cholestatic hepatitis (2), hyperglycaemia (2), hypertriglyceridaemia (2) (1 had severe nausea and vomiting).</p> <p>Lipovenos; nausea (5) vomiting (4), hepatocellular damage (2), cholestasis, hyperglycaemia, hypertriglyceridaemia, and headache (1 each) (1 had severe hyperglycaemia).</p> <p>Most treatment-related AEs were mild or moderate. There was one accidental overdose of Lipovenos that produced nausea and vomiting (the only treatment-related SAE).</p> <p>Patient discontinuations (treatment-related):</p> <p>SMOF; nausea and vomiting (2), vomiting (1).</p> <p>Lipovenos; hyperglycaemia and hypertriglyceridaemia (1).</p>

Depending on the metabolic condition of the patient, the doses of lipids and glucose could each be optionally reduced by up to 50% on the first post-operative day. Electrolytes, trace elements and vitamins were to be administered as required. Treatment was to start on the morning of the day after surgery, and to continue for 5 days. No enteral nutrition during the first 5 post-operative days except for water and tea was allowed, however it was not listed as a reason for exclusion from the study.

Medications to treat concomitant diseases were permitted except for corticosteroids in those centres analysing eicosanoid synthesis. Low weight heparin could be given for prophylaxis of thrombosis.

The objectives were to determine the efficacy, safety and tolerance of SMOF 20% during parenteral nutrition of patients following major abdominal, major thoracic or major urological surgery, compared to standard lipid emulsion Lipovenos 20%.

The study primary hypothesis was that the elimination of SMOF 20%, based on the serum concentrations of triglycerides²⁴, would be at least as fast as the elimination of Lipovenos 20%.

Secondary hypotheses were:

- the mean leukotriene (LT) B₅ values on day 6 would be statistically significant different between the treatment groups (Protocol Amendment 5 December 1997).
- rapid and substantial incorporation of long-chain fatty acids into plasma and cell membrane phospholipids of platelets and leukocytes in the SMOF group, would result in a lower arachidonic acid/EPA ratio compared to the Lipovenos group.
- an associated increase in EPA-derived eicosanoids.
- the two lipid emulsions were expected to be equally well tolerated.

Inclusion criteria: Patients who were in the immediate post-operative period after major abdominal, major thoracic or major urological surgery, e.g. gastrectomy, colectomy, colon resection, pancreatectomy, oesophagectomy or cystectomy, and had an indication for parenteral nutrition over at least 5 days.

Exclusion criteria included:

- hyperlipidaemia (fasting serum triglycerides >250 mg/dL, total cholesterol > 300 mg/dL).
- renal or hepatic insufficiency.

It was possible to remove patients from therapy with serum triglyceride concentration >500 mg/dL on 2 consecutive days.

Endpoints

The primary efficacy variable was the AUC of the difference between baseline²⁵ serum triglyceride concentrations and concentrations at each measurement point up to day 6 (corresponding to 5 complete days of infusion).

Secondary efficacy variables were:

- the plasma and cell membrane fatty acid profile and eicosanoid synthesis (at selected study centres)
- the clinical outcome, mortality and length of stay (LOS) in an intensive care unit (ICU) and in hospital.
- other parameters of lipid metabolism (serum total cholesterol and phospholipids).

Safety variables including laboratory parameters, vital signs, and AEs), and at selected study centres plasma vitamin E (α -, γ -tocopherols).

²⁴ The initial stage in utilisation of the lipid infusions involves binding to endothelial lipoprotein lipase (e.g. in muscle, adipose tissue) with hydrolysis of triglycerides yielding fatty acids.

²⁵ Amended to pre-infusion 16 November 1998. This was in order to take into account the greater variability in post-operative (but pre-infusion) serum triglyceride concentrations compared to baseline values.

Statistical methods

The AUC of the difference between the serum concentration of triglycerides' baseline value and the values stated at each measurement point up to day 6 for the PP population was analysed. The difference between treatment means (mean AUC of difference for Lipovenos - mean for SMOF) and a one sided 95% CI was calculated. The non-inferiority margin was -8mg/dL/day or 20% of the expected value of the AUC for the Lipovenos therapy. If non-inferiority was shown then superiority was to be sought. The overall type I error had an $\alpha \leq 5\%$. The analyses were repeated using results for the ITT population with the last observation carried forward (LOCF) for a missing value, as well as an observed case analysis. Following protocol amendment, missing values in both the PP and ITT results could be replaced by imputation.

Sample size determinations²⁶ indicated 100 patients /treatment group would give an 89% power to show non-inferiority and an 81% power to show superiority. The protocol was also modified to justify the sample size of 15/treatment group for the analysis of eicosanoids (LTB₅) that had a power of 86.6% to detect a statistically significant difference.

A justification of the sample size of 15 patients per treatment group to detect a significant difference in LTB₅ of 18ng/ml with a power of 86% was made by protocol amendment (5 December 1997).

Patient enrolment, disposition and characteristics are summarised in Table 8. 263 patients were enrolled: 126 were randomised to the SMOF group (ITT = 123, PP = 99) and 123 were randomised to the Lipovenos group (ITT = 121, PP = 100). 5 randomised patients were excluded because no triglyceride assessment had been performed after receiving treatment. The two groups were well-matched.

Primary efficacy results

For the PP population serum concentration of mean daily triglycerides (difference from baseline) for SMOFlipid was 0.7340 mmol/L and for Lipovenos it was 0.7197mmol/L with a difference of treatment means of 0.0142. The lower limit of the one sided 95% CI for the difference of the treatment means was -0.0891, that is, the SMOF lipid infusion as assessed by this means was non-inferior to Lipovenos infusion. However because this value was not > 0 , testing for superiority could not occur. An analysis of variance (ANOVA) did not reveal any statistically significant effects by treatment ($p = 0.7729$) or by centre ($p = 0.3354$).

Mean concentrations before surgery on day 0 were 1.436 and 1.410 mmol/L for the SMOF and Lipovenos groups, respectively. On day 1, pre-infusion mean concentrations had decreased to 0.920 and 0.894 mmol/L, respectively. From day 2 to day 5, mean concentrations were increased from 1.651 to 1.994 mmol/L for the SMOF group and from 1.638 to 2.004 mmol/L for the Lipovenos group. On day 6, mean concentrations were lower but still above baseline, at 1.874 and 1.926 mmol/L for the SMOF and Lipovenos groups, respectively.

The ITT treatment difference was 0.0499mmol/L (lower 95% CI -0.0474) (Table 9).

²⁶ Protocol amendment 16 November 1998. Originally 88/group gave 85% power for non-inferiority and 77% for superiority. The source of the assumptions on which these calculations were based is not given but the original is said to be inconsistent with Chapter 3.1.in protocol amendment 4.

Table 9: Serum concentration of triglycerides (mmol/L): mean daily AUC (difference from baseline) ITT Population.

Serum concentration of triglycerides	SMOF N = 123	Lipovenos N = 121
Mean daily AUC (difference from baseline)	0.7806	0.7307
Difference of treatment means	-0.0499	
Lower limit of the one sided 95% CI for the difference of the treatment means	-0.0474	

Note: in cases of missing triglyceride assessments the following methods were used: if assessments were missing on days 0, 1, 3 or 6, safety laboratory data were used. In all other cases, the mean of the first non-missing values preceding and succeeding the missing value was used. If this latter method was not possible the 'LOCF method' was used.

Secondary and efficacy outcomes

Mean serum concentrations of total cholesterol were comparable in the treatment groups at all time points, as were mean serum concentrations of phospholipids.

Mean LOS in Hospital was shorter for the SMOF group (15.688 days) than for the Lipovenos group (17.827 days). However, standard deviations and confidence limits were larger for the Lipovenos group than for the SMOF group. The Mean LOS in ICU was similar for the two treatment groups (4.66 versus 5.19 days).

A subgroup analysis of Fatty Acids (only 19 SMOFlipid and 14 Lipovenos patients) showed:

- Plasma fatty acid profiles were similar at baseline, after treatment there were significant differences between treatments in the change of $\omega 3$ & $\omega 9$ acids reflecting the composition of the infusions.
- Plasma fatty acids in phospholipids were approximately similar at baseline but after treatment there were significant differences in the change of EPA, DHA and linoleic acid. This was also true for leukocyte phospholipids, while platelet phospholipids had significant differences in change for oleic acid as well as for EPA, DHA and linoleic acid.

Eicosanoid²⁷ Synthesis (again only 19 SMOFlipid and 14 Lipovenos patients):

- Leukotrienes: There was a statistical difference for LTB₅ between the treatment groups (but this had a significant centre effect); there was no significant change reported for LTB₄ between treatments nor in the LTB₅/LTB₄ ratios.
- Thromboxanes: There was no significant difference reported in the changes between treatments for TBX₃ or for TBX₂ or for the TBX₃/TBX₂ ratio.

Other Efficacy Results- Children

There was one study submitted in children and infants and two studies in premature infants.

Study 00-SMOF-002 in Infants and Children

This was a double-blind, randomised, active-controlled, parallel-group study of safety and efficacy of SMOF 20% vs. Intralipid 20% in infants and children requiring long-term parenteral nutrition (Table 10).

²⁷ Leukotrienes (LT) and thromboxanes (TX) are formed from fatty acids LTB₅ and TXB₃ are derived from EPA ($\omega 3$ fatty acid), while LTB₄ and TXB₂ are derived from AA ($\omega 6$ fatty acid).

Table 10: Details of Study 00-SMOF-002

Design; Population	Treatments; Dose, Duration; Subjects	Efficacy measures/outcomes	Efficacy results				Safety
Randomized, double-blind, active-control, parallel-group study of safety and efficacy of SMOF 20% vs. Intralipid 20% in infants and children requiring long-term parenteral nutrition (4-5days/week for 4 weeks).	1 week prior to study Intralipid 20%. 1 day washout (TPN no lipid). SMOFlipid 20% or Intralipid 20% as 2g fat/kg/d over 12-14h per day by central IV infusion for 4-5 days per week over 4 weeks. Oral/enteral intake ≤ 50% of calories. SMOF: 1-24 months: 7 patients 2-11 years: 8 patients. Intralipid: 1-24 months: 6 patients 2-11 years: 7 patients.	Primary: Safety of long-term treatment with SMOFlipid 20% vs. Intralipid 20% in children. Secondary : Efficacy of long-term treatment with SMOFlipid 20% vs. Intralipid 20% in children.			Baseline mean ± SD	Change day 29, mean ± SD	SMOF mean 27.3 ± 0.6 days of 1.43 ± 0.50g fat/kg/d ²⁸ (1.54 ± 0.45 g fat/kg/d for 1-24 months age and 1.38 ± 0.52 g fat/kg/d for 2-11y). Intralipid mean 27.5 ± 0.5 days of 1.41 ± 0.50 g fat/kg/d. 2 SAEs (1 on each treatment), no treatment-related SAEs or AEs. Most AEs were mild or moderate, 1 severe on Intralipid.
			weight (kg)	SMOF	12.34 ± 4.72	0.31 ± 0.19	
				Intralipid	16.05 ± 8.06	0.30 ± 0.33	
			height (cm)	SMOF	86.40 ± 17.17	1.56 ± 1.52	
				Intralipid	91.85 ± 18.67	1.08 ± 0.95	
			Secondary variables similar except for SMOF increase in ω-3fatty acids in plasma & RBC membrane and increase in plasma α-tocopherol.				

The study involved male and female infants and children with stable disease requiring PN for at least 4 weeks with 13 patients aged 1 month to 2 years and 15 patients aged 2-11 years. There appeared to be no statistical rationale for the population size. For one week prior to the study all received Intralipid 20%, then there was a one day washout (PN but no lipids), then SMOFlipid 20% or Intralipid 20% as 2 g fat/kg/day was administered over 12-14 hours per day by central IV infusion for 4-5 days per week over weeks. The recommended rate was 0.125 g fat/kg/h with a maximum of 0.15g fat/kg/h. Oral/enteral intake was ≤ 50% of calories. Additional parenteral nutrition (amino acids and glucose) varied dependant on patient total body weight group.

Amendments: Due to technical reasons lipoprotein X evaluation was omitted; single α- tocopherol supplementation was removed from the list of admixtures – multivitamin preparations were given to both groups.

Patient enrolment, characteristics and disposition are summarised in Table 10. In terms of matching of the two groups, not only were there differences between the treatment groups in mean weight overall and when separated into the two age groups, but this was also true for mean BMI where the differences were approximately 10%.

²⁸ The text uses the unit g fat/kg/PN –PN = parenteral nutrition.

Endpoints

The primary objective was the safety of long-term treatment with SMOFlipid 20% vs. Intralipid 20% in children.

The secondary objective was efficacy of long-term treatment with SMOFlipid 20% vs. Intralipid 20% in children as determined by fatty acid profile in plasma and RBC phospholipids.

Primary efficacy variables included body weight, body height and body mass index.

Secondary efficacy variables included retinol binding protein, transthyretin (pre-albumin), and albumin.

Mechanism of action (laboratory parameters) variables included plasma leptine, fatty acid pattern in plasma and red blood cells: C16:0, C18:1 n-9, C18:2 n-6, C20:3 n-9 / C20:4 n-6, C20:4 n-6, C18:3 n-3, C20:5 n-3 + C22:6 n-3, n-3/n-6, phospholipids, plasma anti-oxidative capacity, plasma α -tocopherol, LDL-TBARS (thio barbituric acid reactive substance - a measure of serum lipid peroxidation); Apo (apolipoprotein) A-1, Apo 8-100.

Statistical methods involved standard summary statistics and two-tailed 95% confidence intervals (CIs). All group comparisons were to be hypothesis generating, that is, p-values resulting from statistical tests were to be interpreted in an exploratory way.

Primary efficacy results

SMOF infusion patients:

- Baseline **weight**, mean 12.34 ± 4.72 kg, median 10.40kg.
Increase by day 29, mean 0.31 ± 0.19 kg, median 0.20kg.
- Baseline **height**, mean 86.40 ± 17.17 cm, median 79.00cm.
Increase by day 29, mean 1.56 ± 1.52 cm, median 1.00cm.

Intralipid infusion patients:

- Baseline **weight**, mean 16.05 ± 8.06 kg, median 12.80kg.
Increase by day 29, mean 0.30 ± 0.33 kg, median 0.30kg.
- Baseline **height**, mean 91.85 ± 18.67 cm, median 89.00cm.
Increase by day 29, mean 1.08 ± 0.95 cm, median 1.00cm.

For BMI, SMOF infusion patients showed a small decrease while Intralipid infusion patients showed a small increase. The evaluator noted that, overall, both groups showed similar results.

Other efficacy results

Other efficacy results are shown in Table 11.

Table 11: Secondary Efficacy Results

		SMOF		Intralipid	
		Mean \pm SD	Median	Mean \pm SD	Median
Plasma Phospholipids (mmol/L)	Baseline	1.437 \pm 0.333	1.500	1.880 \pm 0.324	1.950
	Change	0.283 \pm 0.441	0.165	-0.100 \pm 0.366	-0.100
Plasma α -tocopherol (mcmol/L)	Baseline	12.618 \pm 5.074	13.175	16.642 \pm 8.068	17.50
	Change	15.675 \pm 15.900	10.025	5.438 \pm 15.151	1.700
LDL-TBARS (mcmol/L)	Baseline	43.292 \pm 18.344	43.050	37.504 \pm 20.054	40.250
	Change	7.835 \pm 19.017	1.40	8.750 \pm 37.389	0.00
Apo A1 (g/L)	Baseline	0.754 \pm 0.123	0.775	0.765 \pm 0.216	0.700
	Change	0.075 \pm 0.122	0.050	-0.023 \pm 0.224	-0.050
Apo B100 (g/L)	Baseline	0.479 \pm 0.140	0.475	0.608 \pm 0.263	0.450
	Change	0.039 \pm 0.175	0.050	0.012 \pm 0.227	-0.050

The evaluator noted that there were similar results except in fatty acid profiles (reflecting the composition of the infusions) and a more pronounced change in α -tocopherol with SMOF. Only 2/15 children received no additional oral/enteral feed. This section of the paediatric population does not differ from the adult population, in terms of indications, based on the references submitted.

Post hoc analysis

After completion of the report, a review of the amount of amino acids and glucose administered was added.

Other Efficacy Results- Infants

Infants differ from adults in the Indication applied for and handling of lipids.

During the last trimester of gestation ω -3 and ω -6 LCTs are deposited in rapidly growing fetal tissues, particularly in the brain and in the retina. Newborn infants and especially prematures, often have a low capacity to synthesise essential fatty acids (for example, arachidonic acid and docosahexaenoic acid) from linoleic and α -linolenic acids. Neonates should therefore preferably receive an adequate and balanced supply of ω -3 and ω -6 fatty acids when needed.

Study 00-SMOF-004

This was a double-blind, randomized, active-controlled, parallel-group study of the safety and tolerability of 7-14 days of treatment with SMOFlipid 20% vs. Intralipid 20% in premature infants (Table 12).

Table 12: Details of Study 00-SMOF-004

Design; Population	Treatments; Dose, Duration; Subjects	Efficacy measures/outcomes	Efficacy results				Safety	
			Birth weight	Body weight on Day 8 (% increase) Mean ± SD				
				N	SMOF	N	Intralipid	
Double-blind, randomized, active-controlled, parallel-group study of safety & tolerability of 7-14d of SMOFlipid 20% vs. Intralipid 20% in premature infants birth weight 1,000 to 2,500 g and requiring PN including fat for ≥ 7days Age gestation < 34 weeks; 0 to 7 days old.	Infusion over 20-24 h/d for 7 – 14 days of SMOFlipid 20% or Intralipid 20% via umbilical artery or peripherally. Dose (in g fat/kg/d) Day 1: 0.5; Day 2: 1.0, Day 3: 1.5, Days 4-14: 2.0 Additional oral/enteral intake ≤ 30% of energy intake on days 1-3 and ≤ 50% on days 4-14.	Primary: Safety and tolerability of 7 - 14 days of treatment with SMOFlipid 20% vs. Intralipid 20% in premature infants. Secondary: Efficacy of 7 – 14 days of treatment with SMOFlipid 20% vs. Intralipid 20% in premature infants assessed by relative increase in body weight on Day 8.	Overall	30	5.0 ± 6.5	30	5.1 ± 6.6	Changes in Serum triglycerides were similar with similar numbers changing to high levels. 29 AEs in 13 patients on SMOF and 28 AEs in 14 patients on Intralipid, all mild or moderate, none treatment-related. No deaths, discontinuations due to AEs nor any SAEs. Only clinically relevant changes in laboratory values were for CRP due to infections.
			The number of patients without oral nutrition fell from 14 to 2 on SMOF and from 10 to 0 on Intralipid.					

It involved an IV infusion over 20-24 hours per day for 7 - 14 days of SMOFlipid 20% or Intralipid 20% via umbilical artery or peripheral infusion. The dose is shown in Table 12 as is a summary of patient enrolment, characteristics and disposition. Sixty patients were enrolled, 20 to each birth range, and they were then randomised within the range to either SMOF or Intralipid. Nine patients terminated the study prematurely (4 on SMOF) – 2 after consent was withdrawn and 7 due to higher oral/enteral feeding.

Endpoints

The primary variable was the measurement of serum triglycerides (although this is listed as a safety variable). Secondary and other variables included:

- Relative change in body weight between Day 0 and Day 8.
- CRP level, sepsis score, days with antibiotic therapy, the use of oxygen therapy (days with supportive/artificial ventilation) and the change in height during the treatment period.
- Fatty acid pattern in erythrocytes (RBC) (w-3 fatty acids, w-6 fatty acids, EPA, DHA, eicosanoids, arachidonic acid, α -linoleic acid).
- Phospholipids, α -tocopherol, lipid peroxidation in plasma.
- Usual safety variables

Standard summary statistics and two-tailed 95% CIs were calculated. All group comparisons were to be hypothesis generating, that is, p-values resulting from statistical tests were to be interpreted in an exploratory way.

Efficacy results

The mean increase in body weight is shown in Table 12. While overall the weight gains were similar, there were variations within the strata, probably reflecting the small numbers involved.

Mean RBC fatty acid profiles at baseline were similar between the SMOF and Intralipid groups. There were some differences between and among the age groups at baseline. By Day 8 the profiles in RBC differed with an overall greater ω -3 content increase with SMOF (especially eicosapentaenoic acid, while docosahexaenoic acid decreased in both); there was overall a ω -6 increase with Intralipid with a much greater overall decrease with SMOF; with both treatments ω -9 increased - more so with SMOF. This reflected the composition of the infusions. Other secondary variables are shown in Table 13.

Table 13: Secondary variables

		SMOF		Intralipid	
		Mean \pm SD	Median	Mean \pm SD	Median
Plasma α -tocopherol (mmol/L)	Day 0	14.197 \pm 5.894	13.76	13.535 \pm 4.542	13.22
	Day 8	26.974 \pm 18.318	22.17	8.733 \pm 11.409	7.34
Plasma malondialdehyde ^a , (mmol/L)	Day 0	2.949 \pm 0.828	3.02	2.931 \pm 0.962	3.02
	Day 8	-0.686 \pm 1.108	-0.55	-0.770 \pm 0.920	-0.90

^a measure of serum lipid peroxidation.

No measurable changes in height

Sepsis score assessment not submitted. [†]Due to the small number of patients with signs of sepsis, the mean total score displayed negligible changes during the study.[‡]

It was noted that the report discussed the influence of oral nutrition affecting efficacy results across the strata.

Study 03-SMOF-005

This study was entitled a study of the safety, tolerability and efficacy of SMOF 20% vs. Intralipid 20% (for 7-14 days) in premature infants. There were multiple protocol amendments during the trial, and the patients in one centre (31/84 or 37% of ITT) received incorrectly calculated treatment doses. Since patients were treated very differently in the two study centres included, the study report also evaluated centres separately. Centre 2 included most of the patients treated according to the protocol, while in Centre 1 the daily routine practice differed considerably from the study protocol and resulted in protocol variations especially with regard to the lipid dose given. The primary variable, triglyceride levels, was considered safety related and the study revealed no statistical difference between the groups although non inferiority on the basis of serum triglycerides could not be shown in a confirmatory way. Changes in body weight and length were considered biased due to the considerable difference in demographic characteristics between patients of the two centres. Fatty acid data were only presented for Centre 2 as Centre 1 was considered biased. Three patients given SMOF and two given Intralipid received insulin, while five in each group received bicarbonate.

Conclusions regarding efficacy

As indicated at the start of this section, there are three requirements to be shown for efficacy for part of total or partial PN.

Supply of energy to patients, as part of a parenteral nutrition regimen

The possibility to provide condensed energy by using lipids based on soybean oil (Intralipid) which also contains the essential fatty acids enabled smaller daily requirements of glucose to be used which decreased the associated problems with hyperglycemia and insulin requirement. In assessing efficacy by equivalence or non-inferiority it is assumed that superior efficacy of the standard treatment over placebo has been proven for a given indication.²⁹

The superiority of Intralipid over placebo for the supply of energy to patients, as part of a parenteral nutrition regimen lies in the easier and better control of glucose concentration and associated insulin requirements seen when Intralipid is added compared to where no lipid is given as part of the parenteral nutrition regimen. This was not presented or discussed. The sponsor argues that the comparison to placebo would not have been ethical. Among the literature submitted was a 2002 study (with ethical approval) that used glucose infusion as a placebo comparator.³⁰

Plasma triglyceride levels for a given lipid emulsion will depend on the rate of lipid infusion selected, as well as the rate of conversion of that lipid to fatty acids by lipase. This will depend not just on a simple additive effect of the constituent lipids of an infusion as suggested but on: how together they form into chylomicron like particles; how these structures behave in relation to the adherence of apolipoprotein; their behaviour after the adherence of apolipoprotein; and as triglycerides are gradually removed by lipase, leaving an increasing ratio of outer phospholipid shell to internal triglyceride.

The resultant fatty acids have four metabolic pathways in the body:

- as cell membrane,
- storage in adipose tissue,
- synthesis of eicosanoids
- and oxidation to provide energy

Physical characteristics (for example, weight, growth) are measures of anabolism and act as an assessment of adequacy of nutrition, that is, the balance of nutritional input, both enteral plus parenteral (glucose, amino acids and fat) versus metabolism (catabolism and anabolism). There are thus multiple variables between the input of lipid and maintenance or gain in weight. In Study -004 while overall weight gain was similar, it varied among the strata where enteral input and ventilation (respiratory energy requirement) varied. Likewise in study -002 overall weight gain was similar but was different between the age groups and as a relative gain.

Supply of essential fatty acids as part of a parenteral nutrition regimen

To assess efficacy the submission needs to show that the supply of essential fatty acids is adequate either by comparison of plasma levels with Intralipid (or Lipovenos) or by showing evidence of the prevention of deficiency (requires a trial of adequate duration). Without appropriate lipid

²⁹ Scott IA. Non-inferiority trials: determining whether alternative treatments are good enough. MJA 2009; 190: 326-330.

³⁰ Schauder P, Rohn U, Schafer G, Korff G, Schenk HD. Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. Br J Nutr 2002; 87: S 103-110.

supplementation essential fatty acid deficiency develops in adult patients on TPN in 2-4 weeks; changes are seen in 4-5 days in 6 month old infants.³¹ Some of the studies met these durations.

In study SM-03-DE, the mean sum of ω -3 fatty acids in plasma phospholipids increased (from 6.76 ± 1.63 mol% by 4.33 ± 1.66 mol%) on SMOFlipid, while the sum decreased (from 6.53 ± 1.37 mol% by -1.60 ± 1.42 mol%) on Lipovenos. However, the mean sum of ω -6 fatty acids decreased (from 29.46 ± 3.34 mol% by -5.71 ± 3.21 mol%) on SMOFlipid, while the sum increased (from 30.51 ± 1.97 mol% by 1.26 ± 2.96 mol%) on Lipovenos. The evaluator commented that the study was only five days – too short to expect manifestations of essential fatty acid deficiency to occur, while the results suggest that, compared to Lipovenos, SMOFlipid, while improving the ω -3/ ω -6 ratio does not maintain essential ω -6 fatty acid levels in adults.

However, the sponsor noted that the ω -6 essential fatty acid linoleic acid is provided in a surplus in soybean oil based emulsions. Therefore after reduction of soybean oil as done in SMOFlipid the amount of linoleic acid still remains within the recommended amount in current guidelines: 7-10 g per day (Staun et al. 2009 ESPEN HPN guidelines). This is also reflected by the measurements in leukocyte and platelet phospholipids in the above mentioned study where there was an increase in linoleic acid after Intralipid treatment but also - to a slighter extent - after SMOFlipid treatment.

In the sponsor's Clinical Overview in relation to discussions on adequate supply of essential fatty acids, the comment is made:

In preterm infants (study 03-SMOF-005) and children (study 00-SMOF-002), all individual values for the C20:3 ω 9/C20:4 ω 6 ratio (the so-called triene/tetraene ratio) were much lower than 0.2. A triene/tetraene ratio greater than 0.2 is seen as an indicator of essential fatty acid deficiency.

In study SMOF-002, the mean sum of ω -3 fatty acids (ALA, EPA & DHA) in plasma lipoproteins increased (from 2.38 mol% by 1.54 mol%) on SMOFlipid, while the sum decreased (from 2.28 mol% by -0.14 mol%) on Intralipid. However, the mean sum of ω -6 fatty acids (LA & AA) decreased (from 31.21 mol% by -2.45 mol%) on SMOFlipid, while the sum increased (from 29.77 mol% by 1.92 mol%) on Intralipid. The evaluator commented that the study was 4 weeks - long enough to expect manifestations of essential fatty acid deficiency to occur. This did not appear to happen, but in the study oral/enteral intake could be $\leq 50\%$ of calories and only 2/15 patients on SMOFlipid received no enteral nutrition. Likewise compared to Intralipid, SMOFlipid, while improving ω -3/ ω -6 ratio does not maintain essential ω -6 fatty acid levels in children.

The sponsor noted that in red blood cell phospholipids, the essential ω -6 fatty acid linoleic acid slightly decreased in both groups, from 11.7 by -0.2 mol% on SMOFlipid and from 13.7 by -1.2 mol% on Intralipid, despite a larger supply in the Intralipid group. However, these slight changes of ω -6 fatty acids were not significant and not different between groups. Thus sufficient amounts of essential fatty acids are provided as observed by the study results and also according to the latest ESPGHAN/ESPEN guidelines on parenteral nutrition for paediatric patients.

In the infants Study 00-SMOF-004, the mean sum of ω -3 fatty acids (ALA, EPA & DHA) in RBC phospholipids increased (from 95.09 mcmol/L by 4.85 mcmol/L) on SMOFlipid, while the sum decreased (from 103.31 mcmol/L by -7.45 mcmol/L) on Intralipid. However, the mean sum of ω -6 fatty acids (LA & AA) decreased (from 530.8 mcmol/L by -43.3 mcmol/L) on SMOFlipid, while the sum increased (from 591.7 mcmol/L by 23.5 mcmol/L) on Intralipid. The evaluator commented that the study was 7-14 days, long enough to expect manifestations of essential fatty acid deficiency to occur. This did not appear to happen, but in the study oral/enteral intake could be $\leq 30\%$ of energy intake on days 1-3 and $\leq 50\%$ on days 4-14 and only two patient on SMOFlipid received no

³¹ Hamilton C, Austin T, Seidner DL. Essential fatty acid deficiency in human adults during parenteral nutrition. Nutr Clin Pract. 2006; 21:387-94.

enteral nutrition. Compared to Intralipid, SMOFlipid, while improving ω -3/ ω -6 ratio does not maintain essential ω -6 fatty acid levels in red blood cells in infants, however this should be distinguished from plasma level results. The studies do not appear to provide sufficient evidence to support that the supply of essential fatty acids is adequate for total parenteral nutrition.

However, the sponsor noted the essential ω -6 fatty acid linoleic acid in red blood cells increased in the SMOFlipid group as well as to a larger extent in the Intralipid group, while the non essential ω -6 fatty acid arachidonic acid decreased in both groups. By putting together the two fatty acids in order to assess the provision of essential fatty acids arachidonic acid masked the effect of the linoleic acid alone. Therefore it can be concluded that sufficient amounts of essential fatty acids are provided as observed by the study results and also according to the latest ESPGHAN/ESPEN guidelines on parenteral nutrition for paediatric patients.

Supply of omega-3 fatty acids as part of a parenteral nutrition regimen

This would appear to be a redundant statement in the submitted PI if the Indication of “Supply of essential fatty acids” were accepted (ω -3 fatty acids are essential fatty acids).

As set out above, analysis of Study SM-03-DE in 19 SMOFlipid and 14 Lipovenos patients showed significant differences between treatments in change for ω 3 fatty acids.

Of the -3 fatty acids, DHA is an important structural component of cell membranes, whereas EPA is a precursor of eicosanoids as prostaglandins, thromboxanes and leukotrienes. In the primary efficacy study (FM-SM-03-DE) secondary variables assessed were the eicosanoids LTB₄, LTB₅, TBX₂ and TBX₃. There was a statistical difference shown for LBT₅ between SMOFlipid and Lipovenos, but not for any other parameter or their ratios.

The additional ω -3 fatty acids are intended to decrease the pro-inflammatory effect of an excess of the ω -6 linoleic acid (as in soya lipid). The evaluator commented that no clinical effect from any observed difference was apparent. However, the sponsor noted that in a subgroup analysis of study FM-SM-03-DE, length of hospital stay was significantly shorter with SMOFlipid compared to the control group (13.4±2.0 vs. 20.4±10.0 days, p<0.05). In the primary efficacy study (FM-SM-03-DE) a secondary variable assessed was Mean LOS in Hospital which was shorter for the SMOF group (15.688 days) than for the Lipovenos group (17.827 days). However, standard deviations and confidence limits were larger for the Lipovenos group than for the SMOF group. The mean LOS in ICU was similar for the two treatment groups (4.66 vs. 5.19 days). Likewise in Study 00-SMOF-004, Days with Antibiotic Therapy and Days with Oxygen Therapy were similar; however this study was small and neither was designed to demonstrate statistically significant differences in clinical outcomes.

Safety

The safety population is summarised in Table 14. Of 195 adult patients 11 patients (5.6%) had chronic pancreatitis, 9 (4.6%) had pancreatic cancer and 15 (7.7%) had had cholecystectomy.

Duration of exposure (mean ±SD) for adults was 5.3 ± 2.51 (range 1 – 15) days; for children it was 28.3 ± 0.62 (27 – 29) days; and for preterm infants it was 9.8 ± 3.60 (3 – 15) days.

Table 14: Safety Studies and Populations

Study	Population	Treatment	N	Planned duration
FE-SM-01-BE	Volunteers	SMOFlipid 20%	10	4 hours
FE-SM-02-DE	Volunteers	SMOFlipid 20%	12	6 hours
FE-SM-03-DE	Adults	SMOFlipid 20%	126	5 days
FE-SM-04-CH	Adults	SMOFlipid 20%	16	1 0-14 days
03-3CB7-001	Adults	SmofKabiven	26	5-7 days
03-3CB8-001	Adults	SmofKabiven Peripheral	27	5-7 days
00-SMOF-002	Children, infants and toddlers	SMOFlipid 20%	15	4 weeks
00-SMOF-004	Preterm infants	SMOFlipid 20%	30	7-14 days
03-SMOF-005	Preterm infants	SMOFlipid 20%	42	7-14 days

Adverse events

Adverse events were evaluated for each individual study.

The safety data from the clinical studies were pooled in order to create larger safety datasets for analysis and provided for all patients (adult and paediatric patients). In addition, there were multiple sub-group analyses of the pooled data (for example, by age groups, BMI, cancer status, diabetes status, hypertension status etc); most contained small numbers of patients so that the results were of limited value

Pivotal Study FM-SM-03-DE

For SMOFlipid the mean daily dose was 1.431 ± 0.1581 g/kg/d and mean duration was 4.714 days, while for Lipovenos it was 1.447 ± 0.1068 g/kg/d for 4.765 days. Exposure to other components of TPN were stated to be similar between the groups.

A subgroup analysis showed mean plasma α - & γ - tocopherol concentrations (PP subset of 33) increased from Day 1-6 with significantly greater change for α -tocopherol with SMOFlipid, while for γ -tocopherol there was significantly greater change with Lipovenos.

Crude results are shown in Table 15. There were three SMOF deaths and four on Lipovenos with none related to study drug. Eight SMOF and nine Lipovenos patients experienced 30 possibly treatment-related AEs, with a further four SMOF and two Lipovenos patients having another seven AEs that were probably related. Five patients in each group had nausea and four in each group had vomiting that was treatment-related. Most treatment-related AEs were mild or moderate, with one SMOF patient having severe nausea and vomiting, and one Lipovenos patient having severe hyperglycaemia. For SMOF other treatment-related AEs included dysgeusia (2 patients), cholestatic hepatitis (2), hyperglycaemia (2), hypertriglyceridaemia (2), while for Lipovenos they included hepatocellular damage (2 patients), cholestasis, hyperglycaemia, hypertriglyceridaemia, and headache. There was one accidental overdose of Lipovenos that produced nausea and vomiting - the only treatment-related SAE.

Among SMOF patients, two with nausea and vomiting, and one with vomiting discontinued from intolerable treatment-related AEs. In the Lipovenos group, discontinuations with intolerable treatment-related AEs consisted of one patient with hyperglycaemia and hypertriglyceridaemia and one patient with increased therapeutic response (the accidental overdose).

There were no consistent trends for laboratory values. For individual changes more patients on Lipovenos had “normal baseline to above normal at final” for AST, ALT and alkaline phosphatase (ALP). Vital sign changes were consistent with post-operative status.

Table 15: Individual treatment-emergent AEs - Safety Population.

Numbers of patients reporting AEs	SMOF Group (N=126)		Lipovenos Group (N=123)		Total (N=249)	
	N	%	N	%	N	%
Nausea	10	7.9	14	11.4	24	9.6
Hyperglycaemia	9	7.1	5	4.1	14	5.6
Vomiting	6	4.8	7	5.7	13	5.2
Fever	4	3.2	5	4.1	9	3.6
Pneumonia	4	3.2	3	2.4	7	2.8
Hypertension	4	3.2	2	1.6	6	2.4
Sepsis	4	3.2	2	1.6	6	2.4
Tachycardia	4	3.2	1	0.8	5	2.0
Respiratory insufficiency	0	0.0	4	3.3	4	1.6

Study FE- SM-04-CH

This was a double-blind, randomized, active-controlled, parallel-group study of safety and tolerance of SMOFlipid 20% vs. Lipovenos 20% in patients requiring long-term TPN.

Patients received a continuous central IV infusion of SMOFlipid 20% or Lipovenos 20% ≤ 2 g fat/kg/d over 18-24 h/day for 10 - 14 days, together with amino acids 1-1.5 g/kg/d and glucose in the energy ratio of 50/50 with that of lipid. The maximum infusion rate was 0.125 g fat/kg/h and 2 g fat/kg/day. Endpoints were clinical chemistry parameters, haematology, coagulation parameters, vital signs and AEs.

Differences between the two treatment groups were to be described by means of 95% CIs for the mean or median, as appropriate. In the case of a parametric analysis it was planned to estimate the 95% CIs from an ANCOVA model for the last double-blind value including the effects of treatment and the log-transformed baseline value of the respective variable as covariates. Values at the end of double-blind treatment were planned to be log-transformed for the analysis and estimates anti-logged in order to be expressed as ratios. In the case of a non-parametric analysis it was planned to estimate 95% CIs for the median and p-values for the differences (change from pre-study value) between the two treatment groups for each study day by Wilcoxon-Mann-Whitney-U-Tests.

Patients for inclusion had to need TPN for 10-14 days. Exclusion criteria were similar to those for Study FM-SM-03-DE with the additional exclusion of uncontrolled sepsis. The Safety Population consisted of:

- SMOF:16: M/F 12/4; mean age 52.67 (range 22-75) years; mean weight 59.9 (range 47-83) kg
- Lipovenos:16: M/F 9/7; mean age 59.95 (range 25-97) years; mean weight 60.73 (range 30-99) kg.

One SMOFlipid and two Lipovenos patients received enteral nutrition as well. In the SMOFlipid group, three received albumin and one colloids, while four and two respectively did so in the Lipovenos group.

Of the causes of premature terminations, for SMOFlipid two were end of indication for TPN and one was from intercurrent disease, while for Lipovenos four were for end of indication, two were deaths and one each of AE, intercurrent disease and protocol deviation.

Safety results

The mean exposure (\pm SD) was 1.04 ± 0.3 g/kg/d for 10.94 ± 3.66 days for SMOFlipid and 1.04 ± 0.32 g/kg/d for 8.56 ± 3.93 days for Lipovenos.

Twelve SMOF patients had 27 AEs and ten Lipovenos patients had 18 AEs. Most frequent AEs were elevated triglycerides (6 patients) and hepatic enzymes (3) for SMOFlipid and likewise with (3) and (3) for Lipovenos. Eight SMOF patients had 11 possibly or probably treatment-related AEs, while seven on Lipovenos had 10 – none of these AEs were considered severe (Table 16). There were two deaths (the only SAEs) neither treatment-related.

Table 16: Severity of adverse events possibly or probably study drug related - Safety Population

Body system/Preferred term	SMOF 20% N=16				Lipovenos 20% N=16					
	mild		moderate		No statement by principal investigator		mild		moderate	
	N	%	N	%	N	%	N	%	N	%
Liver and biliary system disorders										
Gamma-glutamyl transferase increased	0	0%	1	6.3%	0	0%	2	12.5%	0	0%
Hepatic enzymes increased	2	12.5%	0	0%	0	0%	1	6.3%	1	6.3%
Metabolic and nutritional disorders										
Alkaline phosphatase serum increased	0	0%	1	6.3%	0	0%	2	12.5%	0	0%
Serum lipid abnormal nos.	7	43.8%	0	0%	0	0%	3	18.8%	0	0%
Body as a whole - general disorders										
Pain	0	0%	0	0%	1	6.3%	0	0%	0	0%

There were no differences throughout between the groups in serum triglycerides. Haemoglobin, haematocrit and red blood cells were almost all below normal. The median platelet value on Lipovenos was below normal while that for SMOF was normal; all median white blood cells (WBC) were normal. No relevant differences in clinical chemistry means were found. Median gamma glutamyl transferase (GGT) and ALP increased above normal at final measurement. Most values outside normal were considered to be basic illness/trial indication-related or based on concomitant disease and medications. There were no notable differences in vital signs.

Study 03-3CB7-001

This was an open-label, randomized, active-controlled, parallel-group study of safety and tolerance of SMOF Kabiven versus Kabiven during 5 to 7 days in post-operative patients requiring PN in a single centre. Patients received a continuous central Infusion of SMOF Kabiven or Kabiven in the following pattern: Day 1 = 15.0 mL/kg/day (0.57 g SMOF Kabiven lipid/kg/day); Days 2-4 = 22.5-30.0 mL/kg/d (0.86-1.14 g SMOF Kabiven lipid/kg/day); Days 5-7 = 15.0-30.0 mL/kg/d (0.57-1.14 g SMOF Kabiven lipid/kg/day). SMOF Kabiven has higher glucose and amino acid content than Kabiven peripheral.

In this study, infusion pumps were not used and the infusion was controlled manually.

Patients were statistically considered completers if they received $\geq 50\%$ of the study medication for 5-7 days. Of 53 ITT (60 enrolled) patients, two SMOF Kabiven patients and one Kabiven patient

completed treatment for 7 days. Eight SMOF Kabiven and nine Kabiven patients were considered to have terminated the study prematurely while 19 SMOF Kabiven and 18 Kabiven had an infusion on Day 5.

There were AEs in 25 SMOF Kabiven (5 SAEs) and 23 Kabiven (2 SAEs) patients. Four SMOF Kabiven and four Kabiven patients had severe AEs. Seventeen SMOF Kabiven and 11 Kabiven had possibly or probably treatment-related AEs (no SAEs). Eight SMOF Kabiven and five Kabiven withdrew due to AEs (Table 17).

Table 17: AEs with at least possible relationship to the study drug.

		All subjects N = 53		SMOF K N = 26		Kabiven N = 27	
		n	%	N	%	n	%
Subjects with AEs		48	90.6	25	96.2	23	85.2
Probable	Subjects with remarks	1	1.9	1	3.8		
	Nausea	1	1.9	1	3.8		
Possible	Subjects with remarks	27	50.9	16	61.5	11	40.7
	Nausea	11	20.8	4	15.4	7	25.9
	Vomiting	9	17.0	7	26.9	2	7.4
	Flatulence	5	9.4	4	15.4	1	3.7
	Abdominal Pain	1	1.9			1	3.7
	Hyperglycaemia	1	1.9	1	3.8		
	Hypertension	1	1.9	1	3.8		
	Oedema	1	1.9	1	3.8		

Mean glucose increased by 27.13 (\pm 71.10) and 27.46 (\pm 45.26) mg/dL in the SMOF Kabiven and Kabiven group by Final (LOCF) measurement. Glucose levels showed a high variability in both groups since diabetic and non-diabetic patients were included. Four patients in the SMOF Kabiven group and two patients in the Kabiven group showed at least one clinically relevant increase in serum glucose.

Except for the proportion of granulocytes as well as bilirubin and C-reactive protein concentration, there was no different change in any mean laboratory parameter in SMOF Kabiven and Kabiven treated patients. The reduction in bilirubin serum concentration was more pronounced in the Kabiven group than in the SMOF Kabiven group, but this reduction started from a raised baseline.

Study 03-3CB8-001

This was an open-label, randomised, active-controlled, parallel-group study of safety and tolerance of SMOF Kabiven Peripheral (SMOF Kabiven P) versus Kabiven Peripheral (Kabiven P) for 5 to 7 days in patients. Patients received \leq 40 mL/kg/day (1.13 g SMOF Kabiven lipid/kg/day) by peripheral IV infusion over 14-24 hours per day of either SMOF Kabiven P or Kabiven P, plus \leq 700 kcal of oral/enteral nutrition was acceptable. SMOF Kabiven P has a slightly higher amount of glucose and a higher amino acid content than Kabiven P. Twenty four of 27 patients on SMOF received \geq 5 infusions, two had 6 infusions, and one had 7 infusions; on Kabiven P, 16/25 had \geq 5 infusions, three had 6 infusions and six had 7 infusions. Based on mean volume infused/mean number of infusions/mean weight, those on SMOF Kabiven P received 32.17 mL/kg/day while those on Kabiven P received 29.7 mL/kg/day.

There were 52 patients in the ITT population, of these 27 were in the SMOF Kabiven P ITT group and 25 were in the Kabiven P ITT group. Patients were statistically considered completers if they received $\geq 50\%$ of the study medication for each of at least 5 days. Of those on SMOF Kabiven P, 14 terminated prematurely, as did nine on Kabiven P.

There were 23 AEs reported in nine patients on SMOF Kabiven P, and 32 in 16 on Kabiven. There was one SAE in each group but both were considered unrelated to the study drug. There was one case of thrombophlebitis in each group. Most AEs were mild or moderate with only one patient in each group having severe AEs. One patient on SMOF Kabiven P discontinued as a result of an AE. One death occurred in each group but each was considered not related to the study drug.

Study 00-SMOF-002

This study was described under *Efficacy*. Mean exposure of SMOF treatment was 27.3 ± 0.6 days of 1.43 ± 0.50 g fat/kg/d (1.54 ± 0.45 g fat/kg/d for 1-24 months of age and 1.38 ± 0.52 g fat/kg/d for 2-11 years), while the mean for Intralipid was 27.5 ± 0.5 days of 1.41 ± 0.50 g fat/kg/day. The infusion mean rate was 0.11 ± 0.04 g fat/kg/h for all groups. AEs are shown in Table 18.

There were two SAEs (one on each treatment) with no treatment-related SAEs or AEs. Most AEs were mild or moderate, there was one severe AE on Intralipid. No clinically relevant changes in haematology or clinical chemistry were observed. The normal range varied with age.

On SMOF, systolic and diastolic blood pressure (BP) fell by 7 mmHg, the fall was greater in the 1-24 months age group by a mean 14/11 mmHg. On Intralipid the mean fall was only 1/5 mmHg. Heart rate (HR) fell on SMOF by a mean 10 beats/min versus 4 beats/min on Intralipid. The fall was greater on SMOF in the 1-24 month age group (20 beats/min) but this was from a faster baseline. Mean body temperature remained within normal limits.

Table 18: Summary of AEs by SOC and preferred terms (safety analysis).

SOC / Preferred Tern	All patients n = 28		SMOF N = 15		Intralipid N = 13	
	n	%	n	%	n	%
Patients with at least one AE	13	46.4	7	46.7	6	46.2
General disorders and administration site conditions	6	26.6	4	26.7	4	30.8
Pyrexia	7	25.0	3	20.0	4	30.8
Catheter site inflammation	1	3.6	1	6.7		
Infections and infestations	6	21.4	3	20.0	3	23.1
Ear infection	t	3.6	1	6.7		
Nasopharyngitis	1	3.6	1	6.7		
Staphylococcal infection	1	3.6	1	6.7		
Acute tonsillitis	1	3.6			1	7.7
Campylobacter gastroenteritis	t	3.6			1	7.7
Urinary tract infection	1	3.6			1	7.7
Gastrointestinal disorders	2	7.1	1	6.7	1	7.7
Vomiting	2	7.1	1	6.7	1	7.7
Injury, poisoning and procedural complications	1	3.6	1	6.7		
Femur fracture	1	3.6	1	6.7		
Metabolism and nutrition disorders	1	3.6	1	6.7		
Acidosis	1	3.6	1	6.7		

Study 00-SMOF-004

This study was described under *Efficacy*. The mean and median doses given were close to those in the protocol. The number of patients without oral nutrition fell to one on SMOF and to none on Intralipid.

The primary variable (safety) was assessing the change in serum triglycerides. The changes were similar with similar numbers changing to high levels.

Twenty nine AEs were observed in 13 patients on SMOF and 28 AEs were observed in 14 patients on Intralipid (Table 19); all mild or moderate with none treatment-related. There were no deaths or discontinuations due to AEs nor were there any SAEs. The only clinically relevant changes in laboratory values involved CRP due to infections.

Table 19: Summary of treatment emergent AEs by SOC and preferred terms (SAF).

SOC/ Preferred term	SMOF n = 30				Intralipid n = 30			
	Events		Patients		Events		Patients	
	n	%	n	%	n	%	n	%
Patients with remark	29	100.0	13	43.3	28	100.0	14	46.7
Infections and infestations	11	37.9	11	36.7	8	28.6	8	26.7
Nosocomial infection	7	24.1	7	23.3	5	17.9	5	16.7
Staphylococcal infection	1	3.4	1	3.3	1	3.6	1	3.3
Eye infection	1	3.4	1	3.3				
Infection	1	3.4	1	3.3				
Neonatal infection	1	3.4	1	3.3				
Bacterial infection					1	3.6	1	3.3
Escherichia sepsis					1	3.6	1	3.3
Respiratory; thoracic and mediastinal disorders	6	20.7	6	20.0	4	14.3	3	10.0
Apnoea	4	13.8	4	13.3	4	14.3	3	10.0
Atelectasis	1	3.4	1	3.3				
Hypoventilation	1	3.4	1	3.3				
Blood and lymphatic system disorders	3	10.3	3	10.0	5	17.9	3	10.0
Anaemia.	3	10.3	3	10.0	4	14.3	3	10.0
Thrombocytopenia					1	3.6	1	3.3
Nervous system disorders	4	13.8	3	10.0	3	10.7	1	3.3
Convulsion	2	6.9	1	3.3	3	10.7	1	3.3
Epilepsy	1	3.4	1	3.3				
Hydrocephalus	1	3.4	1	3.3				
General disorders and administration site conditions	2	6.9	2	6.7	2	7.1	2	6.7
Pyrexia	2	6.9	2	6.7	2	7.1	2	6.7
Investigations	2	6.9	2	6.7	2	7.1	2	6.7
Oxygen saturation decreased	2	6.9	2	6.7	1	3.6	1	3.3
Blood pressure increased					1	3.6	1	3.3
Cardiac disorders	1	3.4	1	3.3	2	7.1	1	3.3
Bradycardia	1	3.4	1	3.3	2	7.1	1	3.3
Eye disorders					1	3.6	1	3.3
Conjunctivitis					1	3.6	1	3.3
Gastrointestinal disorders					1	3.6	1	3.3
Abdominal distension					1	3.6	1	3.3

Study 03-SMOF-005

This study was mentioned under *Efficacy*. There were multiple amendments during the study. Since patients were treated very differently in the two study centres included, the study report also evaluated centres separately. Centre 2 included most of the patients treated according to the protocol, while in Centre 1 the daily routine practice differed considerably from the study protocol and resulted in protocol variations especially with regard to the lipid dose given. It was a double-blind, randomised, active-controlled, parallel-group study of the safety, tolerability and efficacy of SMOF 20% versus Intralipid 20% (for 7-14 days) in premature infants with birth weight of 500 to 2000 g and requiring PN including fat for at least 7 days; gestational age < 34 weeks; 0 to 7 days old.

The infusion was over 20-24 hours per day for 7 - 14 days of SMOFlipid 20% or Intralipid 20% via peripheral or central line. The dose (in g fat/kg/d) was as follows: Days 1-3: 1.0; Day 4: 2.0; Day 5: 3.0; Days 6-14: 3.5. The maximum rate was 0.17 g fat/kg/h. If triglycerides were > 300mg/dL the dose of lipid was reduced. During the study it was decided that if the actual dose received was \geq 80% for at least 6 out of 7 initial days (that is, \geq 68.6% over the 7 days), then the patient was considered compliant and could be included in the PP population.

There was additional oral/enteral intake \leq 30% of energy intake on Days 1-3 and \leq 50% on Days 4-17 and \leq 70% on Days 8-14.

The primary variable was safety as assessed by the serum level of triglycerides (as an assessment of the elimination of SMOF which would be at least as fast as the elimination of Intralipid).

Secondary efficacy variables include body weight and height (a number of other clinical variables were cancelled by amendment), fatty acid pattern in RBC and plasma (assessment of RBC phospholipids and α -Tocopherol were cancelled).

Secondary safety variables included vital signs, AEs, haematology; biochemistry: [including ALT, GGT, glucose, creatinine, electrolytes, bilirubin, cholesterol (total, HDL, LDL), serum TG > 300 mg/dL].

The study population was amended twice after the start of the trial, the trial eventually being 84 patients having been enrolled and treated at the two sites; these were included in the safety and IIT analysis. The primary criterion - triglyceride levels was tested (with a one-sided $\alpha = 0.025$ and a lower equivalence margin defined Mann-Whitney estimator = 0.38, the type II error is $\beta = 0.549$). In the sponsor's Summary of Clinical Efficacy an ITT population of Centre 2 only is also presented resulting in 53 patients (26 SMOF and 27 Intralipid).

The problems with following the protocol in the one site led to a PP population of only 52/84 or a 38% exclusion. Further compounding this was that 16 patients in each group were considered non-compliant giving another population.

Primary variable results

Descriptive statistics of the primary safety parameter triglyceride levels revealed no significant difference between the two groups. Non inferiority on the basis of serum triglycerides could not be shown in a confirmatory way.

Other variable results

AEs are shown in Table 20. There were four discontinuations from AEs on SMOF and three on Intralipid with a total of six AEs in five patients on SMOF and 12 in 9 patients on Intralipid which were considered treatment-related. Of the four deaths, one on Intralipid was associated with Enterobacter sepsis that was considered to be possibly treatment-related. Of the four SAEs on SMOF and two on Intralipid, no other SAE were considered to be treatment-related.

Data on laboratory values outside the normal range included low pH (SMOF 7/18, 39% vs. Intralipid 12/20, 60%) and raised glucose (SMOF 17/19, 90% vs. 15/17, 88%).

Table 20: Number of patients with TEAEs: all system organ classes and most frequent TEAEs (reported more than once) (Safety population)

System Organ Class/Preferred Term	SMOF N = 42	Intralipid N = 42	Total N = 84
Blood and lymphatic system disorders	6 (14.3%)	4 (9.5%)	10 (11.9%)
Anaemia	3(7.1%)	1 (2.4%)	4 (4.8%)
Thrombocythaemia	0 (0.0%)	2 (4.8%)	2 (2.4%)
Thrombocytopenia	2 (4.8%)	0 (0.0%)	2 (2.4%)
Cardiac disorders	0 (0.0%)	1 (2.4%)	1 (1.2%)
Gastrointestinal disorders	2 (4.8%)	4 (9.5%)	6 (7.1%)
Ileus paralytic	0 (0.0%)	2 (4.8%)	2 (2.4%)
General disorders and administration site conditions	1 (2.4%)	2 (4.8%)	3 (3.6%)
Hepatobiliary disorders	4 (9.5%)	7 (16.7%)	11 (13.1%)
Hyperbilirubinaemia	3 (7.1%)	5(11.9%)	8 (9.5%)
Infections and infestations	5 (11.9%)	11 (26.2%)	16 (19.0%)
Amniotic infection syndrome of Blane	1 (2.4%)	1 (2.4%)	2 (2.4%)
Eye infection	0 (0.0%)	2 (4.8%)	2 (2.4%)
Infection	1 (2.4%)	1 (2.4%)	2 (2.4%)
Respiratory tract infection	1 (2.4%)	1 (2.4%)	2 (2.4%)
Rhinitis	0(0.0%)	2 (4.8%)	2 (2.4%)
Sepsis	1 (2.4%)	1 (2.4%)	2 (2.4%)
Staphylococcal sepsis	1 (2.4%)	3 (7.1%)	4 (4.8%)
Investigations	0 (0.0%)	1 (2.4%)	1 (1.2%)
Metabolism and nutrition disorders	5 (11.9%)	8 (19.0%)	13 (15.5%)
Hyperglycaemia	2 (4.8%)	2 (4.8%)	4(4.8%)
Metabolic acidosis	3 (7.1%)	5(11.9%)	8 (9.5%)
Nervous system disorders	3 (7.1%)	1 (2.4%)	4 (4.8%)
Intraventricular haemorrhage	2 (4.8%)	0(0.0%)	2 (2.4%)
Respiratory, thoracic and mediastinal disorders	2 (4.8%)	2 (4.8%)	4 (4.8%)
Surgical and medical procedures	2 (4.8%)	3 (7.1%)	5 (6.0%)
Catheter removal	1 (2.4%)	2 (4.8%)	3 (3.6%)
Vascular disorders	1 (2.4%)	1 (2.4%)	2 (2.4%)
Hypotension	1 (2.4%)	1 (2.4%)	2 (2.4%)

Analysis of All Trials Combined

Adverse reactions (drug-related adverse events)

Among the volunteers there were five (22.7%) who had drug-related AEs (none for those on Lipovenos). Among the patients overall there were 45/282 (16.0%) who had drug-related AEs on SMOFlipid vs. 43/276 (15.6 %) on comparator (Lipovenos or Intralipid).

Withdrawals due to adverse events

There were overall 23 discontinuations; 6 (8.2%) on SMOFlipid vs. 17 (6.2%) on comparator (Lipovenos or Intralipid) due to AEs.

Deaths and other serious adverse events

There were no deaths or SAEs related to SMOFlipid.

Post-marketing experience at the time of submission

Postmarketing safety data from patients receiving the dose specified in the European Summary of Product Characteristics (SPC) have not revealed any safety concerns related to dosing. In the period from September 2004 until 31 December 2007, there was only one spontaneous report of an adverse drug reaction (a case of non-serious erythema).

Conclusion

SMOFlipid 20% is comprised of the lipid components Soybean oil, Medium chain triglycerides, Olive oil, and Fish oil.

This composition of the different oils was chosen to:

- Provide sufficient amounts of essential fatty acids
- Decrease the load of ω -6 polyunsaturated fatty acids, especially linoleic acid
- Provide the very long chain ω -3 fatty acids EPA and DHA and thereby
- Decrease the ω -6: ω -3 fatty acid ratio
- Replace part of the polyunsaturated fatty acids by monounsaturated fatty acids (oleic acid)
- Include medium chain triglycerides to provide additional rapidly available energy

The standard dose is 1.0 - 2.0 g fat/kg body weight (bw)/day. The recommended infusion rate is 0.125 g fat/kg bw/hour, and should not exceed 0.15 g fat/kg bw/hour, - this equals 3.6 g fat/kg/day. The highest maximum daily dose in adults in all studies was 2.0 g fat/kg bw/d (mean max was 1.32 g fat/kg bw/d). The highest maximum daily dose in children was 2.2 g fat/kg bw/d (mean max was 1.41 g fat/kg bw/d). The highest maximum daily dose in paediatric patients in all studies was 4.0 g fat/kg bw/d (mean max was 2.28 g fat/kg bw/d).

It was only in study -005 that there was an intended dosing > 2.0 g fat/kg/day (from Day 5). The Centre 2 greatest mean intake of SMOF was on Day 6: 3.4 g fat/kg/d in 24 patients and Day 7: 3.3 g fat/kg/d in 23 patients; after that eight patients had a similar amount for the next 2 days, but only three patients had a mean of 3 g fat/kg/d for 9 days. Oral/enteral intake did boost the total fat intake in most of these patients. No significant difference in effect on triglycerides could be shown in the study.

Thus in adults the upper limit of the recommended standard dose has not really been adequately studied, unlike in paediatrics. Also, except in infants, the recommended maximum daily dose has not been studied, and even in infants this does not seem to have been done adequately. In study -005 treatment-related AEs included: hyperbilirubinaemia in three patients (7.1%) and hyperglycaemia in one patient (2.4%) on SMOF versus hyperbilirubinaemia in five patients(11.9%), hyperglycaemia in two patients (4.8%), hypertriglyceridaemia in one patient (2.4%) and metabolic acidosis in one patient (2.4%) among those on Intralipid.

Seventeen patients on SMOF (89.5%) and 15 patients on Intralipid had a high blood glucose after normal or low at baseline, while seven patients on SMOF and 12 patients on Intralipid had a low pH after a normal or high baseline.

Triglyceride levels were assessed both for efficacy (study -03) and safety (study -005). Overall 39/214 patients (18%) on SMOF and 37/215 (17%) on a comparator showed a change from low or normal baseline to a high triglyceride level at endpoint. Among adults 35/162 (22%) on SMOF and 32/158 (20%) on a comparator showed this, no children did, and in pre-term infants 4/52 (8%) on SMOF and 5/57 on a comparator showed this elevation. Eight (4%) SMOF and five (3%) comparator adult patients had this elevation reported as an AE, and three adults on SMOF and one on comparator had the dose reduced as a result.

Among patients overall, three on SMOF and two on a comparator showed a rise in cholesterol from normal or low to high at end point.

Overall, clinically significant changes in bilirubin, AST, GGT and ALP were less among those on SMOF than those on a comparator; ALT results were similar between the two treatments. Adult patient results were similar to those of the overall comparison. For children there were few (only two with Intralipid) clinically significant changes. Pre-term infant changes were similar with only 4/50 (all GGT) again with Intralipid.

Total bilirubin (mean \pm SD) fell in both pooled treatment groups (SMOF: 116.21 \pm 95.06, Intralipid: 96.19 \pm 78.81). No infants showed a shift from low or normal to high, yet four SMOFlipid 20% and five Intralipid 20% preterm infants had hyperbilirubinaemia, all possibly related to study treatment.

Overall, there were two (0.7%) AEs of metabolic acidosis on SMOF and five (1.8%) on a comparator. Only one case (on Intralipid) was treatment-related, but all occurred in preterm infants from study 03-SMOF-005 (which had the higher protocol dose).

Lipid peroxidation in plasma was assessed in Study 00-SMOF-004 by plasma malondialdehyde, which decreased for both treatments (SMOF from 2.949 by -0.686 mmol/L and Intralipid from 2.931 by -0.770 mmol/L).

In Study 00-SMOF-002 lipid peroxidation was measured in the low density lipoproteins as LDL-TBARS which were not significantly different between both treatments (SMOF from 43.3 by 7.8 μ mol/L and Intralipid from 37.5 by 8.8 μ mol/L); while Lipoprotein X was deleted from the list of planned evaluations due to technical reasons.

Among all patients the incidence of nervous system disorders and psychiatric disorders was low and comparable between the treatments.

Overall, there were five discontinuations (1.8%) on SMOFlipid versus one (0.4%) on Lipovenos due to hypoglycaemia, The overall number of patients with a hyperglycaemic AE was 14 (5.0%) on SMOFlipid and seven (2.5%) on Lipovenos (5 and 3 respectively were treatment-related).

The highest incidence of hyperglycaemic AEs (SMOF 8/74, 10.8%) occurred on a mean daily dose of 1.0 – 1.5 g/kg/d (versus Intralipid 2/77, 2.6% on the same mean dose).

Clinical Summary and Conclusions

The evaluator recommended the proposed mixture should not be registered. The submission was considered inadequate, particularly the following points:

- The quality of the literature search is inadequate. However, there was a prior agreement with the TGA and the sponsor on a non-systematic search for this submission.
- The pivotal trial did not use a placebo (glucose/amino acids only) group, but used for a primary variable endpoint triglyceride levels which were elsewhere used as safety parameters, (the

reference for the expected effect of Lipovenos used to determine the non-inferiority margin was not given).

- There was almost no discussion of the effects on glucose and insulin, yet these parameters were affected by the introduction of Intralipid as a source of energy for parenteral nutrition.
- The combination in this submission contains 2 new chemical entities, thus a different level of information in the submission than for a new combination of already registered products was expected.

The quality of the literature search

The submission is based on that submitted to the EU where the constituents MCTs and fish oil are already approved. The submission was described as a hybrid application containing published literature and clinical studies.

The TGA Library has reviewed the submission and cannot comment since there is no literature search report, search strategy or justification for the search provided.

The Pharmacodynamics section of this evaluation report in particular is of concern being entirely based on the submitted literature which carried no attempt at a systematic search. A PubMed search of the term *intravenous fish oil* produced 293 hits, while a search of *intravenous medium chain triglycerides* produced 344 hits. Alternatively an Ovid Medline search of both the simple terms above did produce thousands of references, but these could have been narrowed down by restricting the search. An Ovid Medline search for the very restricted term *intravenous+fish+oil*, produced eight hits of which only one was in the submission, while *intravenous+medium+chain+triglycerides* produced six hits of which only one was in the submission. The omission from the submitted literature of most of the references resulting from the latter two restricted searches above suggests that the submission is inadequate as a literature-based submission.

The reference guidelines provided in the literature including the Guidelines on Paediatric Nutrition of ESPGHAN, ESPEN and ESPR contain references and more importantly the search strategy – from 1992 to December 2003. In the literature-based submission, there is a lack of even a systematic search of 2004 – 2008 (time of submission) without explanation. However, there was a prior agreement with the TGA and the sponsor on a non-systematic search for this submission.

Of the 125 submitted references only 27 were published since December 2003. Most of these 27 were reviews, two were *in vitro* studies, two were PD studies in volunteers, ten were clinical trials and only two of those trials were with SMOFlipid (118 patients), both of which were based on submitted study FE-SM-03-DE. The individual literature studies were not fully evaluated, however of those relevant to the indications:

- With MCT studies there were 187 neonates in 7 studies, 53 children in 4 studies and 48 adults in 6 studies.
- With fish oil there were 18 neonates in 1 study, no children studied and 102 adults in 7 studies (there were a further 812 patients in 3 studies but these were of limited relevance and/or evidence level).
- With olive oil there were 18 neonates in 1 study, 9 children in 1 study and 31 adults in 3 studies.

Comments on the pivotal trial

The major points for consideration are as follows.

Intralipid was introduced to TPN because of essential fatty acid deficiency as an adjunct to amino acid/glucose regimes. It serendipitously also provided a source of calories that enabled smaller daily

requirements of glucose to be used which decreased the associated problems with hyperglycaemia and insulin requirement.

In assessing efficacy by equivalence or non-inferiority it is assumed that superior efficacy of the standard treatment over placebo has been proven for a given indication.³¹

The superiority of Intralipid over placebo for the supply of energy to patients, as part of a parenteral nutrition regimen lies in the easier and better control of glucose concentration and associated insulin requirements seen when Intralipid is added compared to where no lipid is given as part of the parenteral nutrition regimen. This was not presented or discussed. The sponsor argues that the comparison to placebo would not have been ethical. Among the literature submitted was a 2002 study (with ethical approval) that used glucose infusion as a placebo comparator.³²

Plasma triglyceride levels for a given lipid emulsion will depend on the rate of lipid infusion selected, as well as the rate of conversion of that lipid to fatty acids by lipase. This will depend not just on a simple additive effect of the constituent lipids of an infusion as suggested but on: how together they form into chylomicron like particles; how these structures behave in relation to the adherence of apolipoprotein; their behaviour after the adherence of apolipoprotein; and as triglycerides are gradually removed by lipase, leaving an increasing ratio of outer phospholipid shell to internal triglyceride.

There is almost no discussion of the effects on glucose and insulin. Some of the preceding comments relate to this together with the quote from Oh's Intensive Care Manual¹: *Lipid provides more energy per unit volume than carbohydrate, and also avoids the complications of excess glucose administration.*

The Combination in this Submission contains Two New Chemical Entities

The EU Rules, adopted by the TGA, recommend that in relation to a combination with one substance entirely new, data as for an NCE are required:

4. EFFICACY AND SAFETY It is permissible to distinguish between the extent of the studies required in the case of those fixed combinations which correspond closely to combinations which are already in widespread use provided these are thoroughly and reliably documented, and those studies required in the case of those combinations which are essentially new:

*b) When the fixed combination is essentially new (active substances not usually combined, unusual quantitative composition of usually combined substances or **one substance entirely new**), **the data needed are similar to a new chemical entity** in the situation where the fixed combination is to be proposed (first line or second line therapy). Existing experience with the substances should be taken into account.*³³

Many of these studies were in small populations. While the evaluator accepts that it may be difficult to enrol large numbers of patients reliant solely on long term (weeks or months) TPN, the sponsor's approach of investigating short term postoperative major surgery cases provides a good sized population source for investigation. The following is relevant:

*2. LEVELS OF EVIDENCE Applications for marketing authorisations in small populations will be judged against the same standards as for other products, although limitations on patient recruitment will be taken into account.*³⁴

³² Schauder P, Rohn U, Schafer G, Korff G, Schenk HD. Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. Br J Nutr. 2002 Jan;87 Suppl 1:S 103-110.

³³ pp. 175 - 180 of Rules 1998 (3C) - 3CC10a Fixed-Combination Medicinal Products.

³⁴ CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no pharmaceutical chemistry objections to registration. The pharmaceutical chemistry evaluator noted that all 4 of the oils used in SMOFlipid comply with their respective Ph. Eur. Monographs.

The Pharmaceutical Subcommittee of ADEC (PSC) also recommended the clinical evaluator undertake a detailed evaluation of the pharmacokinetics of this product, particularly with respect to the claim made in the Product Information (PI) that SMOFlipid has different pharmacokinetics to Intralipid. In this context, the Committee also noted that, based on the information provided to PSC, it was not clear that the study, upon which the claim of a difference in pharmacokinetics is based, has sufficient statistical power to demonstrate a difference.

Nonclinical

There were no nonclinical objections to registration. The toxicity studies with SMOFlipid showed no novel or exacerbated toxicities compared with currently registered parenteral nutrition agents. The reproductive studies with soya oil and olive oil containing parenteral nutrition agents have been inadequate. Increased resorptions, prolonged gestation and increased pup birth and postnatal weights were seen in rats given infusion of 20% MCT/LCT for 2 weeks prior to mating. In rabbits this infusion during organogenesis elicited increased resorptions and skeletal abnormalities. The nonclinical evaluator considered that SMOFlipid should not be used during pregnancy.

Parenteral nutrition agents are exempt from pregnancy classification, however the adverse embryofetal effects observed with the MCFA-containing triglycerides warrant the inclusion of a Pregnancy Category. The evaluator has proposed category B3.

Clinical

Pharmacology

No pharmacodynamic studies were submitted. The sponsor submitted published papers describing the pharmacodynamics of the component fatty acids. No search strategy for identification and selection of the papers for this section was included in the submission.

Pharmacokinetics was examined in studies FE-SM-01-BE and FE-SM-02-DE. These were 2-treatment, 2-period, crossover studies. FE-SM001-BE was open-label and FE-SM-02-DE was double-blind. Both studies enrolled healthy volunteers and compared the intravascular metabolism of SMOFlipid with Lipovenos 20%, a soya based parenteral nutrition product not registered in Australia. In FE-SM-01-BE one of the lipid preparations was given by peripheral IV infusion for a total of 4 hours with a 4-week washout period before the other product was also infused over 4 hours. Non-esterified fatty acids increased more with SMOFlipid than with Lipovenos (presumed due to the greater MCT content from which fatty acids are more rapidly released). There was an increase in triglycerides, mostly in the VLDL where there was a 10% rise associated with the SMOFlipid infusion. There was little change in the major apolipoproteins in plasma. For most apolipoproteins, the component in VLDL doubled by 4 hours then fell. In study FE-SM-02-DE infusion occurred over 6 hours at the proposed infusion rate of 0.125 g/kg/h with a washout period of 6 days between products. The increase in triglyceride was greater with Lipovenos than SMOFlipid. Clearance was higher for SMOFlipid.

Efficacy

Four prospective, randomised, active-controlled, double-blind studies, one in adults and three in children including preterm neonates, infants or children aged to 11 years were submitted.

Study FM-SM-03-DE was a randomised, double-blind, active-controlled study in adult patients needing TPN after major abdominal, thoracic or urological surgery who had an indication for parenteral nutrition over at least 5 days. The comparator was Lipovenos 20%, a product containing 200 g/L soya bean oil.

The primary study hypothesis was that the elimination of SMOFlipid would be at least as fast as the elimination of Lipovenos 20%, based on serum triglyceride concentrations. The primary efficacy variable was the AUC of the difference between baseline serum triglyceride concentrations and concentrations at each measurement point up to Day 6 (corresponding to 5 days of infusion). This parameter was intended to demonstrate equivalence to the reference product in terms of provision of energy (effect on triglyceride concentrations). SMOFlipid was to be considered non-inferior to Lipovenos if the 1-sided 95% CI for the difference between treatment means was not smaller than -8 mg/dL/day, which was estimated to be -20% of the expected value of the Lipovenos 20% therapy.

Clinical outcomes (length of stay in ICU and in hospital) and fatty acid profiles were secondary endpoints. The primary analysis was of the PP population with the ITT, LOCF provided as a secondary analysis. The PP population received study drug for at least 5 days, had at least 6 triglyceride concentration assessments (1 pre-treatment, 5 after start of treatment), received daily amounts of fat, amino acids and glucose within pre-specified ranges and had no major protocol deviations.

SMOFlipid was administered at a rate of 1.5 g fat/ kg bw/day starting on the morning of Day 1 (the day after surgery) and continuing for 5 days. Lipovenos 20% was administered at the same infusion rate and for the same duration. Amino acids and glucose were administered concomitantly as additional parenteral nutrition. Electrolytes, trace elements and vitamins were administered as required.

A total of 263 patients were enrolled, 126 were randomised to SMOFlipid and 123 to Lipovenos with 99 and 100 patients in each group included in the PP dataset. Mean weight was 70.5 (range 45 – 92) kg in the SMOFlipid group and 71.6 (range 39 – 104.5) kg in the Lipovenos group. For the PP population the mean daily change from the baseline serum triglyceride AUC was 0.7340 mmol/L in the SMOFlipid group vs. 0.7197 mmol/L in the Lipovenos group (95% CI for the difference was -0.0891 mmol/L). The protocol specified lower bound for non-inferiority was expressed in mg/dL and no conversion to mmol/L was provided in the study report. The sponsor had provided a conversion of the 8 mg/dL to mmol/L in the pre-ADEC response. The ITT results were also stated to demonstrate non-inferiority of SMOFlipid to Lipovenos.

Mean serum total cholesterol and phospholipid were comparable in the treatment groups at all time points. Patients given SMOFlipid were hospitalised for a mean of 15.688 days compared with 17.827 days for patients given Lipovenos. Mean length of stay in ICU was 4.66 days for SMOFlipid vs. 5.19 days for Lipovenos. In a subgroup of 19 SMOFlipid and 14 Lipovenos PP patients examined for differences in fatty acid profiles there were higher mean concentrations of the ω 3 fatty acids EPA and DHA and a lower mean concentrations of the ω 6 fatty acid, linoleic acid in plasma free fatty acids and in plasma, leukocyte and platelet phospholipids. The ω 3/ ω 6 ratio increased in the SMOFlipid group compared to the Lipovenos group. Mean concentration of the EPA derived LTB₅ increased to a greater extent following SMOFlipid administration compared with Lipovenos. Mean concentrations of arachidonic acid-derived LTB₄ increased following administration of Lipovenos and decreased following administration of SMOFlipid.

Study 00-SMOF-002 was conducted in infants and children aged from one month to two years and from two to 11 years with stable disease requiring parenteral nutrition for at least 4 weeks. The comparator was Intralipid 20%, a soya oil product registered in Australia. SMOFlipid or Intralipid were given as 2 g fat/kg/day over 12-14 hours for 4-5 days per week with a recommended infusion rate of 0.125 g fat/kg/hour to a maximum of 0.15 g fat/kg/hour. Oral/ enteral intake was to be no more than 50% of calorie intake. Additional parenteral nutrition (amino acids and glucose) varied, dependent on patient total body weight.

Efficacy was a secondary objective in this study and was assessed by the fatty acid profile in plasma and RBC phospholipids and by body weight, height and body mass index. A total of 28 patients were randomised, 13 were aged ≤ 2 years and 15 received SMOFlipid. Only three SMOF and two Intralipid patients were considered dependent on parenteral nutrition. Changes from baseline in fatty acid concentrations in plasma lipoproteins or RBC phospholipids showed increased in EPA and DHA in patients given SMOFlipid compared with those given Intralipid. Small increases in weight, height and BMI were seen in both groups over the 4 week period.

Studies 00-SMOF-004 and 03-SMOF-005 were conducted in pre-term infants aged 0 to 7 days with a gestation age of < 34 weeks. Intralipid was the comparator in both studies. Patients in study 004 were to have birth weights of 1000 to 2500 g and those in study 005 birth weights of 500 to 2000 g.

Patients required parenteral nutrition including fat for at least 7 days. Oral/ enteral intake of $\leq 30\%$ of energy intake on Days 1 – 3 and $\leq 50\%$ on from Day 4 was permitted in both studies. In both studies patients were stratified by weight prior to randomisation. In study 004 dosing commenced at 0.5 g fat/kg bw/day on Day 1 and increased in steps of 0.5 g fat/kg bw/day on Days 2, 3 and 5 and was given at 2.0 g fat/kg bw/day from Days 4 to 14. In study 005 dosing commenced at 1.0 g fat/kg birth weight/day on Days 1 – 3 then increased in 1.0 g fat/kg birth weight/day on Days 4 and 5 and was then given at a dose of 3.5 g fat/kg birth weight from Days 6 to 14. The maximum infusion rate was 0.125 g fat/kg/hour in 004 and 0.17 g fat/kg/hour in 005.

The primary efficacy measure was change in body weight during treatment, expressed as % change in study 004 and as absolute change in study 005. A total of 60 patients were enrolled in study 004 with 30 receiving each treatment. Weight gain occurred in each group (mean of 5.01% for SMOFlipid vs. 5.1% for Intralipid. There was considerable individual variation in weight gain in both groups. Higher $\omega 3$ fatty acid content was seen in patients given SMOFlipid compared with Intralipid. Plasma α -tocopherol and phospholipids were higher in patients given SMOFlipid compared with those given Intralipid. There were no major differences in clinical outcomes in the two treatment groups. In Study 005 a total of 84 patients were enrolled but 37% of the ITT population received incorrectly calculated treatment doses with dosing based on days of life rather than study days and enteral nutrition being taken into account in the dose calculation. In addition that Centre also had slightly lower doses of SMOFlipid given in comparison to Intralipid due to the slightly younger age of patients given SMOFlipid. These factors limit the efficacy information from this study. No major differences were seen in triglyceride levels in the two study groups.

Safety

Safety of SMOFlipid was examined in nine studies, including the four studies which also examined efficacy. A total of 558 patients were assessed for safety and of these 282 received SMOFlipid (195 adults, and 87 paediatric patients including 72 preterm infants). Mean duration of exposure for adult patients was 5.3 (range 1 – 15) days. For non-infant children the mean duration of exposure was 28.3 (range 27 – 29) days and for preterm infants was 9.8 (range 3 – 15) days. The maximum administered dose was 2 g/kg bw/day for adults, 2.2 g/kg bw/day for older children and 4.0 g/kg bw/day for preterm infants. SMOFlipid was given either as a component of parenteral nutrition supplemented with oral/ enteral intake or as total parenteral nutrition.

There were no deaths attributed to study treatment in adult patients given SMOFlipid. There were seven (3.6%) deaths, all during follow-up. The most frequent serious treatment emergent adverse event was sepsis, reported in 7.7% of the SMOFlipid-treated patients. The most frequently reported adverse events were nausea and vomiting (8.7% and 7.2% respectively). This may reflect that the majority of these patients were post-surgical.

For the paediatric patients in study 002 adverse events were reported by seven (46.7%) patients given SMOF and six (46.2%) given Intralipid. The most frequent adverse events concerned general disorders and administration site conditions. There were two serious adverse events (one on each treatment) but these were not considered treatment-related. In study 004 adverse events were reported in 13 (43.3%) of preterm infants given SMOFlipid vs. 14 (46.7%) given Intralipid. The most frequently reported events were infections, respiratory, thoracic and mediastinal disorders and nervous system disorders. None were considered treatment-related.

A total of 84 preterm infants were enrolled in study 005 with 42 were given SMOFlipid. There were six adverse events in five patients given SMOFlipid which were considered treatment-related compared with 12 events in 9 patients given Intralipid. There were four deaths, with one (given Intralipid) due to sepsis which was considered possibly treatment-related.

Risk-Benefit Analysis

Both the pharmacokinetic studies compared the intravascular metabolism of lipids contained in SMOFlipid with those in a comparator product not registered in Australia. In these studies healthy subjects received a single infusion at a total dose lower than the proposed total daily dose. It is likely the metabolism of components of SMOFlipid would be different in subjects requiring parenteral nutrition who received this product over a number of days. The studies provide some assurance that the components are metabolised. No information on the pharmacokinetics of SMOFlipid in children was submitted, though this product has been proposed for use in children, including neonates and infants. Data in support of the proposed paediatric dose regimens were provided in the efficacy and safety studies.

There are no guidelines for the development of parenteral nutrition products. The sponsor chose a combination of growth parameters and fatty acid profiles as the primary measures of efficacy. In all the studies which examined efficacy, factors other than study treatment were able to influence these parameters. No long term data were provided and data on use within a TPN regimen were limited to 5 days in adults.

The study in adults (FE-SM003-DE) enrolled post-surgical patients who were not required to have nutritional deficiencies and who received TPN for only 5 days. The comparator was a soya oil product not registered in Australia, however a similar product containing 20% soya oil is registered (Intralipid 20%). The rationale for the primary efficacy parameter in this study is not clear. As noted by the evaluator, plasma triglyceride levels for a given lipid emulsion will depend on the rate of lipid infusion selected, as well as the rate of conversion of that lipid to fatty acids by lipase. Nevertheless there were no clinically significant differences in lipid metabolism as measured between the two products. The daily infusion rate was consistent with that requested by the sponsor. This study showed differences in fatty acid levels consistent with the higher levels of ω 3 fatty acid in SMOFlipid compared with the comparator. The clinical evaluator was concerned that SMOFlipid may lead to deficiency of ω 6 fatty acids because levels decreased relative to baseline over the 5 day period of measurement. Deficiency of ω 6 fatty acids was not demonstrated, and would not be expected in such a short term study in adults.

In all three studies in children supplementary oral/enteral feeding was permitted, thus any deficiencies which may occur with SMOFlipid could be masked by oral intake. These studies were quite small. The comparator in all three studies, Intralipid 20%, is registered in Australia for use in children, including neonates. The maximum period of assessment was 4 weeks for older children

and 2 weeks for infants and neonates. Comparisons of weight/height and BMI gain in these studies are of limited relevance given that supplementary oral/enteral feeding was permitted. As in the adult studies, changes in blood lipoproteins due to the higher level of ω 3 fatty acid in SMOFlipid were apparent.

As noted by the clinical evaluator, safety concerns associated with soya-based lipid parenteral nutrition include hyperlipidaemia, fatty infiltration of the liver, cholestasis and reticulo-endothelial system accumulation. The MCT formulations are associated with hyperlactacidaemia, hyperketonaemia and central nervous system toxicity. These events are more likely to occur with higher doses. Therefore it is important to assess the safety of SMOFlipid at the highest proposed dose. The proposed maximum dose in children and infants is 3 g fat/kg bw/day however the maximum dose assessed in clinical trials in this age group was 2.2 g fat/kg bw/day. Given the concerns about elevated triglycerides with increasing dose and/or infusion rate the maximum rate examined in the clinical study should be the maximum dose recommended for this age group. For preterm infants a maximum daily dose of 3.0 mg/kg bw/day has been proposed. This is less than the maximum rate given in one of the studies in preterm infants but above the maximum dose in the other study.

Efficacy and safety of SMOFlipid as a component of total parenteral nutrition (TPN) in children has not been examined. All studies in children, including in preterm infants, involved concomitant oral/enteral feeding. SMOFlipid as a component of TPN in adults has been assessed only in a short term (5 day) study. These limitations should be reflected in the Product Information for SMOFlipid. Changes in laboratory parameters reflect the parenteral nutrition (lipid, amino acids and glucose), oral/enteral intake and other treatments given to the patients as well as their underlying medical condition. As patients in the clinical studies were randomised to treatment groups this would have minimised differences due to these factors. Changes in liver function were less in patients given SMOFlipid compared with comparator treatment, though few of these changes were clinically significant.

In the Delegate's final assessment, all questions concerning clinical aspects raised during the review process have been sufficiently answered and approval was recommended.

The Delegate proposed to register SMOFlipid for

Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated.

The maximum daily dose for children should be 2 g fat/kg bw/day because this is consistent with the maximum dose given in clinical trials in children. The PI should reflect that there are no long term data on use of SMOFlipid as a component of Total Parenteral Nutrition.

In the pre-ADEC response the sponsor was requested to address the following issues:

- Provide a conversion of 8 mg/dL to mmol/L;
- Justify the proposed dose of 3 g fat/kg bw/day in children;
- Comment on long term use of SMOFlipid as a component of Total Parenteral Nutrition.

The Delegate requested advice from the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) specifically on whether the indications should reflect that there are no data on long term use of the product and that its use as a component of TPN is limited to short term data in adults.

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission for the indication:

Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated

In making this recommendation, the Committee agreed with the Delegate that there was no need to distinguish omega 3 fatty acids separate from essential fatty acids in the indication. The Committee also concurred with the Delegate that the maximum daily dose for children should be 2 g fat/kg bw/day because this is consistent with the maximum dose given in clinical trials in children. Additionally, the Committee endorsed the PSC recommendation, regarding greater prominence be given in the CMI regarding the allergies to fish, eggs and soy products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of SMOFlipid lipid emulsion 20% emulsion for intravenous infusion bag which consists of soya oil, medium-chain triglycerides (MCT), olive oil and fish oil for the indications:

Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated

Attachment 1. Product Information

PRODUCT INFORMATION

NAME OF MEDICINE

SMOFLIPID 20%

DESCRIPTION

SMOFlipid emulsion for infusion is a white homogenous emulsion.

Each 1000mL contains:

Soya Oil	60 g
Medium-chain Triglycerides	60 g
Olive oil	50 g
Fish oil	30 g

Excipients includes:

Glycerol	25 g
Egg Lecithin	12 g
dl-alpha-Tocopherol	163 – 225 mg
Sodium Hydroxide	pH approx. 8
Sodium Oleate	300 mg
Water for injections	to 1000mL

Total energy:	8400 kJ (2000kcal)
pH:	approx. 8
Osmolality	380 mOsm/kg water

PHARMACOLOGY

The fat emulsion has a particle size and biological properties similar to those of endogenous chylomicrons. The constituents of SMOFlipid: Soya oil, Medium-chain Triglycerides, Olive Oil and Fish Oil have their own pharmacodynamic properties in addition to their energy contents.

Soya Oil has a high content of essential fatty acids. The omega-6 (ω 6) fatty acid linoleic acid is the most abundant (approx. 55-60%). Alpha-linolenic acid, an omega-3 (ω 3) fatty acid, constitutes about 8%. This part of SMOFlipid provides essential fatty acids.

Medium-chain fatty acids are rapidly oxidised.

Olive Oil mainly provides energy in the form of mono-unsaturated fatty acids.

Fish Oil is characterised by a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is an important structural component of cell membranes, whereas EPA is a precursor of eicosanoids as prostaglandins, tromboxanes and leucotrienes.

Vitamin E protects unsaturated fatty acids against lipid peroxidation.

Pharmacokinetics

The individual triglycerides have different clearance rates.

Pharmacokinetic parameters of triglycerides following administration of SMOFlipid 20% at a dose of 0.125 g fat/kg/hour for 6 hours to 12 healthy adult volunteers are presented in the table below.

Parameter (unit)	SMOFlipid 20% Mean \pm SD Median (range)
AUC _(0-t) (mg*h/dL)	3002 \pm 1331 2598 (1288 – 6164)
C _{max} (mg/dL)	291 \pm 144 260 (100 – 657)
t _{max} (h)	3.50 \pm 0.80 3.00 (3.00 – 5.00)
t _{1/2} (h)	0.34 \pm 0.11 0.35 (0.16 – 0.54)

SD=standard deviation

AUC_(0-t) = Area under the serum concentration-time curve from time zero until the last quantifiable concentration.

C_{max} = Maximum observed serum concentration.

t_{max} = Time to reach C_{max}

t_{1/2} = Apparent terminal disposition half-life

CLINICAL TRIALS

Nine studies examined the safety and tolerance of SMOFlipid with efficacy assessed in 4 studies. A total of 558 patients were assessed for safety and of these 282 received SMOFlipid (195 adults, and 87 paediatric patients including 72 preterm infants).

Adults

Two hundred and forty-nine post-surgical adult patients received either SMOFlipid (n=126) or an unregistered comparator containing 200g/L soya oil (n=123) for 5 days in a randomised, double-blind study. SMOFlipid 20% or the comparator were administered at a rate of 1.5g fat/kg bw/day starting on the morning of Day 1 (the day after surgery) and continuing for 5 days. Patients also received amino acids and glucose as additional parenteral nutrition. Electrolytes, trace elements and vitamins were administered as required.

Elimination of SMOFlipid 20% was at least as rapid as the elimination of the soya oil product over the 5 days of infusion. Mean serum total cholesterol and phospholipid were comparable in the treatment groups at all time points. Patients given SMOFlipid were hospitalised for a mean of 15.7 days compared with 17.8 days for patients given the comparator. Mean length of stay in ICU was 4.7 days for SMOFlipid vs. 5.2 days for the comparator. In a subgroup of 19 patients given SMOFlipid and 14 given the comparator who were examined for differences in fatty acid profiles there were higher mean concentrations of the ω 3 fatty acids EPA and DHA and a lower mean concentrations of the ω 6 fatty acids, linoleic acid in plasma free fatty acids and in plasma, leukocyte and platelet phospholipids. The ω 3/ ω 6 ratio increased in the SMOFlipid group compared to the comparator group. The mean concentration of the EPA derived LTB₅ increased to a greater extent following SMOFlipid administration compared with the comparator. Mean concentrations of arachidonic acid-derived LTB₄ increased following administration of Lipovenos and decreased following administration of SMOFlipid.

Children

Twenty eight infants and children aged from 5 months to 2 years and from 2 to 11.5 years with stable disease requiring parenteral nutrition for at least 4 weeks received SMOFlipid or Intralipid 20% in a randomised, double-blind study. SMOFlipid or Intralipid were to be given as approx. 2g fat/kg/day over 12-14 hours for 4-5 days per week with a recommended infusion rate of 0.125g fat/kg/hour to a maximum of 0.15g fat/kg/hour. Oral/enteral intake was to be no more than 50% of caloric intake. Additional parenteral nutrition (amino acids and glucose) varied, dependent on patient total body weight.

Efficacy was a secondary objective in this study and was assessed by the fatty acid profile in plasma lipoproteins and RBC phospholipids and by body weight, height and body mass index. Changes from baseline in fatty acid concentrations in plasma lipoproteins or RBC phospholipids showed increased in EPA and DHA in patients given SMOFlipid compared with those given Intralipid. Small increases in weight, height and BMI were seen in both groups over the 4 week period.

Pre-term infants

Two randomised, controlled, double blind studies were conducted in pre-term infants aged 0 to 9 days with a gestation age of < 34 weeks. Intralipid 20% was the comparator in both studies. In one study, patient's birth weight was from 1000 to 2500g and in the other, birth weight was from 500 to 2000g. Patients required parenteral nutrition including fat for at least 7 days. Oral/enteral intake of $\leq 30\%$ of energy intake on Days 1-3 and $\leq 50\%$ on from Day 4 was permitted in both studies. In one study dosing commenced at 0.5g fat/kg/bw/day on Day 1 and increased in steps of 0.5g fat/kg bw/day on Days 2, 3 and 4 and was given at 2.0g fat/kg bw/day from Days 4 to 14 with a maximum infusion rate of 0.125g fat/kg/hour. In the other study dosing commenced at 1.0g fat/kg birth weight /day on Days 1-3 then increased in 1.0g fat/kg/birth weight/day on Days 4 & 5 and was then given at a dose of 3.5g fat/kg birth weight/day from days 6 to 14 with a maximum infusion rate of 0.17g fat/kg/hour. If actual body weight exceeded birth weight during treatment, dosing was to be adjusted according to actual body weight.

The primary efficacy measure in both studies was change in body weight during treatment. In one study 60 patients were enrolled with 30 receiving each treatment. Weight gain occurred in each group (mean of 5.01% for SMOFlipid vs. 5.1% for Intralipid 20%). There was considerable individual variation in weight gain in both groups. Higher $\omega 3$ fatty acid content was seen in patients given SMOFlipid compared with Intralipid. Plasma α -tocopherol was higher in patients given SMOFlipid compared with those given Intralipid 20%. There were no major differences in clinical outcomes in the 2 treatment groups. In the other study 84 patients were enrolled but 37% of the ITT population received incorrectly calculated treatment doses. No major differences were seen in triglyceride levels in the 2 study groups.

INDICATIONS

Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated.

CONTRAINDICATIONS

- Hypersensitivity to fish-, egg-, soya- or peanut protein or to any of the active ingredients or excipients.
- Severe hyperlipidaemia.
- Severe liver insufficiency.
- Severe blood coagulation disorders.
- Severe renal insufficiency without access to hemofiltration or dialysis.
- Acute shock.
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency.
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis and severe sepsis and hypotonic dehydration).

PRECAUTIONS

The capacity to eliminate fat is individual and should therefore be monitored routinely by the clinician. This is in general done by checking the triglyceride levels. Special precaution should be taken in patients with a marked risk for hyperlipidaemia (e.g. patients with high lipid levels, severe sepsis and extremely low birth weight infants). The concentration of triglycerides in serum should in general not exceed 3mmol/L during infusion. Reduction of the dosage or cessation of the lipid emulsion should be considered if serum or plasma triglyceride concentrations during or after infusion exceed 3mmol/L. An overdose may lead to fat overload syndrome.

This medicinal product contains Soya Oil, Fish Oil and Egg Lecithin, which may rarely cause allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut.

SMOFlipid should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with renal failure, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism and sepsis.

Clinical data in patients with diabetes mellitus or renal failure are limited.

Administration of medium-chain fatty acids alone can result in metabolic acidosis. This risk is to a great extent reduced by the simultaneous infusion of the long chain fatty acids included in SMOFlipid. Concomitant administration of carbohydrates will further reduce this risk. Hence, simultaneous infusion of carbohydrate or a carbohydrate-containing amino acid solution is recommended.

Any signs or symptoms of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.

Effects on fertility

The potential effects of SMOFlipid on fertility and general reproductive performance have not been determined in animal studies.

Use in pregnancy (Category B3)

There are no adequate and well-controlled studies in pregnant women with SMOFlipid or its individual components; therefore the safety of SMOFlipid in pregnant women is not known.

No animal studies have been conducted with the combined lipid components of SMOFlipid to evaluate effects on reproduction. Embryotoxicity and increased incidences of fetal skeletal variations have been observed in rabbits that had received medium chain fatty acid-containing lipids similar to SMOFlipid during the period of organogenesis. SMOFlipid should not be used during pregnancy unless the expected therapeutic benefit clearly outweighs the potential risk to the fetus.

Use in lactation

It is not known whether SMOFlipid can enter maternal milk. Therefore, SMOFlipid should be used during lactation only if clearly needed.

Paediatric use

SMOFlipid should be given with caution to neonates and premature infants with hyperbilirubinaemia and cases with pulmonary hypertension. In neonates, particularly premature infants on long term parenteral nutrition, blood platelet counts, liver function tests and serum triglycerides should be monitored.

Genotoxicity

SMOFlipid was not mutagenic or clastogenic in a battery of genotoxicity studies, including the Ames bacterial mutagenicity assay, a mammalian mutagenicity assay, a chromosome aberration assay in human peripheral lymphocytes, and an *in vivo* rat micronucleus assay.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of SMOFlipid.

Interactions with other medicines

The addition of other medications or substances to SMOFlipid should generally be avoided unless compatibility is known (please also refer to section "Instructions on use and handling").

Heparin given in clinical doses causes a transient increase in lipoprotein lipase release into the circulation. This may initially result in increased plasma lipolysis, followed by a transient decrease in triglyceride clearance.

Soya Oil has a natural content of vitamin K₁. The content is however so low in SMOFlipid that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

Effects on laboratory tests

Laboratory tests generally associated with monitoring of intravenous nutrition should be checked regularly. These include blood glucose levels, liver functions tests, acid base metabolism, fluid balance, full blood count and electrolytes.

As with all lipid emulsions, SMOFlipid may interfere with certain laboratory measurements (bilirubin, haemoglobin, lactate dehydrogenase, oxysaturation), if blood is sampled before fat has adequately been cleared from the bloodstream. In most patients, fat is cleared after a fat free period or interval of 5 to 6 hours.

Fat Overload Syndrome

Impaired capacity to eliminate triglycerides can lead to “Fat Overload Syndrome” which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient’s clinical condition, such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopaenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued.

Should signs of a Fat Overload Syndrome occur, the infusion of SMOFlipid should be discontinued.

ADVERSE EFFECTS

Most common drug-related Treatment-Emergent Adverse Events (TEAEs) in SMOFlipid 20% and comparator pooled groups (i.e those occurring in more than 2 patients of any pooled group) observed in 7 clinical trials are presented in the table below.

Drug-related TEAEs n(%) of patients	SMOFlipid 20% pooled (n=282)	Comparator pooled (n=276)
Number of patients with at least 1 drug-related TEAE	45 (16.0)	43 (15.6)
Nausea	12 (4.3)	13 (4.7)
Vomiting	12 (4.3)	6 (2.2)
Blood triglycerides increased	6 (2.1)	3 (1.1)
Hyperglycaemia	5 (1.8)	3 (1.1)
Hyperbilirubinaemia	4 (1.4)	5 (1.8)
Flatulence	4 (1.4)	1 (0.4)
Liver function test abnormal	2 (0.7)	3 (1.1)
Hypertriglyceridaemia	2 (0.7)	3 (1.1)
Gamma-glutamyltransferase increased	1 (0.4)	3 (1.1)

Since SMOFlipid has been marketed, there was only 1 spontaneous report of an adverse drug reaction (a case of non-serious erythema) in a 75 year old female patient.

Should triglyceride levels during infusion of SMOFlipid rise above 3mmol/L, the infusion should be stopped or, if necessary, continued at a reduced dosage.

SMOFlipid should always be a part of a complete parenteral nutritional treatment including amino acids and glucose. Nausea, vomiting and hyperglycaemia may sometimes be associated with parenteral nutrition.

Monitoring of triglycerides and blood glucose levels are recommended to avoid elevated levels, which may be harmful.

DOSAGE AND ADMINISTRATION

The patient's ability to eliminate the fat infused should govern the dosage and infusion rate, (please also refer to section "PRECAUTIONS").

Adults

The standard dose is 1.0 – 2.0 g fat/kg body weight (b.w) / day, corresponding to 5 – 10 mL / kg b.w / day.

The recommended infusion rate is 0.125 g fat / kg b.w / hour, corresponding to 0.63 mL SMOFlipid / kg b.w / hour, and should not exceed 0.15 g fat / kg b.w / hour, corresponding to 0.75 mL SMOFlipid / kg b.w / hour.

Neonates and infants

The initial dose should be 0.5 – 1.0 g fat / kg b.w / day followed by a successive increase by 0.5 – 1.0 g fat / kg b.w / day up to 3.0 g fat / kg b.w / day.

It is recommended not to exceed a daily dose of 3g fat / kg b.w / day, corresponding to 15 mL SMOFlipid / kg b.w / day.

The rate of infusion should not exceed 0.125 g fat / kg b.w / hour.

In premature and low birth weight neonates, SMOFlipid should be infused continuously over around 24 hours.

Children

It is recommended not to exceed a daily dose of 2g fat / kg b.w / day, corresponding to 10 mL SMOFlipid / kg b.w / day. With increased requirements in the youngest children a dose up to a maximum of 3g fat / kg b.w / day can be considered.

The daily dose should be increased gradually during the first week of administration.

The infusion rate should not exceed 0.15 g fat / kg b.w / hour.

Administration

Intravenous infusion into a peripheral or central vein.

Instructions for use and handling

Use only if the emulsion is homogeneous.

For Excel bag: The integrity indicator (Oxalert) should be inspected before removing the overpouch. If the indicator is black, oxygen has penetrated the overpouch and the product should be discarded.

Inspect the emulsion visually for phase separation prior to administration. Ensure that the final emulsion for infusion does not show any evidence of phase separation.

For single use only. Any unused emulsion should be discarded.

Additives

SMOFlipid may be aseptically admixed with amino acid, glucose, and electrolyte solutions to produce "All-In-One" Total Parenteral Nutrition (TPN) admixtures.

Additions should be made aseptically. Any mixture remaining after infusion must be discarded.

Shelf life after first opening the container

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view the emulsion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

OVERDOSAGE

Overdose leading to Fat Overload Syndrome may occur as a result of a too rapid infusion rate, or chronically at recommended rates of infusion in association with a change in the patients clinical conditions e.g. renal function impairment or infection.

Over dosage may lead to side-effects (please also refer to section "ADVERSE EFFECTS"). In these cases the lipid infusion should be stopped or, if necessary, continued at a reduced dosage.

STORAGE CONDITIONS

Store below 25°C. Do not freeze.

Storage after mixing

If additions are made to SMOFlipid, the admixtures should be used immediately from a microbiological point of view. If admixtures are not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

PRESENTATION

SMOFlipid 20% is available in pack sizes of 100mL, 250mL and 500mL

The excel bag consist of an inner bag (primary package) with an overpouch. An oxygen absorber and an integrity indicator (Oxalert™) are placed between the inner bag and the overpouch.

- The Excel inner bag consists of a poly(propylene/ethylene) copolymer, a thermoplastic elastomer and a copolyester.

- The oxygen barrier overpouch consists of polyethylene terephthalate and polyolefin or polyethylene terephthalate, polyolefin and ethylene-vinyl alcohol copolymer (EVOH).
- The oxygen absorber consists of iron powder in a polymer sachet.
- The integrity indicator consists of oxygen sensitive solution in a polymer sachet.

The overpouch, the oxygen absorber and the integrity indicator should be discarded after opening of the overpouch. The integrity indicator (Oxalert™) will react with free oxygen and change colour from clear to black in case of damage in the overpouch.

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POISON SCHEDULE

Australia: Not Scheduled
New Zealand: General Sale Medicine

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