SYNOPSIS

Name of Company: Fresenius Kabi Deutschland GmbH	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: SMOFlipid 200 mg/mL emulsion for infusion	Volume:	
Name of Active Ingredients: Soy bean oil/medium chain triglycerides (MCT)/olive oil/fish oil	Page:	
Title of the study: A double-blind, randomized study comparing the safety and torelance of SMOFlipid® 20% and Intralipid® 20% in long-term treatment with parenteral nutrition		
Coordinating Investigator: Hope Hospital Salford, Manchester United Kingdom M6 8HD		

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Publication (reference)	None
Study centres:	The patients were enrolled in 11 centres in total: in Australia (2 centres), Denmark (2 centres), France (2 centres), Israel (1 centre), Netherlands (1 centre), Poland (1 centre) and United Kingdom (2 centres), a list of investigators is shown in Appendix 16.1.4 and Section 6 of the report.
Studied period:	Date of first patient enrolled: 23-Oct-2007 Date of last patient completed: 23-Oct-2008
Phase of development:	III
Objective:	The objective was to compare the safety and tolerance of SMOFlipid® 20% with Intralipid® 20% during 4 weeks in patients requiring parenteral nutrition (PN).
Methodology:	This was a multi-national, multi-centre, randomized, double-blind, active-controlled parallel phase III study.
Sample size:	Twenty-four (24) patients in each of the two treatment groups were expected to give sufficient evidence of the safety and tolerance of the study treatments of SMOFlipid® 20% compared to Intralipid® 20% during 4 weeks. As the drop-out rate was estimated to be 25%, approximately 60 patients were to be treated with study medication. As a maximum, 80 patients were planned to be treated with study drug, dependent of the results of continuous evaluability checks during the study.
Number of patients (planned and analyzed):	Planned: A maximum of 80 patients were planned to be treated with study drug Randomized: 75 patients (SMOFlipid: 35 pts., Intralipid: 40 pts.) Safety Set: 73 patients (SMOFlipid: 34 pts., Intralipid: 39 pts.) Evaluable Set: 57 patients (SMOFlipid: 28 pts., Intralipid: 29 pts.)
Diagnosis and main criteria for inclusion:	Male and female patients between 18 and 85 years of age unable to sustain an adequate oral/enteral food intake for at least 4 weeks and in need of parenteral nutrition (PN); written informed consent.

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Test product, dose and mode of administration, and batch number:	SMOFlipid® 20% was infused at a dose of 1-2 g fat/kg body weight (bw)/day corresponding to 5-10 mL/kg bw/day emulsion via central vein catheter (CVC), 10-24 hours/day, 5-7 days/week. Batch numbers used were 16BB0122, 16AI0037 and WD1501, refer also to Appendix 16.1.6.
Duration of treatment:	4 weeks
Reference therapy, dose and mode of administration, batch number:	Intralipid® 20% was infused at a dose of 1-2 g fat/kg bw/day corresponding to 5-10 mL/kg bw/day emulsion via CVC, 10-24 hours/day, 5-7 days/week. Batch numbers used were 16BB0138, 16AI0044 and WC1565, refer also to Appendix 16.1.6.
Oral/enteral nutrition:	Additional oral/enteral intake could be given at the discretion of the investigator. The intake of oily fish meals and dietary vitamin supplements was to be documented in the Case Report Form (CRF) of each patient. The home-patient documented such information in a diary. The oral/enteral intake of capsules containing fish oil or essential fatty acids was not permitted.
Criteria for evaluation:	Only assessments of safety were evaluated in this study.

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Safety:

Laboratory variables:

- Biochemistry: triglycerides, total cholesterol, alkaline phosphatase (AP), aspartate transaminase (AST), gamma-glutamyltransferase (γ-GT), alanine transaminase (ALT), sodium, potassium, chloride, magnesium, calcium, phosphate, total bilirubin, conjugated bilirubin, S-creatinine, urea, glucose, albumin, total protein, C-reactive protein (CRP)
- Hematology: leucocytes, platelets, erythrocytes, hemoglobin, hematocrit
- Coagulation: International normalized ratio (INR)
- Special laboratory tests: Interleukin 6 (IL-6), soluble tumor necrosis factor-receptor II (s-TNF-RII)
- Other tests: vitamin E (α-tocopherol) in serum, fatty acid pattern in red blood cells (RBC) phospholipids and plasma lipoproteins, serum pregnancy tests in females not surgically sterile or postmenopausal for at least two years.

Clinical variables:

- Incidence of cholestasis, defined as:
  either conjugated bilirubin above 1.5 fold upper limit of normal (ULN) and either γ-GT or AP above 1.5 fold ULN, too
  or conjugated bilirubin alone was > 2 mg/dL without any explanation for another etiology, e.g. viral hepatitis
- Adverse events (AEs)
- Vital signs (blood pressure [mmHg], heart rate [beats/min.], body temperature [°C])

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Statistical Methods:	Data were summarized using descriptive statistics (number of patients [n], mean, standard deviation [SD], minimum, 25% quartile, median, 75% quartile, and maximum) for continuous variables, and using frequency and percentage (i.e., number [n] and proportion of patients [%]) for discrete/categorical variables, unless otherwise specified. Patient listings of all data from the CRFs, as well derived variables (as appropriate), were presented. Analyses were based on the **Safety Set** and the **Evaluable Set**. The **Safety Set** included all randomized patients who received at least one dose of study product. The **Evaluable Set** included all sufficiently treated (i.e., at least 0.75 g fat per kg bw on at least 18 days) patients in the Safety Set who had no major protocol deviations. The Evaluable Set was used for the per-protocol analysis of selected parameters. For analysis of AEs, a Poisson regression on AE rates was conducted. For laboratory values and vital signs, 95% confidence intervals were also provided. These were generated by a covariance analysis (ANCOVA) of the changes from baseline to last observation under incurrence of the baseline values and the treatment as factor: change from baseline = baseline+treatment.
Summary - conclusions	
Efficacy results:	No efficacy parameters were examined in this study.

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Summary - conclusions

Safety results:

Extent of exposure

Both treatment groups had a similar exposure to study drug and also with regard to daily and total amount of glucose and amino acid intake per kg bw in the Safety Set and the Evaluable Set.

AEs

Overall, 85 AEs were reported in 38 (52.1%) patients, thereof 31 AEs in 15 (44.1%) in the SMOFlipid® group and 54 AEs in 23 (59.0%) patients in the Intralipid® group. Of these, 3 AEs in 2 (5.1%) patients in the Intralipid® group were pre-treatment AEs while the remaining 82 AEs were treatment-emergent AEs (TEAEs). These 82 TEAEs were reported in 36 (49.3%) patients, thereof 31 TEAEs in 15 (44.1%) patients in the SMOFlipid® group and 51 TEAEs in 21 (53.8%) patients in the Intralipid® group.

Infections and infestations in 6 (17.6%) patients in the SMOFlipid® group and in 9 (23.1%) patients in the Intralipid® group and gastrointestinal disorders in 5 (14.7%) patients in the SMOFlipid® group and in 4 (10.3%) patients in the Intralipid® group were most frequently reported. Headache and nausea, both in 5 (6.8%) patients, catheter sepsis in 4 (5.5%) patients and urinary tract infection in 3 (4.1%) patients were the only events mentioned more than twice.

A premature study discontinuation due to TEAE was reported in 8 (11.0%) patients with 14 TEAEs, thereof 2 TEAEs in 2 (5.9%) patients in the SMOFlipid® group and 12 TEAEs in 6 (15.4%) patients in the Intralipid® group. Premature discontinuation was considered to be related to treatment with investigational product in two patients with increased triglycerides and in one patient with post gastric surgery syndrome and tremors. Moreover, catheter-related complications were reported as serious TEAEs leading to premature withdrawal.

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Safety results:	**AEs (continued)** Eleven (11) TEAEs related to study drug were reported in 5 (6.8%) patients, thereof 5 TEAEs in 2 (5.9%) patients in the SMOFlipid® group and 6 TEAEs in 3 (7.7%) patients in the Intralipid® group. None of the TEAEs related to study drug were serious. Six (6) TEAEs related to study procedure were reported in 6 (8.2%) patients, thereof 1 TEAE in 1 (2.9%) patient in the SMOFlipid® group and 5 TEAEs in 5 (12.8%) patients in the Intralipid® group. Twelve (12) serious TEAEs were reported in 10 (13.7%) patients, thereof 2 serious adverse events (SAEs) in 2 (5.9%) patients in the SMOFlipid® group and 10 SAEs in 8 (20.5%) patients in the Intralipid® group. No deaths were reported in this study. None of the SAEs were related to the study drug and the outcome of all SAEs was reported as recovered. The frequency of SAEs was higher in the Intralipid® group than in the SMOFlipid® group, and the Poisson regression yielded a p-value of p=0.0288, i.e. a statistically significant difference (p<0.05) between treatment groups in the number of SAEs in favor of SMOFlipid® could be shown. **Laboratory parameters** In both treatment groups, hematology, biochemistry and coagulation parameters as well as inflammatory markers IL-6 and sTNF-RII remained stable throughout the study. Serum vitamin E levels changed from (arithmetic mean±SD [median]) 30.1 ± 15.9 (27.2) µmol/L at baseline to 39.5 ± 13.6 (39.1) µmol/L at Week 4/End of Study in the SMOFlipid® group and from 28.9 ± 13.0 (26.6) µmol/L at baseline to 29.7 ± 12.7 (26.0) µmol/L at Week 4/End of Study in the Intralipid® group with statistically significant higher levels of serum vitamin E in SMOFlipid® treated patients which were however still within normal range (p=0.0004 for the Safety Set, p=0.0003 for the Evaluable Set; 2-sided t-test).

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Safety results:	**Fatty acid patterns** Most of the fatty acid patterns remained stable or were only slightly changed during the study. In RBC phospholipids, the ratio of ω6/ω3-fatty acids changed from (arithmetic mean±SD [median]) 16.89 ± 12.50 (11.56) at baseline to 8.03 ± 4.47 (6.39) at Week 4/End of Study in the SMOFlipid® group, but only from 14.76 ± 9.45 (11.12) at baseline to 14.02 ± 6.73 (12.72) at Week 4/End of Study in the Intralipid® group. In plasma lipoproteins, the ratio of ω6/ω3-fatty acids changed from 29.70 ± 13.73 (27.95) at baseline to 12.35 ± 8.68 (11.21) at Week 4/End of Study in the SMOFlipid® group, but only from 31.39 ± 16.84 (28.69) at baseline to 30.84 ± 13.43 (29.32) at Week 4/End of Study in the Intralipid® group. Moreover, the proportion of the fatty acid fractions C20:5ω3 and C22:6ω3 was increased both in RBC phospholipids and plasma lipoproteins only in the SMOFlipid® group, but remained almost unchanged in the Intralipid® group which reflects the addition of these two fractions in the new composition of SMOFlipid® compared to Intralipid®. Similar results were obtained for the Evaluable set. **Vital signs and cholestasis** Overall, vital signs did not show any clinically significant trends. Regarding occurrence of cholestasis, only patient 71-126 in the SMOFlipid® group had cholestasis from Week 2 on. In the Intralipid® group, the same 4 patients (12-121, 31-155, 71-105 and 72-134) had cholestasis at the beginning and at the end of the study.
Conclusion:	In conclusion, the study treatments SMOFlipid® and Intralipid® were safe and well tolerated as long-term PN treatment over 28 days. SMOFlipid® revealed a favorable safety profile which is reflected by the low incidence of AEs and SAEs and by the evaluation of laboratory parameters and vital signs. Regarding the ratio of ω6/ω3-fatty acids in RBC phospholipids and plasma lipoproteins, differences in favor of SMOFlipid® were observed which reflected the new composition of SMOFlipid® compared to Intralipid®.