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APPLICATION NUMBER:

210589Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	New Drug Application
Application Number(s)	210589
Priority or Standard	Priority Review
Submit Date(s)	December 1, 2017
Received Date(s)	December 1, 2017
PDUFA Goal Date	August 1, 2018
Division/Office	Division of Gastroenterology and Inborn Errors Products
Review Completion Date	July 27, 2018
Established Name	Fish oil triglycerides injectable emulsion
(Proposed) Trade Name	Omegaven
Pharmacologic Class	Intravenous Lipid Emulsion
Code name	8013001
Applicant	Fresenius Kabi
Formulation(s)	Intravenous Infusion
Dosing Regimen	1 gram lipid/kg/day
Applicant Proposed Indication(s)/Population(s)	Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC). Limitations of Use: • Omegaven is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition (PN)-dependent patients *[see Clinical Studies (14)].* • It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6: omega-3 fatty acid ratio of the product *[see Clinical Studies (14)].*

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Regulatory Affairs/ Project Management	Mimi Phan	OND/ODEIII/DGIEP	**Sections: All**	**Select up to two:** ☐Authored ☒Acknowledged ☐Cleared
	Signature: Mimi T. Phan -A Digitally signed by Mimi T. Phan -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mimi T. Phan -A, 0.9.2342.19200300.100.1.1=1300381542 Date: 2018.07.27 11:09:53 -04'00'			
ODEIII Office Director	Julie Beitz	OND/ODEIII	**Sections: authored 15, cleared all**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature:			
Division Signatory	Joyce Korvick	OND/ODEIII/DGIEP	**Sections: authored 14, cleared all**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Joyce A. Korvick -S Digitally signed by Joyce A. Korvick -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300087128, cn=Joyce A. Korvick -S Date: 2018.07.27 10:47:26 -04'00'			
Clinical Team Leader	Anil Rajpal	OND/ODEIII/DGIEP	**Sections: authored 1.3, 4** **Reviewed/cleared all**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Anil K. Rajpal -S Digitally signed by Anil K. Rajpal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anil K. Rajpal -S, 0.9.2342.19200300.100.1.1=1300170204 Date: 2018.07.26 14:20:04 -04'00'			
Clinical Reviewer	Suna Seo	OND/ODEIII/DGIEP	**Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, Appendix 16.1-16.6,16.8, 16.10**	**Select up to two:** ☒Authored

			Acknowledged all	☒Acknowledged ☐Cleared
	Signature: Suna Seo -S Digitally signed by Suna Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suna Seo -S, 0.9.2342.19200300.100.1.1=0011249481 Date: 2018.07.26 14:11:09 -04'00'			
Clinical Pharmacology Reviewer	Elizabeth Shang	OTS/OCP/DCPIII	**Section: co-authored 6**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Elizabeth Shang -S Digitally signed by Elizabeth Shang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000383853, cn=Elizabeth Shang -S Date: 2018.07.25 17:58:52 -04'00'			
Clinical Pharmacology Team Lead	Insook Kim	OTS/OCP/DCPIII	**Sections: 6**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Insook Kim -S Digitally signed by Insook Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Insook Kim -S, 0.9.2342.19200300.100.1.1=1300416436 Date: 2018.07.25 18:21:20 -04'00'			
Pharmacometrics Reviewer	Jee Eun Lee	OTS/OCP/DPM	**Sections: co-authored 6**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Jee Eun Lee -A Digitally signed by Jee Eun Lee -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jee Eun Lee -A, 0.9.2342.19200300.100.1.1=2000365056 Date: 2018.07.25 19:15:54 -04'00'			
Pharmacometrics Team Lead	Lian Ma	OTS/OCP/DPM	**Section: 6**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2018.07.25 19:09:09 -04'00'			
Division Director (Acting)(OCP)	Michael Pacanowski	OTS/OCP/DCPIII	**Section: 6**	**Select up to two:** ☐Authored

				☐Acknowledged ☒Cleared
	Signature: Michael Pacanowski -S Digitally signed by Michael Pacanowski -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000350707, cn=Michael Pacanowski -S Date: 2018.07.25 19:06:07 -04'00'			
Pharmacologist	Vinay Patil	OND/ODEIII/DGIEP	**Sections: 5**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Vinay A. Patil -A Digitally signed by Vinay A. Patil -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vinay A. Patil -A, 0.9.2342.19200300.100.1.1=2001232169 Date: 2018.07.26 09:10:36 -04'00'			
Lead Pharmacologist	David Joseph	OND/ODEIII/DGIEP	**Sections: 4.2, 5**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: David B. Joseph -S Digitally signed by David B. Joseph -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300134835, cn=David B. Joseph -S Date: 2018.07.26 09:23:54 -04'00'			
ODE Associate Director for Pharmacology and Toxicology (Acting)	Ronald Wange	OND-IO	**Sections: 4.2, 5**	**Select up to two:** ☐Authored ☐Acknowledged ☒Cleared
	Signature: Ronald L. Wange -S Digitally signed by Ronald L. Wange -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300236480, cn=Ronald L. Wange -S Date: 2018.07.26 10:17:34 -04'00'			
Statistical Reviewer	Sara Jimenez	OTS/OB/DBIII	**Sections: 7, 8.1, 8.3, 16.4, 16.5, 16.6, 16.7**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Sara Jimenez -S Digitally signed by Sara Jimenez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sara Jimenez -S, 0.9.2342.19200300.100.1.1=2002241423 Date: 2018.07.26 10:47:58 -04'00'			
Statistical Team Leader	Yeh-Fong Chen	OTS/OB/DBIII	**Sections: 7, 8.1, 8.3, 16.4, 16.5, 16.6, 16.7**	**Select up to two:** ☒Authored

				☐Acknowledged ☒Cleared
	Signature: Yehfong Chen -S Digitally signed by Yehfong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yehfong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2018.07.26 11:38:31 -04'00'			
Biometrics III Director (Acting)	Laura Lee Johnson	OTS/OB/DBIII	**Sections: 7, 8.1, 8.3, 16.4, 16.5, 16.6, 16.7**	**Select up to two:** ☐Authored ☐Acknowledged ☒Cleared
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2018.07.26 17:36:16 -04'00'			
Statistical (Safety) Reviewer	Tae Hyun Jung	OTS/OB/DBVII	**Sections: 16.9**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Taehyun Jung -S Digitally signed by Taehyun Jung -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Taehyun Jung -S, 0.9.2342.19200300.100.1.1=2001755340 Date: 2018.07.26 10:27:50 -04'00'			
Statistical (Safety) Team Leader	Clara Y. Kim	OTS/OB/DBVII	**Sections: 16.9**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Clara Y. Kim -S Digitally signed by Clara Y. Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Clara Y. Kim -S, 0.9.2342.19200300.100.1.1=1300382748 Date: 2018.07.26 10:30 53 -04'00'			
Biometric VII Director	Mark Levenson	OTS/OB/DBVII	**Sections: 16.9**	**Select up to two:** ☐Authored ☐Acknowledged ☒Cleared
	Signature: Mark S. Levenson -S Digitally signed by Mark S. Levenson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300384235, cn=Mark S. Levenson -S Date: 2018.07.26 13:18:06 -04'00'			

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Mimi Phan, PharmD
Nonclinical Reviewer	Vinay Patil, PhD
Nonclinical Team Leader	David Joseph, PhD
Office of Clinical Pharmacology Reviewer(s)	Elizabeth Shang PhD, Jee Eun Lee, PhD
Office of Clinical Pharmacology Team Leader(s)	Lian Ma, PhD, Insook Kim, PhD
Clinical Reviewer	Suna Seo MD MSc
Clinical Team Leader	Anil Rajpal MD
Statistical Reviewer	Sara Jimenez, PhD
Statistical Team Leader	Yeh-Fong Chen, PhD
Cross-Disciplinary Team Leader	Anil Rajpal MD
Division Director (DGIEP)	Joyce Korvick MD, MPH
Office Director (Office of Drug Evaluation III)	Julie Beitz MD

Additional Reviewers of Application

OPQ	Martin Haber PhD, Hamid Shafiei PhD, Yuesheng Ye PhD, Vincent Duan PhD, Jennifer Patro PhD
OPDP	Meeta Patel PharmD
OSI	Susan Leibenhaut MD
OSE/DEPI	Patricia Bright PhD
OSE/DMEPA	Sarah Vee PharmD, Sherly Abraham PharmD
OSE/DRISK	Charlotte Jones MD, Donella Fitzgerald PharmD
OSE/DPV	Lisa Harinstein PharmD, Michelle Hines PharmD
DPMH	Ethan Hausman MD, Hari Sachs MD

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPV=Division of Pharmacovigilance
DPMH=Division of Pediatric and Maternal Health

Glossary

AC	advisory committee
ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	aspartate aminotransferase
BCH	Boston Children's Hospital
BPCA	Best Pharmaceuticals for Children Act
BPD	bronchopulmonary dysplasia
BRF	Benefit Risk Framework
CA	chronological age
CAIR	Center for Advanced Intestinal Rehabilitation
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DB	Division of Biometrics
DBil	direct bilirubin
DHOT	Division of Hematology Oncology Toxicology
DSMB	data safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
EFAD	essential fatty acid deficiency
ELBW	extremely low birth-weight
EN	enteral nutrition
EPV	enhanced pharmacovigilance
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act

FK	Fresenius Kabi
FM	full matched
GA	gestational age
GCP	good clinical practice
GGT	gamma-glutamyl transpeptidase
GRMP	good review management practice
HC	historical control
ICH	International Conference on Harmonization
IIT	investigator-initiated trial
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVH	intraventricular hemorrhage
LFV	loss function value
LGA	large for gestational age
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NEC	necrotizing enterocolitis
NI	non-inferiority
NICU	neonatal intensive care unit
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDA	patent ductus arteriosus
PELD	pediatric end-stage liver disease
PI	prescribing information
PK	pharmacokinetics
PM	pair-matched
PMA	post-menstrual age
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	parenteral nutrition
PNAC	parenteral nutrition associated cholestasis
PNALD	parenteral nutrition associated liver disease
PP	per-protocol
PPI	patient package insert

PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
ROPNAC	resolution of PNAC
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SGA	small for gestational age
SGE	special government employee
SOC	standard of care
SMD	standard mean difference
TCH	Texas Children's Hospital
TEAE	treatment emergent adverse event
UCLA	University of California Los Angeles
VLBW	very low birth weight
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Fresenius Kabi submitted NDA 210589 for OMEGAVEN (fish oil triglycerides) injectable emulsion, for intravenous use, a new molecular entity (NME) highly refined fish oil, for the proposed indication as a "source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)."

1.2. Conclusions on the Substantial Evidence of Effectiveness

In support of the proposed indication of source of calories and fatty acids in pediatric patients with PNAC, the Applicant submitted data from two investigator-initiated studies: OMEG-034-IP3 (Study 34) and OMEG-035-IP3 (Study 35). Both studies were prospective, open-label, single-center studies designed to compare the efficacy and safety of Omegaven administered to neonates, infants, and young children with PNAC to retrospective historical data from pediatric patients with PNAC who received a soybean oil-based lipid emulsion, Intralipid, as part of their PN regimen. A dose of 1 g/kg/day (infusion duration between 8 and 24 hours) is supported based on dosing used in these studies.

Although Study 34 and Study 35 were not adequately designed and powered to demonstrate noninferiority or superiority of Omegaven to the soybean oil comparator, they support Omegaven as a source of calories and fatty acids in pediatric patients with PNAC. Nutritional efficacy was assessed by biomarkers of lipid metabolism, anthropometric indices (body weight, length/height and head circumference), and/or mean changes in fatty acid parameters. The study data were compared to gender- and age-standardized Fenton, World Health Organization (WHO) and Center for Disease Control (CDC) growth charts to assess appropriate growth in pediatric PNAC patients.

These studies, together with generally accepted scientific knowledge (long chain fatty acids provided by fish oil provide 9 kcal/g), support a finding of substantial evidence of effectiveness for the proposed indication. As an injectable lipid emulsion, Omegaven provides the purported nutritional support which is self-evident by assessing the product's component contents.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Omegaven belongs to the pharmacotherapeutic group "fish oil triglycerides" and contains predominantly the omega 3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Intravenous (IV) lipid emulsions (ILEs) are intended for patients with gastrointestinal dysfunction, who lack the capacity to absorb adequate nutrients to maintain or recover body mass and function and cannot tolerate oral or enteral feeding. Administration of IV lipid emulsions to these patients reduces the amount of glucose that would otherwise have to be administered to achieve the necessary calories per 24 hour period. The administration of concentrated glucose solutions may cause hyperglycemia, particularly in more severely ill patients; hyperglycemia is associated with adverse effects including immunosuppression and a higher incidence of infectious complications.[1] ILEs are primarily used as a source of calories (energy) and essential fatty acids.

Currently available ILEs include Intralipid (10%, 20%, 30%) approved January 1981, Nutrilipid (10%, 20%) approved May 1993, and Smoflipid (20%) approved July 2016. Intralipid and Nutrilipid are soybean oil-based ILE's. Smoflipid contains soybean oil, medium chain triglycerides, olive oil, and fish oil. In addition, Kabiven/Perikabiven is a combination of soybean oil-based ILE, dextrose, amino acids, and electrolytes, approved August 2014. Intralipid and Nutrilipid each have pediatric indications.

Previous approvals of ILEs were largely premised on the fact that the products provided a known amount of calories based on the amount of fat (fish oil = 9 kcal/g) present and that they served as a source of essential fatty acids. Also, nutritional efficacy was assessed by biomarkers of lipid metabolism, anthropometric indices, and/or mean changes in fatty acid parameters. In addition, the Omegaven study data for pediatric patients exclusively receiving Omegaven was compared to gender- and age-standardized Fenton and World Health Organization (WHO) growth charts to assess age appropriate growth in PNAC patients.

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

PNAC has been defined by expert consensus[2] as direct or conjugated bilirubin (DBil) level ≥ 2.0 mg/dL in the absence of other liver dysfunction in patients with a need for long-term PN.

Although soybean oil-based ILEs contain high levels of pro-inflammatory omega-6 fatty acids and phytosterols, which both have been implicated in the multifactorial pathogenesis of PNAC, including impairment of bile flow, the development of hepatic steatosis, and pro-inflammatory effects,[3,4,5,6] there are little to no clinical data to conclude that phytosterols are causative factors in the development of PNAC.

The efficacy of Omegaven as a source of calories and essential fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC) was evaluated, in part, in two open-label, single-center, single-arm historically-controlled studies (Studies 34 and 35).

Although Study 34 and Study 35 were not adequately designed and powered to demonstrate noninferiority or superiority of Omegaven to the soybean oil comparator, they support Omegaven as a source of calories and fatty acids in pediatric patients with PNAC. Nutritional efficacy was assessed by biomarkers of lipid metabolism, anthropometric indices (body weight, length/height and head circumference), and/or mean changes in fatty acid parameters.

Additional evidence was reviewed to support the proposed indication due to the above limitations. We determined Omegaven's effect by comparing Omegaven study data to gender- and age-standardized growth charts (Fenton for preterm, WHO for 0-2 yrs, and CDC for 2-18 yrs) to assess age appropriate growth in PNAC patients. In addition, the well-established scientific fact that fatty acids in the form of triglycerides are major sources of dietary energy and the long chain fatty acids provide 9kcal/g of energy[7,8], and the 100% bioavailability of Omegaven as an intravenously administered lipid product was collectively considered.

[2] https://www.regulations.gov/document?D=FDA-2012-N-0001-0093
[3] Carter BA, Taylor OA, Prendergast DR, Zimmerman TL, Von Furstenberg R, Moore DD, Karpen SJ. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. Pediatr Res. 2007;62(3):301-6.
[4] El Kasmi KC, Anderson AL, Devereaux MW, Vue PM, Zhang W, Setchell KD, Karpen SJ, Sokol RJ. Phytosterols promote liver injury and kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med. 2013;5(206):206ra137.
[5] Kurvinen A, Nissinen MJ, Andersson S, Korhonen P, Ruuska T, Taimisto M, Kalliomaki M, Lehtonen L, Sankilampi U, Arikoski P, Saarela T, Miettinen TA, Gylling H, Pakarinen MP. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. J Pediatr Gastroenterol Nutr. 2012;54(6):803-11.
[6] Rangel SJ, Calkins CM, Cowles RA, Barnhart DC, Huang EY, Abdullah F, Arca MJ, Teitelbaum DH, American Pediatric Surgical Association O, Clinical Trials C. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2012;47(1):225-40.
[7] Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter17 Citric Acid Cycle).
[8] Berg, Chapter 22.

And finally, we considered the safety profile of 189 Omegaven-treated patients with PNAC who were dependent on parenteral nutrition. The median duration of Omegaven treatment in the safety population was 13.5 weeks (min 3 days, max 7.8 years).

Enrolled patients in Studies 34 and 35 were pediatric patients with PNAC (defined as direct or conjugated bilirubin [DBil] equal to or greater than 2 mg/dL) who required PN for at least 14 days. Patients were expected to require PN (which also included dextrose, amino acids, vitamins and trace elements) for at least 30 days (Study 34) or 14 days (Study 35). Study 34 enrolled patients less than 2 years of age and Study 35 enrolled patients less than 5 years of age. Patients with another cause of chronic liver disease (in the absence of intestinal failure) were excluded. Patients with an international normalized ratio (INR) greater than 2 and patients with portal vein thrombosis or reversal of portal flow by abdominal ultrasound were also excluded.

In each of the studies, patients received Omegaven at a maximum dose of 1 g/kg/day; historical control patients received a soybean oil-based lipid emulsion at a maximum dose of 3 g/kg/day. It should be noted that fatty acids are being given not only as a source of calories (9 kcal/g for long chain fatty acids) but also to supply essential fatty acids Linoleic acid and Alpha-linolenic acid. Intralipid contains approximately (b) (4) mg/mL linoleic acid (omega-6), and (b) (4) mg/mL of alpha-linolenic acid (omega-3). Omegaven contains (b) (4) mg/mL of linoleic acid and (b) (4) mg/mL of alpha-linolenic acid. EPA and DHA are (b) (4) mg/mL and up to (b) (4) mg/mL, respectively.

In Studies 34 and 35, Omegaven-treated patients were pair-matched in a 2:1 manner to historical control patients primarily based on DBil levels and postmenstrual age at baseline. There were 123 patients (82 Omegaven; 41 historical control) in this population, 78 (52; 26) were from Study 34, and 45 (30; 15) were from Study 35.

The majority of patients received concurrent enteral or oral nutrition (Study 34: Omegaven 88% vs. historical control 100%; Study 35: Omegaven 80% vs. historical control 93%). The median (minimum - maximum) percentage of total calories provided enterally or orally were the following in Study 34: Omegaven 24% (1% - 53%) vs. historical control 25% (0.4% - 68%). The median (minimum - maximum) percentage of total calories provided enterally or orally were the following in Study 35: Omegaven 21% (1% - 75%) vs. historical control 12% (3% - 40%).

In the combined analysis population from Studies 34 and 35, median chronological age was 9 weeks (range: 3 to 42 weeks) in the Omegaven group and 7 weeks (range: 0 to 41 weeks) in the historical control group. The majority of these patients were preterm infants at birth (90% Omegaven; 83% historical control), with gestational age categories as follows: extremely preterm (31%; 20%); very preterm (20%; 24%); moderate or late preterm (40%; 39%). A majority of patients were also considered to have low, very-low, or extremely-low birth weights, with

birth weight categories as follows: extremely-low birth weight (34%; 24%); very-low birth weight (17%; 21%); low birth weight (25%; 37%). The analysis population had more males (51%; 59%) than females, and the majority of patients were White (60%; 66%).

At baseline, the median age-adjusted body weight (Z-score) was -1.3 for the Omegaven group and -1.1 for the historical control group; 27% and 28% were low-for-age in body weight, 43% and 40% were low-for-age in body height/length, and 25% and 15% were low-for-age in head circumference for the Omegaven and historical control groups, respectively (low-for-age corresponded to Z-scores less than or equal to -1.9 for each growth parameter).

In the analysis population, baseline median DBil, AST, and ALT levels were 3.8 mg/dL, 101 U/L, and 67 U/L, respectively, for the Omegaven group; and 3.8 mg/dL, 115 U/L, and 52 U/L, respectively, for the historical control group.

The median (range) of the duration of treatment was 2.7 months (5 days to 8 years) for the Omegaven group and 3.6 months (16 days to 2 years) for the historical control group.

The primary endpoint was changes over time in body weight adjusted for age; secondary endpoints included: changes over time in body length/height adjusted for age, and changes over time in head circumference adjusted for age. The changes in median age-adjusted body weight (Z-scores) over time for Omegaven-treated patients appeared similar to those for historical control patients. In both Omegaven-treated and historical control groups, there was an initial decline in weight over the initial weeks of treatment, followed by catch-up growth and more age-appropriate values through the remainder of the study. By comparing the Omegaven study data to gender- and age-standardized Fenton and World Health Organization (WHO) growth charts, patients treated with Omegaven as their exclusive lipid source also achieved age-appropriate growth.

Secondary endpoints included: time to and number of patients who achieve full enteral feeding (defined as ≥ 100 kcal EN/kg/day or evidence of patient weaned from PN). In the combined analysis from Studies 34 and 35, the number of Omegaven and historical control patients who achieved full enteral feeding by the end of the study was 52 (63%) patients and 24 (59%) patients, respectively. The median time to full enteral feeding was approximately 15 weeks for both groups.

The safety profile was generally comparable to the known safety profile described in the product labels for other intravenous lipid emulsions.

The following evaluations were used to assess safety. Time to and number of patients with resolution of PNAC (ROPNAC) (defined as the time [weeks] from baseline to when DBil levels decrease to < 2.0 mg/dL) was considered a safety endpoint. At the end of the studies, the median

DBil level for Omegaven-treated patients was 0.60 mg/dL (interquartile range: 0.1 to 2.8 mg/dL). The Kaplan Meier estimate of the median time for DBil values to return to less than 2.0 mg/dL was approximately 5.7 weeks.

The most common adverse reactions in the two trials were vomiting (Omegaven 46% vs. historical control 44%), agitation (35% vs. 34%), bradycardia (35% vs. 33%), apnea (20% vs. 19%), viral infection (16% vs. 10%), erythema (12% vs. 8%), rash (8% vs. 5%), abscess (7% vs. 5%), neutropenia (7% vs. 4%), hypertonia (6% vs. 3%), and incision site erythema (6% vs. 0%).

Overall adverse events leading to discontinuation in the two trials were 2% (Omegaven) vs. 4% (historical control). Adverse events leading to discontinuation in the Omegaven group were coagulopathy, intestinal hemorrhage, device related infection, and *Staphylococcal* infection. Adverse events leading to discontinuation in the historical control group were hepatic failure and *Escherichia coli* urinary tract infection.

A total of 35 patients died in the studies (24 patients [13%] in the Omegaven group and 11 patients [15%] in the historical control group). The reported deaths appeared to be the result of events related to prematurity and complications of underlying disease.

Serious adverse events were 81% (Omegaven) and 82% (historical control). Specific serious adverse events included dependence on respirator (Omegaven 18% vs. historical control 18%), bradycardia (13% vs. 12%), apnea (11% vs. 8%), temperature instability (9% vs. 4%), and multiorgan failure (6% vs. 3%). Higher rates of these events in the Omegaven group may be related to the higher proportion of Omegaven-treated patients in the extremely preterm gestational age category (Omegaven 31% vs. historical control 20%). The Omegaven safety evaluation did not identify any new or unexpected safety signals.

Some published studies have demonstrated prolongation of bleeding time in patients taking antiplatelet agents or anticoagulants and oral omega 3 fatty acids. The prolongation of bleeding times reported in those studies did not exceed normal limits and there were no clinically significant bleeding episodes. Nonetheless, it is recommended to periodically monitor bleeding time in patients receiving Omegaven and concomitant antiplatelet agents or anticoagulants.

There are no available data on Omegaven use in pregnant women to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Omegaven.

No data are available regarding the presence of fish oil triglycerides from Omegaven in human milk, the effects on the breastfed infant, or the effects on milk production. Lactating women receiving oral omega-3 fatty acids have been shown to have higher levels of omega-3 fatty acids in their milk.

The benefit-risk profile for Omegaven is favorable. A REMS is not necessary for Omegaven to ensure the benefits outweigh the risks.

Enhanced pharmacovigilance is recommended:

- We request that for a period of 2 years from the U.S. approval date, the Applicant submit all cases of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported with Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use, as 15-day Alert reports, and that the Applicant provide detailed analyses of events of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported from clinical study and post-marketing reports in their periodic safety report.

The following postmarketing requirements (PMRs) are recommended:

- Conduct a prospective, longitudinal cohort study with an external control to assess the long-term safety (defined as patient monitoring for ≥ 1 year of continuous treatment) of Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use in pediatric patients with PNAC, evaluating the potential for essential fatty acid deficiency (EFAD) by measuring:
  1. long-chain polyunsaturated fatty acid (LCPUFA) profiles with prespecified thresholds during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and
  2. the occurrence of serious bleeding events during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and
  3. neurodevelopmental delays assessed later in life to include at least the baseline Bayley assessments at 6 months, 12 months and 2 years; and age appropriate assessment at 5 years of age.

  In addition, life-threatening pleural and pericardial effusions will also be reported during Omegaven infusion and 4 weeks after discontinuation of Omegaven. Clinical narratives will be assessed to determine whether the pleural/pericardial effusions are clinically related to the infusions.

- Conduct a study to show that the levels of the elemental impurities, (b) (4), are controlled in Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use.

  This study should include a risk assessment and screening of the finished product for the elemental impurities as stated above including analysis of at least three batches of the product. Develop and validate a detailed rationale for the calculation of control

thresholds and acceptance criteria for all elements stated above, with consideration of the amount of each element that may be intentionally added to TPN.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Intravenous (IV) lipid emulsions (ILEs) are intended for patients with gastrointestinal dysfunction, who lack the capacity to absorb adequate nutrients to maintain or recover body mass and function and cannot tolerate oral or enteral feeding. Administration of ILEs to these patients reduces the amount of glucose that would otherwise have to be administered to achieve the necessary calories per 24 hour period. The administration of concentrated glucose solutions may cause hyperglycemia, particularly in more severely ill patients; hyperglycemia is associated with adverse effects including immunosuppression and a higher incidence of infectious complications.[9] ILEs are primarily used as a source of calories (energy) and essential fatty acids. PNAC has been defined by expert consensus[10] as direct or conjugated bilirubin (DBil) level ≥ 2.0 mg/dL in the absence of other liver dysfunction in patients with a need for long-term PN. Although soybean oil-based ILEs contain high levels of pro inflammatory omega-6 fatty acids and phytosterols, which both have been implicated in the multifactorial pathogenesis of PNAC, including impairment of bile	There is an unmet need for an alternative parenteral source of nutrition for PN dependent patients with PNAC. In particular, there is a need to reduce administration in PNAC patients of soy-based lipid emulsions in these patients, which are believed to contribute to progression of the manifestations of PNAC. The proposed indication received orphan drug status.

[9] Waitzberg DL, Torrinhas RS, and Jacintho TM. "New Parenteral Lipid Emulsions for Clinical Use"; J Parenteral Enteral Nutr 2006; 30:351-367.
[10] https://www.regulations.gov/document?D=FDA-2012-N-0001-0093

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	flow, the development of hepatic steatosis, and pro-inflammatory effects,[11,12,13,14] there are little to no clinical data to conclude that phytosterols are causative factors in the development of PNAC.	
Current Treatment Options	Currently available ILEs include Intralipid (10%, 20%, 30%) approved January 1981, Nutrilipid (10%, 20%) approved May 1993, and Smoflipid (20%) approved July 2016. Intralipid and Nutrilipid are soybean oil based ILE's. Smoflipid contains soybean oil, medium chain triglycerides, olive oil, and fish oil. In addition, Kabiven/Perikabiven is a combination of soybean oil based ILE, dextrose, amino acids, and electrolytes, approved August 2014. Intralipid and Nutrilipid each have pediatric indications.	Omegaven belongs to the pharmacotherapeutic group "fish oil triglycerides" and contains triglycerides, predominantly the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Of the currently available ILE's (Intralipid, Nutrilipid, Smoflipid, and Kabiven/Perikabiven), only Intralipid and Nutrilipid are approved for use in pediatric patients. All the currently available ILEs (Nutrilipid, Smoflipid, and Kabiven/Perikabiven) contain soybean oil (see discussion above under Analysis of Condition dimension).

[11]Carter BA, Taylor OA, Prendergast DR, Zimmerman TL, Von Furstenberg R, Moore DD, Karpen SJ. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. Pediatr Res. 2007;62(3):301-6.
[12] El Kasmi KC, Anderson AL, Devereaux MW, Vue PM, Zhang W, Setchell KD, Karpen SJ, Sokol RJ. Phytosterols promote liver injury and kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med. 2013;5(206):206ra137.
[13] Kurvinen A, Nissinen MJ, Andersson S, Korhonen P, Ruuska T, Taimisto M, Kalliomaki M, Lehtonen L, Sankilampi U, Arikoski P, Saarela T, Miettinen TA, Gylling H, Pakarinen MP. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. J Pediatr Gastroenterol Nutr. 2012;54(6):803-11.
[14] Rangel SJ, Calkins CM, Cowles RA, Barnhart DC, Huang EY, Abdullah F, Arca MJ, Teitelbaum DH, American Pediatric Surgical Association O, Clinical Trials C. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2012;47(1):225-40.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Although Study 34 and Study 35 were not adequately designed and powered to demonstrate noninferiority or superiority of Omegaven to the soybean oil comparator, these investigator-initiated studies support Omegaven as a source of calories and fatty acids in pediatric patients with PNAC. Nutritional efficacy was assessed by biomarkers of lipid metabolism, anthropometric indices (body weight, length/height and head circumference), and/or mean changes in fatty acid parameters. The primary endpoint was changes over time in body weight adjusted for age; secondary endpoints included: changes over time in body length/height adjusted for age, and changes over time in head circumference adjusted for age. The changes in median age-adjusted body weight (Z-scores) over time for Omegaven-treated patients appeared similar to those for historical control patients. Median age-adjusted height/length and head circumference values over time followed patterns similar to that observed for body weight. In both Omegaven treated and historical control groups, there was an initial decline in all growth parameters over the initial weeks of treatment, followed by catch-up growth and more age-appropriate values through the remainder of the study. By comparing the Omegaven study data to gender- and age-standardized Fenton and World Health Organization (WHO) growth charts, pediatric patients treated with Omegaven as their exclusive lipid source also achieved age-appropriate growth. Secondary endpoints included: time to and number of patients who achieve full enteral feeding (defined as ≥ 100 kcal EN/kg/day or	The effectiveness of Omegaven as a source of calories and fatty acids in pediatric patients with PNAC was supported, in part, by two open-label, single-center, single-arm historically-controlled trials. The eligibility criteria were considered appropriate to ensure a study population sufficiently representative of the target patient population and the interpretability of efficacy assessments. In addition, the primary endpoint was considered an appropriate measure of a clinically meaningful treatment benefit upon which to base efficacy assessments. Additional evidence was reviewed to support the proposed indication due to the above limitations. We determined Omegaven's effect by comparing Omegaven study data to gender- and age-standardized growth charts (Fenton for preterm, WHO for 0-2 yrs, and CDC for 2-17 yrs) to assess age appropriate growth in PNAC patients. In addition, the well-established scientific fact that fatty acids in the form of triglycerides are major sources of dietary energy and the long chain fatty acids provide 9 kcal/g of energy,[15,16] and the 100%

[15] Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter17 Citric Acid Cycle).
[16] Berg, Chapter 22.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	evidence of patient weaned from PN). In the combined analysis from Studies 34 and 35, the number of Omegaven and historical control patients who achieved full enteral feeding by the end of the study was 52 (63%) patients and 24 (59%) patients, respectively. The median time to full enteral feeding was approximately 15 weeks for both groups.	bioavailability of Omegaven as an intravenously administered lipid product was collectively considered. .
Risk and Risk Management	The safety profile was generally comparable to the known safety profile described in the product labels for other intravenous lipid emulsions. The safety profile of 189 Omegaven-treated patients with PNAC who were dependent on parenteral nutrition was evaluated in this NDA. The median duration of Omegaven treatment in the safety population was 13.5 weeks (min 3days, max 7.8 years). Time to and number of patients with resolution of PNAC (ROPNAC) (defined as the time (weeks) from baseline to when DBil levels decrease to < 2.0 mg/dL) was considered as a safety endpoint. At the end of the studies, the median DBil level for Omegaven-treated patients was 0.60 mg/dL (interquartile range: 0.1 to 2.8 mg/dL). The Kaplan Meier estimate of the median time for DBil values to return to less than 2.0 mg/dL was approximately 5.7 weeks. The most common adverse reactions in the two trials were vomiting (Omegaven 46% vs. historical control 44%), agitation (35% vs. 34%), bradycardia (35% vs. 33%), apnea (20% vs. 19%), viral infection (16% vs. 10%), erythema (12% vs. 8%), rash (8% vs. 5%), abscess (7% vs. 5%), neutropenia (7% vs. 4%), hypertonia (6% vs. 3%), and incision site erythema (6% vs. 0%).	The safety profile was generally comparable to the known safety profile of other intravenous fat emulsions. The most commonly reported adverse events in Omegaven-treated patients were vomiting, agitation, bradycardia, apnea, viral infrection, erythema, rash, abscess, neutropenia, hypertonia, and incision site erythema. The reported deaths were lower in the Omegaven group than the historical control group; the deaths appeared to be related to prematurity and complications of underlying disease. The rates of SAEs were similar in the Omegaven group and the historical control group. The Omegaven safety evaluation did not identify any new or unexpected safety signals

	Overall adverse events leading to discontinuation in the two trials were 2% (Omegaven) vs. 4% (historical control). Adverse events leading to discontinuation in the Omegaven group were coagulopathy, intestinal hemorrhage, device related infection, and Staphylococcal infection. Adverse events leading to discontinuation in the historical control group were hepatic failure and Escherichia urinary tract infection. A total of 35 patients died in the studies (24 patients [13%] in the Omegaven group and 11 patients [15%] in the historical control group). The reported deaths appeared to be the result of events related to prematurity and complications of underlying disease. Serious adverse events (SAEs) were 81% (Omegaven) and 82% (historical control). Specific serious adverse events included dependence on respirator (Omegaven 18% vs. historical control 18%), bradycardia (13% vs. 12%), apnea (11% vs. 8%), temperature instability (9% vs. 4%), and multiorgan failure (6% vs. 3%). Higher rates of these events in the Omegaven group may be related to the higher proportion of Omegaven-treated patients in the extremely preterm gestational age category (Omegaven 31% vs. historical control 20%). The Omegaven safety evaluation did not identify any new or unexpected safety signals. ➢ Enhanced Pharmacovigilance is recommended:We request that for a period of 2 years from the U.S. approval date, the Applicant submit all cases of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported with Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use, as 15-day Alert reports, and that the Applicant provide detailed analyses of events of serious hemorrhage, pleural	or serious reactions, including risk of EFAD, attributable to treatment. Although the safety data did not demonstrate an increased frequency of EFAD with Omegaven compared to the historical control, the safety database from the two trials of Omegaven was too small to yield an event frequency high enough to statistically rule out an increased risk of EFAD with Omegaven treatment. The product labeling adequately reflects the overall safety profile of Omegaven and class-wide safety concerns for intravenous fat emulsions. Because a risk for this product of EFAD has not been established, a specific warning and precaution for EFAD has not been included in the labeling that goes beyond the recommendation for EFAD monitoring found in the labeling for other ILE's. However, postmarketing data from a study comparing Omegaven to an external control are needed to adequately address this concern. Because a risk for this product of pleural effusion and pericardial effusion has not been established, a boxed warning (as found in other ILE's for death in preterm infants due to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	effusion, pericardial effusion, and fat overload syndrome reported from clinical study and post-marketing reports in their periodic safety report. The following postmarketing requirements (PMRs) are recommended: ➢ Conduct a prospective, longitudinal cohort study with an external control to assess the long-term safety (defined as patient monitoring for ≥ 1 year of continuous treatment) of Omegaven (fish oil triglycerides) injectable mulsion, for intravenous use in pediatric patients with PNAC, evaluating the potential for essential fatty acid deficiency (EFAD) by measuring: 1. long-chain polyunsaturated fatty acid (LCPUFA) profiles with prespecified thresholds during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and 2. the occurrence of serious bleeding events during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and 3. neurodevelopmental delays assessed later in life to include at least the baseline Bayley assessments at 6 months, 12 months and 2 years; and age appropriate assessment at 5 years of age. In addition, life-threatening pleural and pericardial effusions will also be reported during Omegaven infusion and 4 weeks after discontinuation of Omegaven. Clinical narratives will be assessed to determine whether the pleural/pericardial effusions are clinically related to the infusions.	fat accumulation in the lungs) is not included in the labeling though a recommendation for monitoring for signs and symptoms of pleural effusion or pericardial effusion is included. Postmarketing data from a study comparing Omegaven to an external control are needed to adequately address this concern. An additional strategy of enhanced safety reporting, including expedited reporting and detailed analyses in periodic safety reports, will be utilized to manage the risks of pleural effusion, pericardial effusion, fat overload syndrome, and serious hemorrhage. Although there are no outstanding issues related to the Pharmacology and Toxicology safety qualification of any excipients, impurities, degradants, or leachables which preclude the approval of this NDA, a risk assessment is needed for (b) (4) potential elemental impurities that are intentionally added to Total Parenteral Nutrition. A postmarketing study is needed to adequately address this concern.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	➢ Conduct a study to show that the levels of the elemental impurities, (b) (4), are controlled in Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use. This study should include a risk assessment and screening of the finished product for the elemental impurities as stated above including analysis of at least three batches of the product. Develop and validate a detailed rationale for the calculation of control thresholds and acceptance criteria for all elements stated above, with consideration of the amount of each element that may be intentionally added to TPN.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
X	Patient experience data was not submitted in the application, and was not considered in this review.	

2 Therapeutic Context

Analysis of Condition

Patients who are unable to ingest or adequately absorb oral or enteral nutrients due to insufficient intestinal length or function become dependent on parenteral nutrition (PN). Early PN in clinical practice (1950s and 60s) began with amino acid and dextrose infusion without lipids which resulted in fatty infiltration of the liver and essential fatty acid deficiency (EFAD).[17,18] Since then, lipid emulsions have become a necessary component of PN to serve two main functions: 1. supply of energy (9 kcal/g long chain fatty acid)[19], and 2. supply of essential fatty acids. Lipid emulsion products are used in conjunction with amino acids, electrolytes, trace elements and dextrose to provide total parenteral nutrition (TPN).

Although PN saves the lives of affected patients, its long-term use is sometimes associated with hepatic complications such as parenteral nutrition-associated cholestasis (PNAC) and parenteral nutrition-associated liver disease (PNALD). PNAC has been defined by expert consensus[20] as direct or conjugated bilirubin (DBil) level ≥ 2.0 mg/dL in the absence of other liver dysfunction in patients with a need for long-term PN. If the patient cannot be weaned from PN, the progression of PNAC may result in PNALD which leads to fibrosis, cirrhosis, fulminant hepatic failure leading to death or liver transplant.[21,22] The serious and life-threatening disease of PNALD is more frequent and severe in infants than adults, especially premature and very-low-birth-weight (VLBW) infants with intestinal failure due to necrotizing enterocolitis (NEC), gastroschisis, or intestinal resection.[23]

The apparently multifactorial etiology of PNAC/PNALD includes the underlying medical condition, absence of enteral nutrition (EN), and infection. Other potential causes may include nutrient deficiencies (protein, essential fatty acids [EFAs], carnitine, choline, vitamin E, selenium, glutamine, taurine), nutrient excess (dextrose, lipids), or various heavy metal

[17] Fat-free parenteral alimentation of infants. Nutrition reviews. 1974;32(5):134-6.
[18] Faulkner WJ, Flint LM, Jr. Essential fatty acid deficiency associated with total parenteral nutrition. Surgery, gynecology & obstetrics. 1977;144(5):665-7.
[19] Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter 17 and 22).
[20] https://www.regulations.gov/document?D=FDA-2012-N-0001-0093
[21] Yang CF, Lee M, Valim C, Hull MA, Zhou J, Jones BA, Gura K, Collier S, Lo C, Duggan C, Jaksic T. Persistent alanine aminotransferase elevations in children with parenteral nutritionassociated liver disease. J Pediatr Surg. 2009;44(6):1084-7; discussion 7-8.
[22] Buchman AL, Iyer K, Fryer J. Parenteral nutrition-associated liver disease and the role for isolated intestine and intestine/liver transplantation. Hepatology. 2006;43(1):9-19.
[23] Christensen RD, Henry E, Wiedmeier SE, Burnett J, Lambert DK. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. J Perinatol. 2007;27(5):284-90.

toxicities (manganese, aluminum). The long-term exposure to soybean oil-based injectable lipid emulsions (ILEs), which are used in the United States (US) as a key component of PN to provide energy and EFAs, may also contribute to the pathogenesis of PNAC/PNALD. Soybean oil-based ILEs contain high levels of phytosterols and omega-6 fatty acids which can cause impairment of bile flow, the development of hepatic steatosis, and both hepatic and systematic pro-inflammatory effects.

The incidence and prognosis of PNAC/PNALD vary considerably among studies depending on the study population, underlying medical condition, diagnostic criteria for liver dysfunction, and composition and duration of PN. The condition is both more frequent and severe in infants than adults, especially premature and very low birth weight (VLBW) infants with intestinal failure. A systematic review found that in children who received PN for ≥ 14 days, the incidence of PNAC and IFALD were 28.2% and 49.8% respectively[24]; and rates as high as 56% to 85% have been reported from US multicenter cohort of infants.[25] Transition to enteral feeds is the best way to recover but sometimes impossible, and those patients who remain dependent on PN or are prematurely weaned from the PN are at risk for suboptimal nutritional support and poor growth.

In summary, there is an unmet need for an alternative parenteral source of nutrition for PN dependent patients with PNAC. In particular, there is a need to reduce administration of soy based lipid emulsions in these patients, which are believed to contribute to progression of the manifestations of PNAC.

[24] Lauriti G, Zani A, Aufieri R, Cananzi M, Chiesa PL, Eaton S, Pierro A. Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure associated liver disease in infants and children: a systematic review. JPEN J Parenter Enteral Nutr. 2014;38(1):70-85.
[25] Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, Rhee S, Sudan D, Mercer D, Martinez JA, Carter BA, Soden J, Horslen S, Rudolph JA, Kocoshis S, Superina R, Lawlor S, Haller T, Kurs-Lasky M, Belle SH, Pediatric Intestinal Failure C. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. J Pediatr. 2012;161(4):723-8 e2.

2.2. Analysis of Current Treatment Options

Currently there are no FDA approved products to treat or prevent PNAC. There are also no other sources of lipid emulsions for PN dependent pediatric patients besides those based on 100% soybean oil, Intralipid and Nutrilipid.

Table 1. Currently Approved Intravenous Lipid Emulsions

Product Name	Type	Pediatric Indication	Approval Date
Intralipid (10%, 20%, 30%)	Soybean oil / LCT	✓	January 1981
Nutrilipid (10%, 20%)	Soybean oil / LCT	✓	May 1993
Kabiven/Perikabiven	Soybean oil / LCT (with electrolytes, amino acids and glucose)		August 2014
Clinolipid*	Soybean oil / LCT Olive oil		October 2013
SMOFlipid (20%)	Soybean oil / LCT Medium Chain Triglycerides Olive oil Fish oil		July 2016

LCT = Long Chain Triglycerides; *Currently not marketed
Source: S. Seo

Soybean oil-based ILEs contain high levels of pro-inflammatory omega-6 fatty acids and phytosterols, which both have been implicated in the multifactorial pathogenesis of PNAC, including impairment of bile flow, the development of hepatic steatosis, and pro-inflammatory effects.[26,27,28,29] It is important to note that although nonclinical animal data would suggest that the phytosterols adversely affect bile acid clearance and subsequent hepatocyte damage, there are little to no clinical data to conclude that phytosterols are causative factors in the development of PNAC.

[26] Carter BA, Taylor OA, Prendergast DR, Zimmerman TL, Von Furstenberg R, Moore DD, Karpen SJ. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. Pediatr Res. 2007;62(3):301-6.
[27] El Kasmi KC, Anderson AL, Devereaux MW, Vue PM, Zhang W, Setchell KD, Karpen SJ, Sokol RJ. Phytosterols promote liver injury and kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med. 2013;5(206):206ra137.
[28] Kurvinen A, Nissinen MJ, Andersson S, Korhonen P, Ruuska T, Taimisto M, Kalliomaki M, Lehtonen L, Sankilampi U, Arikoski P, Saarela T, Miettinen TA, Gylling H, Pakarinen MP. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. J Pediatr Gastroenterol Nutr. 2012;54(6):803-11.
[29] Rangel SJ, Calkins CM, Cowles RA, Barnhart DC, Huang EY, Abdullah F, Arca MJ, Teitelbaum DH, American Pediatric Surgical Association O, Clinical Trials C. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2012;47(1):225-40.

No phytosterol-free non-soybean oil products that deliver calories to PN dependent pediatric patients exist. SMOFlipid 20%, while it contains fish oil (30 g/L), also contains 60 g/L of soybean oil, and is not indicated in pediatric populations due to insufficient data to demonstrate adequate delivery of essential fatty acids in these populations.[30]

The current standard of care for PN dependent patients with PNAC includes reducing the soybean oil-based lipid infusion to reduce the cumulative exposure,[31,32] cycling TPN to allow intermittent infusion[33,34], Ursodial (Actigall) to promote cholestasis clearance, and aggressive transition to enteral feeding.[35] However, in many cases transition from parenteral to enteral feeds and establishing enteral autonomy are impeded by underlying intestinal failure or intolerance. Surgical intervention such as serial transverse enteroplasty (STEP) has been used to promote intestinal rehabilitation and reduce the need for intestinal transplant. However, if PNAC progresses to PNALD and eventually to end-stage liver disease, liver transplantation (or combined intestinal-liver transplantation) is the only option for survival.[36] It is estimated that approximately 1 of every 3 patients on the liver transplant waiting list dies before a donor organ becomes available.[37]

Infants with intestinal failure or feeding intolerance are nutritionally compromised and are at risk for significant extrauterine growth restriction.[38]

Exclusive non-soybean based source of lipids, including omega-3 predominant fish oil, could address some of this unmet medical need for patients with PNAC/PNALD.

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[30] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207648lbl.pdf
[31] Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. Nutr Clin Pract. 2006;21(3):279-90.
[32] Rollins MD, Ward RM, Jackson WD, Mulroy CW, Spencer CP, Ying J, Greene T, Book LS. Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for parenteral nutrition-associated liver disease: a pilot study. J Pediatr Surg. 2013;48(6):1348- 56.
[33] Jensen AR, Goldin AB, Koopmeiners JS, Stevens J, Waldhausen JH, Kim SS. The association of cyclic parenteral nutrition and decreased incidence of cholestatic liver disease in patients with gastroschisis. J Pediatr Surg. 2009;44(1):183-9.
[34] Nghiem-Rao TH, Cassidy LD, Polzin EM, Calkins CM, Arca MJ, Goday PS. Risks and benefits of prophylactic cyclic parenteral nutrition in surgical neonates. Nutr Clin Pract. 2013;28(6):745-52.
[35] Repa A, Lochmann R, Unterasinger L, Weber M, Berger A, Haiden N. Aggressive nutrition in extremely low birth weight infants: impact on parenteral nutrition associated cholestasis and growth. PeerJ. 2016;4:e2483.
[36] Puder M, Valim C, Meisel JA, Le HD, de Meijer VE, Robinson EM, Zhou J, Duggan C, Gura KM. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg. 2009;250(3):395-402.
[37] Kaufman SS, Pehlivanova M, Fennelly EM, Rekhtman YM, Gondolesi GE, Little CA, Matsumoto CS, Fishbein TM. Predicting liver failure in parenteral nutrition-dependent short bowel syndrome of infancy. J Pediatr. 2010;156(4):580-5.e1.
[38] Morton DL, Hawthorne KM, Moore CE. Growth of Infants with Intestinal Failure or Feeding Intolerance Does Not Follow Standard Growth Curves. *Journal of Nutrition and Metabolism*. 2017;2017:8052606. doi:10.1155/2017/8052606.

3 Regulatory Background

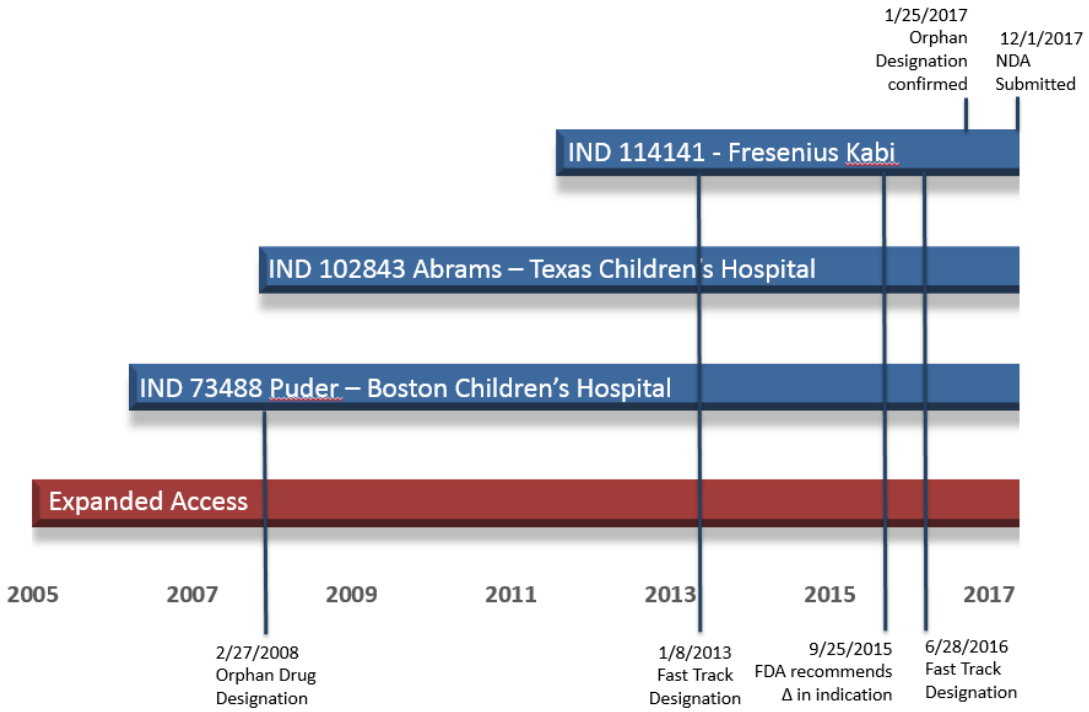
3.1. U.S. Regulatory Actions and Marketing History

Omegaven fish oil has been determined to be a new molecular entity (NME). Although fish oil is currently marketed as part of SMOFlipid® which contains soybean oil, medium chain triglycerides, olive oil and fish oil, the fish oil in Omegaven was deemed significantly different to warrant this NME determination. (Refer to CMC review for further details).

3.2. Summary of Presubmission/Submission Regulatory Activity

The development program for Omegaven began in 2005-7 with single-patient expanded access compassionate-use INDs submitted by Dr. Mark Puder, followed by intermediate size expanded access INDs with investigator-initiated protocols submitted under IND 73488 (Sponsor: Boston Children's Hospital [BCH]) and IND 102843 (Sponsor: Texas Children's Hospital [TCH]). The final pre-submission development occurred under IND 114141 (Sponsor: Fresenius Kabi [FK]).

Figure 1. Regulatory History Timeline



Source: S. Seo

Key regulatory interactions are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting.

February 9, 2006: Type B PIND Meeting and October 22, 2007: Type C Meeting
[IND 73488 - DGIEP meeting with BCH]

- Clarification of proposed indication as treatment of PNALD
- Discussed potential future partnership between BCH and FK, manufacturer of product
- FDA cautioned against a trial design using historical control (HC), and advised additional centers outside of BCH to prove reproducibility
- CMC and nonclinical study requirements for IND and NDA
- Recommended population pharmacokinetics approach (sparse sampling) to understand the exposure-response relationship for dose selection
- In addition to the 6-month data on growth and neurodevelopment, long-term follow up at 1 and 2 years of growth and neurodevelopment is suggested for patients treated in the proposed study

Under IND 73488, four protocols had been submitted to evaluate Omegaven (b) (4) .

Table 2. Research IND 73488 (Sponsor: Mark Puder, MD) Protocols

Protocol	Title	Proposed Indication	Status
#0504048	"Compassionate use of an intravenous fat emulsion comprised of fish oil (Omegaven) in the treatment of parenteral nutrition induced liver injury"	Treatment	Ongoing
(b) (4)			

Source: S. Seo

December 12, 2007 [IND 73488 - BCH]

- Protocol # (b) (4)

February 27, 2008 [IND 73488 - BCH]

- Omegaven received Orphan Drug Designation based on low prevalence rates of PNALD (between 7,500 - 42,500) and preliminary animal and human data demonstrating efficacy of Omegaven in the treatment of PNALD.

September 7, 2010 [IND 73488 - BCH]

- Protocol # (b) (4)

March 19, 2012: Type B pre-IND Meeting [IND 114141 – FK]

- A clinical study in which Omegaven is compared to an approved soy-based formulation in patients with PNALD was advised. A prospective randomized well-designed trial to assess the benefits and risks of Omegaven in the treatment of cholestasis secondary to PNALD was recommended.
- FDA expressed concern over (b) (4).
- The operational feasibility of conducting an active controlled study was discussed, and the Sponsor expressed concerns about their ability to execute such a trial successfully.
- The disease definition of PNALD needs to be supported with adequate evidence to support DBil as a surrogate marker.
- While DBil is acceptable as a marker for cholestasis, its appropriateness as a surrogate for PNALD remains unclear.[39] FDA recommended that other clinical correlates such as Pediatric End-Stage Liver Disease (PELD) score be considered as part of the definition and potentially as a component of the responder definition.
- FDA agreed that assessment of liver histology would not be required.
- Agreement reached that the Sponsor will submit older mostly adult FK-sponsored trials from Europe as narrative summaries and/or clinical study reports (CSRs) as supportive safety information. No datasets will be submitted.
- Agreement was reached regarding the adequacy of the PK proposal.
- Since, due to technical difficulties, repeated-dose IV infusion nonclinical toxicity studies beyond 3 months are not feasible, the proposed labeled duration should be supported with clinical studies of appropriate duration.
- Agreed that the anthropometric measurements and neuro-cognitive development assessments are necessary, and suggested additional assessments of clinical benefit (e.g., full enteral feeding tolerance, length of hospital stay, need for liver transplant, etc.).
- FDA requested that the Sponsor submit all available data of adverse events and serious adverse events on all patients, not just from 30% of the patients "from selected time-frames" as proposed by the Sponsor.
- Safety data from Baylor, equivalent to the safety data from BCH, should be submitted unless an explanation and rationale are provided.

April 2, 2012: Teleconference

- FDA waived the 6-month rodent study since the infusion toxicity studies longer than 4 weeks are not feasible.
- The Sponsor agreed to conduct a 4-week IV infusion toxicity study in rats aged 21 days

[39] The concern of using a biomarker, i.e. DBil, is reflected by Soden et al (J Pediatr 2010; 156: 327-31) who reported persistence of portal fibrosis despite biochemical improvement in cholestasis in patients treated with Omegaven.

(post-weaning) after conducting a feasibility study.

- The Division accepted the Sponsor's proposal to test 2 doses of Omegaven, 1 and 3 g/kg/day, in addition to a group treated with IL, and a saline control group. Toxicokinetics were to be studied in a separate group treated with Omegaven.
- The 6-week and 3-month IV toxicity studies of Omegaven in dogs and the requested 4-week study in juvenile rats are needed to support an NDA submission.
- Reproductive toxicity studies may not be needed.

January 8, 2013

- Fast Track Designation granted (b) (4)

November 26, 2013: Type C Meeting

- FDA reiterated that the clearest path for regulatory approval for Omegaven as a treatment for PNALD is to conduct a prospective study with an adequate control group. This would reduce bias, enhance the ability to draw statistical inference and enhance the ability to make safety comparisons.
- FDA found the historical matching proposal inadequate. Matching criteria should include a previous history of Intralipid dosing (dose and duration), underlying clinical diagnosis, gestational age and year the patient was treated.
- FDA recommended increasing the HC group to include other institutions (in addition to Baylor) in order to improve the comparisons to Omegaven treatment.
- Only considering out of range lab values as AEs if they were documented as clinically relevant, is not an acceptable approach. Sponsor agreed to provide all adverse event data, including laboratory data, in a format that will allow comparison to historical controls.
- Labeling will be based on the ages enrolled/exposed to Omegaven. There must be sufficient numbers of patients in each pediatric age group to support labelling for the various pediatric age groups, including neonates.
- Data to support the Sponsor's proposed dosing regimen were requested.
- FDA suggested FK look at the nutritional outcomes of patients at Boston and Baylor in support of an NDA with a nutritional indication.
- Complete chemistry, manufacturing and controls information, providing information about the components, composition, manufacturing procedures, and specifications to which the product will conform will be required for NDA submission. The product the Sponsor plans to commercialize in the US needs to be the same as the one used in the pivotal trials.

April 16, 2015: Type B Meeting

- FDA expressed concerns regarding the quantity and quality of the data proposed to demonstrate substantial evidence of effect for Omegaven.
- Under the proposed indication as treatment of PNALD, FDA suggested a co-primary endpoint of time to resolution of both direct bilirubin to less than 2mg/dL and GGT normalization, along with assessment of multiple secondary endpoints: time to transplantation, time to death, individual liver function parameters, body weight, length/height, and head circumference standardized for age and gender (Z-scores according to the WHO multicenter growth reference study), albumin and prealbumin, fatty acid profiles, and essential fatty acid deficiency using triene/tetraene ratio.
- FDA recommended that the Sponsor augment the proposed matching criteria of DBil and post-menstrual age (PMA) at baseline with gamma-glutamyl transpeptidase (GGT) levels. Due to issues with the availability of baseline values in the historical controls, FK stated that GGT cannot be used as a matching criterion.
- FDA recommended FK conduct 2 analyses of efficacy: the first analysis based on currently available data from the enrolled sites, and a second analysis based on the new data prospectively accrued from ongoing enrollment in the expanded access INDs, assuming the efficacy findings from the first set are favorable. However, FK clarified that as a coordinator of the two investigator-initiated intermediate sized INDs, FK has not continued to enroll Omegaven-treated patients from 2012-2015, and only a single dataset is available from 2005-2012; therefore, only the first recommended analysis of efficacy will be conducted.
- FDA stated that patients treated since the cutoff date (2012) will also need to be included in the safety database.
- FDA recommended that the product must conform to the referenced USP specifications. FDA noted that the Sponsor's proposal for reduced elemental impurities testing was unacceptable, and recommended elemental impurity limits be included in the drug product specification, with testing required for release of every batch.
- FK plans to submit 18 months of long-term stability data for 3 batches of product with (b) (4) stoppers and 18 months of data for 2 batches of product with (b) (4) stoppers, in addition to 6 months of accelerated stability data for each of the batches.
- FK proposed submitting information on 49-52 matched pairs in the NDA (i.e., matching 25 patients out of 91 Omegaven-treated patients from BCH, 20 patients out of 60 Omegaven-treated patients from TCH) due to difficulty retrieving information on historical controls. FDA suggested a 2:1 (Omegaven: HC) matching scheme.

September 25, 2016: Type C Meeting (WRO)

- FDA recommended a change in indication from treatment of PNALD to nutritional support in infants with PNAC. FK agreed to this proposed indication.
  - o (b) (4) Its administration as a source of fat and calories allows removal or reduction of the purported key contributor to the cholestasis, i.e., soy derived lipid emulsion.

  - To support a nutrition claim, the primary endpoint should assess outcomes such as pediatric anthropometric measurements (e.g., change in body weight, length, and skin-fold measurements). For these revised primary efficacy endpoints, longer duration data (e.g., >3 months) will be needed.
  - The Sponsor will need to propose a plan to monitor for the development of EFAD; specify how they will assess EFAD.
- The available data will not establish the effect of Omegaven on underlying liver injury, such as fibrotic changes or portal hypertension. For this reason, use of the terminology "PNALD" will not be supported by the data.
- A comprehensive matching approach is recommended using clinical factors and liver biomarkers:
    - Sepsis
    - Duration of PN
    - Underlying surgical condition
    - Gestational age
    - Birth weight
    - Bilirubin and aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
    - GGT (if possible)
- Agreement reached on pair-matching strategy of 2:1 (Omegaven-treated patients: HC) ratio.
- FDA recommended adding a composite liver biomarker endpoint that includes bilirubin, AST and ALT as a safety endpoint.
- The endpoints to document resolution of PNAC should be included as prespecified safety endpoints.
- Agreement was reached that no sequential analyses will be conducted.
- FDA recommended that the Sponsor submit a revised statistical analysis plan (SAP) with the new primary endpoint (nutritional) and comprehensive matching criteria.

January 4, 2016: Type C Meeting (WRO)

- FK agreed to change the indication from treatment of PNALD to nutritional support in infants with PNAC, and to make corresponding alterations in the efficacy and safety endpoints for analysis.
- FDA clarified that a new Fast Track Designation request should be submitted for the new proposed indication.
- FK argued against the comprehensive matching, and proposed using Dbil and PMA as they felt these are the most appropriate and clinically meaningful matching variables for the patient population. FDA stated that this is not acceptable, and recommended that FK perform a comprehensive match on multiple variables (see above).
- FDA clarified that a composite liver endpoint should be defined as either change in direct bilirubin and AST, or in direct bilirubin and ALT. FDA explained that the composite liver endpoint would allow a determination that these markers did not worsen during treatment.

June 3, 2016: Type C Meeting (WRO)

- FDA reiterated that the (b) (4) biochemical composite analyses will provide safety data to inform the risk/benefit analysis for the nutritional indication, that is, providing assurance that the liver biochemical markers did not worsen on Omegaven.
- FDA stated that because the development plan was not designed to show that Omegaven itself caused any observed improvement in the biochemical markers, any improvements in the markers can only be attributed to stopping the drug that has been associated with these adverse biochemical changes.
- FDA expressed concerns about FK's plan to use only bilirubin without transaminase levels in the liver endpoint. FDA recommended that the historical controls be matched for relevant composite biochemical (i.e., AST, ALT, etc.) and demographic characteristics.
- FDA requested that FK submit a detailed SAP for the composite liver endpoint for review, including a plan to monitor for the development of EFAD, and specify how EFAD will be assessed in the proposed population.

June 28, 2016

- Fast Track Designation granted for indication of "source of calories and fatty acids in pediatric patients with PNAC." Use of Omegaven in the targeted population could reduce the need for administration of soy based lipid emulsions, which are believed to contribute to progression of the manifestations of PNAC. The program is designed to show that Omegaven provides adequate nutrition and allows progression of the PNAC manifestations, and potentially reducing these manifestations. While available therapy exists, Fast Track was granted due to the ability of Omegaven to provide benefits similar to those of alternatives while avoiding serious toxicity, and has the potential to address an unmet medical need.

January 25, 2017

- Orphan Drug status verified.

3.3. Foreign Regulatory Actions and Marketing History

Omegaven® was first approved in Germany in 1998, and since then is currently marketed in 40 countries worldwide for PN supplementation with long-chain omega-3 fatty acids, when oral or enteral nutrition is impossible, insufficient, or contraindicated. In non-US countries, Omegaven® is indicated for adults only, and the product label states that "due to limited experience, Omegaven should not be given to premature infants, newborns, infants and children up to 11 years." Additionally, the indicated dose in Europe is 0.1 - 0.2 gram lipid/kg/day, to comprise 10-20% of total lipid parenteral intake, as an adjunctive supplement to soybean based lipids to provide additional EPA and DHA for the purported anti-inflammatory effects of omega-3 fatty acids. The recommended clinical use list includes:

- Post-traumatic and post-surgical patients
- Patients in early stages of sepsis/SIRS
- Patients at risk of hyper-inflammatory processes
- Patients with inflammatory bowel disease
- Patients with inflammatory skin disease (psoriasis, atopic eczema)

Although Omegaven has been approved and marketed for 20 years outside of the US, there are noteworthy differences between the approved indication in Europe to the currently proposed US indication under review. The proposed indication in the US is for pediatric patients, including neonates, the age range particularly contraindicated in the European label. The proposed dose for pediatric patients in this application is for a 10-fold higher dose as an exclusive source of parenteral lipids as a replacement, not supplementation, of soybean based lipids. Most importantly, the proposed indication is to be used in a smaller subset of pediatric patients, those with PNAC, a serious condition not previously evaluated by the foreign regulatory agencies.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

- All clinical trial sites, including the site which supplied HC data only, and a sponsor-level inspection was requested. The inspection was conducted from January 2018 to April 2018. The inspection evaluated documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.
- From TCH, 20 (approximately 30%) of the 64 enrolled patients, and from BCH 30 (approximately 27%) of the 111 enrolled patients were identified from the per-protocol (PP) population based on several factors:
    - Discrepancies in the data review meeting enrollment decision (e.g., decided to exclude, but included)
    - CRFs submitted / missing
    - Death
    - Time period (selected from each year)
- PP population data were verified because this was the population that served as the pool from which the HC matching occurred. This allowed for verification of the reliability of the pair-matched (PM) efficacy population as well as the reliability of the matching process. An inspection of the PP population was considered to be more informative.

An overview of the investigators / sites inspected and final classifications are presented in the table below.

Table 3. Overview of Investigators / Sites Inspected and Final Classifications

Name and Type of Inspected Entity/Address	Protocol # /# of Subjects (safety population/matched)	Classification
CI: Dr. Mark Puder, M.D. Boston Children's Hospital 300 Longwood Ave. Boston, MA 02115	OMEG-034-IP3 Active: 128/52 Historical: 47/14+ OMEG-035-IP3 Historical: 6/6	NAI
CI: Dr. Muralidhar H. Premkumar Texas Children's Hospital 6621 Fannin St., W6104 Houston, TX 77030	OMEG-034-IP3 Historical: 6/6 OMEG-035-IP3 Active: 61/30 Historical: 15/4^	NAI
CI: Dr. Kara L. Calkins UCLA Mattel Children's Hospital 10833 Le Conte, Room B2375 Los Angeles, CA 90095	OMEG-034-IP3 Historical: 6/6 OMEG-035-IP3 Historical: 5/5 Met eligibility but not matched: 7	NAI
Applicant: Fresenius Kabi Archive, Borkenberg 14, 61440 Oberursel (Taunus), Germany	OMEG-034-IP3 OMEG-035-IP3	*NAI
CRO: (b) (4) Inspection Location: Boston Children's Hospital 300 Longwood Ave. Boston, MA 02115	OMEG-034-IP3 Active: 128/52 Historical: 47/14+ OMEG-035-IP3 Historical: 6/6	NAI

Table above is modified from the OSI Addendum Review dated May 5, 2018.
Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.
+Additional historical controls are from TCH and UCLA
^ Additional historical controls are from BCH and UCLA

The inspections of the clinical sites, the UCLA site and the CRO have the final classifications of no action indicated (NAI). The inspection of FK has the preliminary classification of NAI.

FK: For the FK inspection, OSI concluded that the data appear to have been collected reliably, and the data generated by this sponsor may be used in support of the respective indication.

CRO: For the CRO, OSI concluded that the data verification at all the sites was conducted under the inspection of the clinical investigators, and the data were able to be verified.

BCH (Puder): For the BCH (Puder) site, OSI concluded that the data from the active patients and the historical controls appear to have been collected adequately at this site and the data generated by this site may be used in support of the respective indication.

TCH (Premkumar): For the TCH (Premkumar) site, OSI concluded that the data from the active patients and the historical controls appear to have been collected adequately at this site and the data generated by this site may be used in support of the respective indication.

UCLA (Calkins): For the UCLA (Calkins) site, OSI concluded that the data from the source documents of the historical controls appear to have been collected adequately at this site and the data generated by this site may be used in support of the respective indication.

Refer to the OSI Review dated March 26, 2018, and the OSI Addendum Review dated May 5, 2018.

4.2. Product Quality

CMC information provided for Omegaven (fish oil triglycerides) injectable emulsion in this NDA has been reviewed by the quality review team in the Office of Pharmaceutical Quality, and is found to be acceptable. The review team recommended approval for the NDA from the product quality standpoint. Refer to the Quality Summary Review by Hamid Shafiei dated July 13, 2018.

There are no outstanding issues related to the Pharmacology and Toxicology safety qualification of any excipients, impurities, degradants, or leachables which preclude the approval of this NDA. However, a risk assessment is needed for (b) (4) potential elemental impurities that are intentionally added to Total Parenteral Nutrition (see section 5.1 Executive Summary). This risk assessment may be conducted post-approval.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant, FK, is seeking marketing approval for OMEGAVEN (fish oil triglycerides) injectable emulsion, for intravenous use containing omega-3 (n-3) fatty acids, specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for use as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC). Omegaven is supplied as a homogenous emulsion for intravenous infusion containing 0.1 g/mL of fish oil. The intended pediatric patient population for Omegaven is limited to those unable to ingest or adequately absorb oral or enteral nutrients due to insufficient intestinal length or function. The proposed maximum dose for Omegaven for pediatric subjects is 1.0 g lipid/kg/day (10 mL/kg/day) over 8- 24 hours (maximum infusion rate of 0.15 g/kg/hr). Omegaven is supplied in (b) (4) USP colorless glass bottles containing 50 mL or 100 mL, and can be administered by IV infusion into a central or peripheral vein.

Most of the nonclinical pharmacology and toxicology studies that were submitted in support of the current application were previously reviewed under NDA 207648 for Smoflipid (see Pharmacology/Toxicology review dated June 30, 2015 by Dr. Babatunde Akinshola). FK is the Applicant for both the Smoflipid and Omegaven NDAs.

In a 4-week toxicity study in rats (# 5874-630/6), daily IV doses of up to 5 g/kg did not cause systemic toxicity or localized reactions at the injection site. Deaths of four males in the 5 g/kg/ day dose group, and two males and one female in the 1 g/kg/day dose group were due to technical errors with the infusion procedure, and were unrelated to the Omegaven treatment. In a 4-week study in juvenile rats (# AB13616), an 8-hour daily intravenous administration of Omegaven did not have any effects on clinical signs, sexual maturation, physical development, behavior, or mortality.

In a 4-week toxicity study in beagle dogs (# 5820-630/5), intravenous administration of Omegavenous (aka Omegaven) at doses of 0.25, 1, or 5 g lipid/kg/day for 1 month did not cause any mortality. There was no evidence of systemic toxicity or intravascular irritancy in treated animals. Periphlebitis at the injection site was more frequent in animals receiving the test article than in animals receiving the saline control. The test article was well tolerated in male and female dogs.

In a 6-week study in beagle dogs (# AA76191), Omegaven was administered intravenously at 4 g lipid/kg/day using a 16-hr daily intravenous infusion (Phase I of study). There were no deaths or treatment-related clinical signs noted in this Phase. However, in Phase II of the study, one male dog treated with 6 g lipid/kg/day was found dead on treatment day 1. At necroscopy, this animal was observed with edematous areas in the thymus, dilated right cardiac ventricle, large amount of froth in the trachea, and un-collapsed lungs with dark foci in all lobes. The death was associated with changes in the respiratory tract that were histologically correlated

with marked alveolar edema. Because of the observed changes, the dose of 6 g/kg/day was reduced to 4 g/kg/day starting on day 2. After the dose reduction, occasionally marked clinical signs noted in the animals included decreased activity, retching, labored/rapid/deep breathing and/or pale ocular and/or buccal mucous membrane, subdued behavior, and intermittent tremors, which were observed between treatment days 4 through day 41. Dose-related reduction in mean food consumption was observed in animals treated with 6 g/kg/day; treatment-related increases in cholesterol levels (total, free and LDL) were observed at the 4 g/kg/day dose level, when compared to pretest or control values. The absolute and relative liver weights were higher in all treatment groups compared to the control group. The higher liver weights were histologically correlated with diffuse sinusoidal inflammatory cell infiltration, and considered to be treatment related. In the lungs, the main macroscopic finding included dark foci in all treatment groups, which were associated with histological changes (i.e., alveolar inflammation with vacuolated macrophages and alveolar abscess). The changes in the liver and lungs occurred with a variable dose-response effect. Changes in the 6 g/kg/day group were slightly more severe than in the 2 and 4 g/kg/day groups. Based on these findings, the highest dose selected for administration in dogs in the 13-week toxicity study was 3 g lipid/kg/day.

In a 13-week toxicity study (# AA76192) in beagle dogs, Omegaven was administered intravenously to males and females at doses of 1, 2, or 3 g lipid/kg/day using a 16-hr daily intravenous infusion. A comparator group treated with a soy lipid emulsion (Intralipid) was also included in the study (3 g lipid/kg/day). Omegaven produced acute and chronic inflammatory changes in multiple organs which were partially reversed after a 4-week recovery period. Major treatment-related changes were observed in the liver, kidneys, heart, lungs, lymph nodes, thymus and spleen. Treatment-related changes of low severity were seen in the jugular vein, duodenum, adrenal glands, tibiofemoral joint, and bone marrow. Overall, there were no clear dose-related effects in Omegaven-treated animals, because the changes observed in the 1 and 2 g/kg/day groups were generally of higher severity than those in the 3 g/kg/day group. The changes observed in the 3 g/kg/day Omegaven group were generally less severe than those in the comparator group treated with 3 g/kg/day Intralipid.

Omegaven was not mutagenic in the Ames test or in cultured mammalian cells (HGPRT-V79), and was not clastogenic in human peripheral lymphocytes or the in vivo bone marrow cytogenetic test in rats.

To determine the clinical outcomes of administering Omegaven through routes other than the intended therapeutic route in humans, local tolerance in rabbits was assessed after a single intravenous and intra-arterial infusion (30 mL Omegaven/hr for 4 hours) and single injections through the paravenous, intramuscular, or subcutaneous routes. The intravenous and intra-arterial infusions did not lead to any Omegaven-related local reactions, whereas paravenous, intramuscular, and subcutaneous administration caused mild Omegaven-related local intolerance reactions.

A guinea pig maximization test was conducted to investigate the ability of intradermal injections of Omegaven to induce contact sensitization in adult albino guinea pigs. Under the

conditions tested, intradermal injections of Omegaven caused contact sensitization without any evidence of dermal irritation. In a systemic antigenicity test, Omegaven administered in guinea pigs through the peritoneal cavity did not lead to systemic anaphylaxis reactions. The Applicant assessed the biocompatibility and hemolytic properties of Omegaven in EDT-anticoagulated human blood. Results show that Omegaven had no influence on the erythrocyte morphology or hematocrit values. Omegaven did not cause hemolysis, and was compatible with human plasma.

The Applicant's assessment of extractables and leachables for Omegaven emulsion was adequate to provide a reasonable assurance of safety for the worst-case exposure to each leachable (see Appendix Section 16.3 for details).

The Applicant conducted a risk assessment for elemental impurities in Omegaven, in accordance with the recommendations in ICH Q3D (report titled "Risk Assessment for Elemental Impurities (Omegaven 10%, Emulsion for Infusion)". The levels of the analyzed elements (10 total) were below the control thresholds. However, since Omegaven is a parenteral nutrition product, additional consideration is needed for the risk from elemental impurities that may be intentionally added as nutrients in TPN. One of these elements (b) (4) was included in the Applicant's risk assessment cited above. In the amendment dated 07/24/2018, the Applicant provided a risk assessment for five additional elements that may be intentionally added as nutrients in TPN (b) (4) . The Applicant's analysis of (b) (4) in Omegaven assures that each of these elements is either absent or present only at very low levels, such that the maximum exposure levels will only be a small fraction ((b) (4)% or less) of the dose levels routinely used in TPN for the target patient population. This assessment provides a reasonable assurance of safety for the total amount of each element in TPN with Omegaven (i.e. intentionally added element + elemental impurity in Omegaven). However, the following elements that may be used as nutritional additives in TPN were not evaluated: (b) (4). Therefore, we recommend that a post-marketing study be conducted to address this concern.

There are no nonclinical issues which preclude the approval of this application.

5.2. Referenced NDAs, BLAs, DMFs

NDA 207648 (Smoflipid)

5.3. Pharmacology

Primary pharmacology

No primary pharmacology studies were submitted.

Secondary Pharmacology

No secondary pharmacology studies were submitted.

Safety Pharmacology

The Applicant has not conducted safety pharmacology studies to investigate the CNS, cardiovascular, or respiratory effects of Omegaven in the therapeutic range and above. However, the Applicant has evaluated safety pharmacology parameters using daily IV administration of Omegaven in two studies, including a 4-week toxicity study in post-weaning juvenile (PND-25) rats and a 13-week toxicity study in dogs.

Blood pressure and electrocardiography recordings taken pre-dose and in week four during the 4-week intravenous toxicity study with Omegaven (0.25, 1, or 5 g/kg/day) in conscious Beagle dogs were without changes in heart rate, ECG (RR-, PR-, QRS-, QT- and QT_C intervals) or systolic, diastolic, or mean arterial blood pressure (# 5820-630/5).

Cardiovascular parameters (blood pressure, heart rate, PR, RR, QRS, QT, and QT_C intervals) and respiratory parameters (rate, tidal volume, minute volume) were unaffected in the 13-week intravenous infusion study in dogs with Omegaven (# AA76192).

5.4. ADME/PK

None submitted.

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: (# AB13616) A 4-week (8-hour) daily intravenous administration toxicity study in the post-weaning juvenile Han Wistar rat followed by a 4-week treatment-free period.

Key Study Findings

At the end of the treatment-free phase, mean body weights of animals given 3 g lipid/kg /day doses were increased by 4% and 3% in males and females, respectively, compared to control group mean values.

- Test-article related changes in hematology parameters were noted on Day 28 and Day 56
- Test-article related changes in lipid parameters were noted on Day 28. The NOAEL for Omegaven in this study was 3 g/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (0.9% NaCl), 1 and 3 g/kg/day
Route of administration:	Intravenous (8-hour infusion)
Formulation/Vehicle:	Emulsion/0.9% sodium chloride
Species/Strain:	Rats/Han Wistar
Number/Sex/Group:	10 rats/sex/group
Age:	Post-natal day 25 (PND 25)
Satellite groups/ unique design:	Toxicokinetic and Recovery groups
Deviation from study protocol affecting interpretation of results:	No

Note: This study was preceded by a 4-week feasibility study in juvenile rats, with dosing initiated on PND 25 using the same dose levels (# AB12870). This study is not reviewed here.

Observations and Results: changes from control

Table 4: Major findings in the four-week intravenous repeated-dose toxicity study of Omegaven in juvenile rats

Parameters	Major findings
Mortality	One male from the 1 g/kg/day dose group was found dead on Day 3 of treatment. The cause of death was not determined from histological examination.
Clinical Signs	Scabs, sores, and localized hair-loss noted in several animals including control animals; these effects were reported as due to the harness used for infusion procedure, unrelated to the test article.
Body Weights	At the end of treatment-free phase, mean body weight gains of animals in the 3 g/kg/day group were increased by 4% and 3% in males and females, respectively, compared to control group mean values.
Ophthalmoscopy	Ophthalmological findings including corneal opacities, persistent pupillary membrane and hyaloid artery remnant with blood, were reported to be incidental, not related to the test-article.
ECG	ECG was not evaluated.
Hematology	Day 28 relative to start date: 1 g/kg/day: platelet -9% (males), -16% (females) 3 g/kg/day: platelet -20% (males), -21% (females) 1 g/kg/day: -2.9% mean corpuscular volume (females) 3 g/kg/day: -4.5% hemoglobin, -5% packed cell volume, -2.9% mean corpuscular volume, +8.6% activated partial thromboplastin time (females) Day 56 relative to start date: 1 g/kg/day: hemoglobin +2.9% (males), +3.7% (females); -18.7% reticulocyte% (males); -3.6% mean cell hemoglobin (females); +3.6% red blood cells; -2.6% mean corpuscular hemoglobin concentration

	3 g/kg/day: +3.6% hemoglobin (males); +3.7% packed cell volume (males); -3.3% mean cell hemoglobin (females); +3.1% red blood cells; -1.7% mean corpuscular hemoglobin concentration; Changes in hematology parameters not seen at the end of recovery.
Clinical Chemistry	Day 28 relative to start date: 1 g/kg/day: -42.2% triglycerides (females), -5.4% albumin (males) 3 g/kg/day: +86% free cholesterol (males); -14.9% cholesterol (females); +49.6% LDL cholesterol (males); -18.9% HDL cholesterol (females); -41.4% triglycerides (females); -5.9% creatine (females) Day 56 relative to start date: 1 g/kg/day: +2.3% albumin (males); +8.1% albumin:globulin ratio (males); 3 g/kg/day: +4.0 % albumin (males); +9.9% albumin:globulin ratio (males); The minor changes in clinical chemistry parameters were not significantly different than controls at the end of recovery.
Urinalysis	There were no treatment-related changes in volume, specific gravity, or pH.
Gross Pathology	Most common observations in both treated and control animals were procedural injection site lesions and catheterized vein lesions. Treatment-related changes in lungs (dark foci) were noted in the 1 g/kg/ day (1/10 females) and 3 g/kg/day (1/10 males) groups. Small lesions in the prostate gland were noted in the 1 g/kg/day group (1/10 males). Enlarged iliolumbar lymph node was noted in a single male in the 1 g/kg/ day group. In the recovery group, lesions on the prostate gland and seminal vesicles were seen in the 1 and 3 g/kg/day groups (1/9 and 1/10 males, respectively). Enlarged uterus was noted in the 1 and 3 g/kg/day (1/10 and 3/10 females, respectively).
Organ Weights	There were no treatment-related changes in organ weights.
Histopathology **Adequate battery:** Yes	Histological findings in the injection sites and lungs showed similar incidence/severity in the control and test-article treated groups. Oil red o staining in the kidney and lungs was considered to be within the normal limits in all treated animals. Minimal increase in amount of periportal lipid in the liver of control and treated animals was consistent with the expected background levels. A treatment-related incidence of adrenal cortical hypertrophy and vacuolation was noted in the 3 g/kg/ day groups (3/10 males and 1/10 females). Multifocal alveolar hemorrhage and mural thrombosis was noted in the 1 and 3 g/kg/day groups (1/10 males, each), and mural thrombosis was noted in the 1 and 3 g/kg/day groups (1/10 females, each). Effects at the injection sites (i.e. endothelial thickening/proliferation, venous thrombosis, and phlebitis/periphebitis) and perivascular cell infiltration and venous thrombosis in lungs were considered as related to long-term intravenous catheterization or as non-specific effects of intravenous infusion. At the terminal sacrifice, two males in the low-dose group had thrombotic purulent changes in the catheterized vein, which was likely related to dissemination of inflammation from the injection site, rather than the test-article.
Other evaluations	Evaluation of hemolysis and lipemia was performed on plasma samples taken on Day 0 and Day 28 [0 hr (prior to infusion), and 4, 8,

	12, and 24 hr post-dose on both days]. Plasma from the 3 g/kg/day group was mildly lipemic at 4 and 8 hr post-dose on Days 0 and 28.

General toxicology; additional studies

All other general toxicology studies were previously reviewed under NDA 207648 (see Pharmacology/Toxicology review dated June 30, 2015 by Dr. Babatunde Akinshola).

5.5.2. Genetic Toxicology

All genetic toxicology studies, except # 8198/93, were previously reviewed.

In Vitro Mutation Assay in Mammalian Cells (HGPRT-V79)

Study title/number: Mutagenicity study of Omegavenos (aka Omegaven) in mammalian cells (HGPRT-V79) in the in vitro gene mutation assay HGPRT test / Study No. 8198/93

Key Study Findings

- Toxicity study: The test-article was not cytotoxic in V79 cells at 5.0% (v/v) in the presence of metabolic activation (S9 mix). The test-article was cytotoxic at 0.0313% (v/v) and 0.0625% (v/v) in the absence of metabolic activation.
- Mutagenicity test: The mutation frequency in cell cultures treated with test-article at concentrations of 0.0039%, 0.0078%, 0.0156%, 0.0313% and 0.0625% (v/v) in the absence of metabolic activation ranged from 1.7 to 17.7 x 10^{-6} clonable cells. Although the mutation frequency (17.7 x 10^{-6}) at the highest dose exceeded the historical control range of the negative controls (1.6 to 15.0 x 10^{-6} clonable cells), this was considered related to pronounced cytotoxicity rather than indicative of mutagenicity. Mutation frequencies at the lower dose levels were within the control range.

  The mutation frequency of the cultures treated with test-article at concentrations of 0.313%, 0.625%, 1.25%, 2.5% and 5.0% (v/v) with metabolic activation ranged from 3.2 to 11.4 x 10^{-6} clonable cells. The mutation frequency values in the Omegaven groups were within the historical control range of the negative controls (0.6 to 15.2 x 10^{-6} clonable cells), and there was no dose-dependent increase. Therefore, under the conditions tested, the test-article was considered to be non-mutagenic.

GLP compliance: Yes
Test system: V79 cells (fetal hamster lung derivation) forward mutation at HGPRT locus S9 from Aroc1or 1254 induced rats, in the absence and presence of S9 mix.
Study is valid: Yes

5.5.3. Reproductive and Developmental Toxicology

Animal reproductive and development studies have not been conducted with Omegaven.

5.5.4. Other Toxicology Studies

A guinea pig maximization test (# 90C-05014-00) was conducted to investigate the ability of intradermal injections of Omegaven to induce contact sensitization in adult albino guinea pigs (10 animals received test article, 5 animals received negative control article, and 5 animals received positive control article, 1-chloro-2,4-dinitrobenzene [DNCB]). The assay was initiated in two induction phases, I and II. In phase I, 10 animals were administered with intradermal injection (2 x 4 cm area) of test-article + adjuvant, and 5 animals were given injections of positive control + adjuvant. In phase II, one week post-dose, previous test injection sites were massaged with 10% sodium lauryl sulfate solution and treated with the test-article + adjuvant (10 animals) or positive control + adjuvant (5 animals), and the test-regions were covered with a bandage for 48 hours. Eleven days after induction phase II, 0.5 mL of test-article was topically patched to the flank on each of the test and negative control pigs, and application regions were securely taped. The five positive control animals were treated using 0.01% DNCB. Each site of treatment was examined for erythema and edema at 24, 48, 72 and 96 hours, post-dose. Under the conditions tested, 50% of the animals challenged with the test-article were sensitized, compared to the 80% animals in the positive control group. Results show that Omegaven is a moderate dermal sensitizer.

Biocompatibility and hemolytic properties of Omegaven at multiple concentrations (5%, 10%, 25%, and 50% in 0.9% sodium chloride, and undiluted) were investigated in fresh EDTA-anticoagulated human blood obtained from three human volunteers (# OMEG-022-CNC). Equal volumes of human blood and the test solutions or vehicle (0.9% NaCl) were mixed and incubated at 37˚C for 30 min. Visual inspection for color and precipitate was performed, and microscopic examination was performed to evaluate erythrocyte morphology and the presence of precipitate in blood smears. Under the conditions tested, the test-article did not precipitate or affect erythrocyte morphology or hematocrit values. Additionally, the test-article did not produce hemolysis, and did not show signs of incompatibility with human plasma.

6 Clinical Pharmacology

6.1. Executive Summary

The proposed daily dose (and the maximum dose) of 10 mL/kg/day (1 g lipid/kg/day) is based on the calorie needs calculated based upon the patient's body weight. The proposed dosing scheme is consistent with total parenteral nutrient (TPN) dosing rationale, which is based upon caloric needs of each patient.

Study 05-04-048 collected PK samples for six essential fatty acids (FAs) including EPA and DHA in neonatal patients with PNAC. The majority of patients received additional lipid supplementation. PK samples were available from 58 patients. Five of the 58 patients received Omegaven exclusively, while 53 of the 58 patients received concurrent lipid supplementation in addition to Omegaven. The sponsor conducted a population PK analysis to derive PK parameters for these FAs. However, due to multiple confounders, (e.g., concurrent enteral feeds, prior plant-based lipids infusions), and the sparseness of the data in patients who received Omegaven exclusively, these PK parameter estimates are considered not reliable for informing dosing for Omegaven.

(b) (4)

the concentration-time profile of mead acid will not be included since Omegaven does not contain mead acid (Figure 2). Given the importance of mead acid, Section 6.1 Clinical Trial Experience of the product label described the clinical trial data of mead acid in the form of triene:tetraene (mead acid:arachidonic acid) ratio. From the concentration-time profiles of five FAs, plasma concentrations for DHA and EPA appear to increase to a steady-state in about 2 weeks following the administration of Omegaven while alpha-linolenic acid, arachidonic acid, and linoleic acid concentrations did not increase.

6.2. Summary of Clinical Pharmacology Assessment

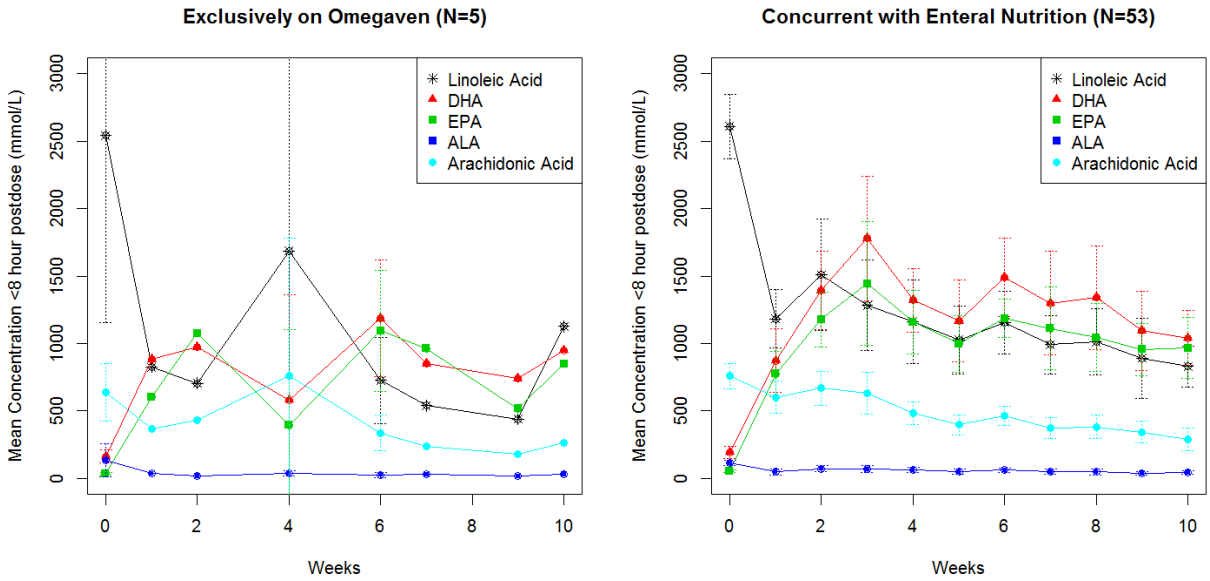
6.2.1. Pharmacology and Clinical Pharmacokinetics

Omegaven provides a biologically utilizable source of calories and essential fatty acids. Fatty acids serve as important substrates for energy production. The most common mechanism of action for energy production derived from fatty acid metabolism is beta oxidation. Fatty acids are also important for membrane structure and function, as precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

The plasma concentrations of EPA and DHA, major fatty acids in Omegaven, as well as linoleic acid and alpha-linolenic acid (essential fatty acids) were measured along with the markers of essential fatty acid status (e.g., arachidonic acid and mead acid) in 58 pre-term neonatal

patients with PNAC enrolled in Study 05-04-048 (median [range] gestational age: 29.5 [24.0-39.0] Weeks) within 8 hours after completion of an intravenous infusion of 1 mg/kg/day of Omegaven for over 10 weeks (Figure 2). The exact timing of the PK blood sampling varied among patients. Five patients received Omegaven as the exclusive lipid source while the others (N=53) received concurrent enteral or oral nutrition. The mean concentration-time profiles of these 5 FAs over 10 weeks are presented in Figure 2. Mead acid was not included in the figure as it is not a component of Omegaven.

Figure 2. Mean plasma concentrations of DHA and EPA over 10 weeks of Omegaven infusion



Source: Reviewer's analysis

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended maximum daily dose of Omegaven for pediatric patients is 10 mL/kg/day (1 g lipid/kg/day). The recommended duration for infusion of Omegaven is between 8 and 24 hours, depending on the clinical situation.

Reviewer's comment: The infusion duration is consistent with the common clinical practice in administration of TPN.

Therapeutic Individualization

The proposed dosing is a weight-based dosing scheme consistent with total parenteral nutrient (TPN) dosing rationale. The calorie needs are calculated based upon the patient's body weight.

Although the 1 g lipid/kg/day is lower than the 3 – 3.5 g lipid/kg/day recommended by Guidelines from ASPEN, the pediatric patients in the clinical trial and in the compassionate-use program received a higher dose of glucose and amino acids to meet their calorie needs. In addition, there was no evidence indicating that patients were at a higher risk of developing essential fatty acid deficiency during the exposure period studied (see Section 8.2.5.2). The safety profile of Omegaven was acceptable. Refer to Section 8.2 in this review.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Refer to Section 6.2.1 for the pharmacokinetic characteristics of fatty acids in pediatric patients with PNAC.

The sponsor submitted clinical pharmacokinetic data of fatty acids from five legacy clinical studies conducted in healthy subjects by various investigators from 1988 to 1995. In two of the five studies, Omegaven was co-administered with Lipovenos 20% (Study FE-OV-08-DE) or Medialipide 20% (Study FE-OV-15-BE). The rest of the three studies were single dose studies with Omegaven infusion duration ranging from 45 minutes to 4 hours, much shorter than the proposed 8 to 24 hours infusion duration.

For these legacy clinical trials, the bioanalytical assay for each analyte was conducted by the local laboratories at the study sites. The method validation from each site was not provided, and there was no cross-site validation for these methods. Thus, the PK data from these studies (b) (4) lack of cross-validation for the analytical methods.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable. The indication for Omegaven is a source of calories and fatty acids in pediatric patients with PNAC.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed maximum daily dose of Omegaven for pediatric patients is 10 mL/kg/day (1 g lipid/kg/day). The recommended duration for infusion of Omegaven is between 8 and 24

hours, depending on the clinical situation. The proposed dosing scheme is consistent with total parenteral nutrient (TPN) dosing rationale, which is based upon caloric needs of each patient. ASPN Guidelines (2002) for infants and preterm neonates recommend 0.5 to 1.0 g lipids/kg/day upon initiation of parenteral nutrition, increasing by 0.5 g/d to a maximum of 3.0 g lipids/kg/day. The studied dose of 1 g lipid/kg/day is lower than that recommended by the Guideline. However, patients in the clinical trial and in the compassionate-use program received a higher dose of glucose and amino acids to meet their calorie needs. The safety profile from these patients is acceptable. In addition, there was no evidence indicating that patients were at a higher risk of developing essential fatty acid deficiency during the studied treatment duration. See relevant review section on clinical safety.

The relationships between systemic exposures of DHA or EPA, and measures of liver function (bilirubin, ALT, AST) and serum triglycerides were assessed in pediatric patients from Study 05-04-048. The findings based on exploratory regression analyses are summarized below:

- No correlation between changes in conjugated or direct bilirubin and concentrations of DHA or EPA.
- Decreases in ALT or AST were correlated with decreases in concentrations of DHA but not with those of EPA.
- Decreases in triglycerides were correlated with decreases in concentrations of DHA but not with those of EPA.

Although these exploratory analyses showed some correlations between concentrations of analytes and biomarkers of interest, a definitive conclusion could not be drawn due to overall lagtime between them.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Omegaven is used as a source of calories and fatty acids.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Since Omegaven is administered by IV infusion, a food-effect study was not conducted as food-drug interactions are not anticipated or applicable.

No pharmacokinetics related drug-drug interaction study has been conducted. Fatty acids are metabolized through the beta oxidation pathway, not CYP P450 enzymes. Therefore, major drug-drug interactions are not expected.

Question on clinically relevant specifications (TBD)?

None.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support, in part, of the proposed indication of source of calories and fatty acids in pediatric patients with PNAC, the Applicant submitted data from two investigator-initiated studies: OMEG-034-IP3 (Study 34) and OMEG-035-IP3 (Study 35). Study 34 and Study 35 were prospective, open-label, investigator-initiated, single-center studies designed to compare the efficacy and safety of Omegaven administered to neonates, infants, and young children with PNAC to retrospective historical data from pediatric patients with PNAC who received a soybean oil-based lipid emulsion, Intralipid, as part of their PN regimen. Table 5 summarizes these studies.

Table 5. Listing of Clinical Trials Relevant to this NDA

Trial ID	Trial Design	Treatment Duration	Study Population	Treatment Groups (Sample Size)	Primary Endpoint
Study 34	Investigator-initiated, open-label, prospective, single-center study with HC	The initial treatment period began with the first administration of Omegaven or, for HC patients, first determination of PNAC. The initial treatment period ended when the patient experienced resolution of PNAC, the patient was weaned from PN, the patient discontinued the study, or June 30, 2012, whichever occurred first. The extended treatment period began the day after resolution of PNAC and continued until the patient was weaned from PN, the patient discontinued the study, June 30, 2012, or, for HC patients only, 12	Omegaven-treated patients were neonates and infants 2 years of age or younger who were diagnosed with PNAC. HC patients included neonates at BCH who were < 2 years of age, born between 1999 and 2007, and received long-term PN between 1999 and 2007.	A total of 141 patients at BCH were treated with Omegaven and screened for enrollment. Of these 141 patients, 128 were retained in the safety population, including 37 patients who were in the compassionate-use group. There were 59 HC patients included in the safety population, including all 47 HC patients from BCH, as well as 6 patients from TCH and 6 patients from UCLA who could be matched to Omegaven-treated patients at BCH. The PP population comprised 91 Omegaven-treated patients and 52 HC patients. The PM population comprised 52	Change in body weight adjusted for age

		months post resolution of PNAC, whichever occurred first.		Omegaven-treated patients and 26 HC patients.	
Study 35	Investigator-initiated, open-label, prospective, single-center study with HC	The initial treatment period began with the first administration of Omegaven or, for HC patients, first determination of PNAC. The initial treatment period ended when the patient experienced resolution of PNAC, the patient was weaned from PN, the patient discontinued the study, or June 30, 2012, whichever occurred first. The extended treatment period began the day after resolution of PNAC and continued until the patient was weaned from PN, the patient discontinued the study, June 30, 2012, or, for HC patients only, 12 months post resolution of PNAC, whichever occurred first.	Omegaven-treated patients were neonates, infants, and children between 14 days and 5 years of age who were diagnosed with PNAC. HC patients consisted of patients at TCH who were < 2 years of age, born between 2005 and 2007, and received long-term PN with soybean oil-based lipid emulsion. HC patients from BCH and UCLA consisted of patients who were < 2 years of age.	A total of 61 patients at TCH were treated with Omegaven and screened for enrollment. Of these 61 patients, all 61 were retained in the safety population. There were 26 HC patients included in the safety population, including 15 patients from TCH who could be matched to Omegaven-treated patients at either BCH or TCH, as well as 6 patients from BCH and 5 patients from UCLA who could be matched to Omegaven-treated patients at TCH. The PP population comprised 60 Omegaven-treated patients and 24 HC patients. The PM population comprised 30 Omegaven-treated patients and 15 HC patients.	Change in body weight adjusted for age

Source: Reviewer's table
PP = per-protocol, PM = pair-matched, UCLA = University of California Los Angeles

7.2. Review Strategy

The Applicant submitted two clinical studies, Study 34 and Study 35, that were originally conducted under Investigator-Sponsor expanded use INDs for the proposed indication of treatment of PNAC. The Applicant provided matched historical controls to the data, and per discussions with the Division, changed the submission's proposed indication to that of nutritional support. Consistent with the nature of the indication, the clinical review evaluated the drug intended for use as a source of calories.

The submitted study results should be considered descriptive or observational only as they do not rely on appropriate inferential statistics or trial designs that would be considered adequate to support specific endpoint testing.

From an efficacy perspective, an intravenous lipid emulsion for clinical use should be expected to supply adequate amounts of calories and adequate amounts of essential fatty acids to prevent the development of essential fatty acid deficiency. Thus, in light of the known biochemistry of fat, the descriptive and observational anthropometric changes were reviewed for efficacy. The protocol design and results for the two studies are reviewed separately from Section 8.1.1 through Section 8.1.5, and the integrated efficacy analysis is discussed in Section 8.1.7. The review of HC matching conducted by the Division of Biometrics VII (DB VII) is included in Appendix Section 16.9 and is also discussed in Section 8.

From a safety point of view, an intravenous lipid product should be able to restore essential fatty acids stores to prevent the development of EFAD. Also, due to the known risks of hepatotoxicity of intravenous lipid product, such as PNAC or PNALD, the liver safety profile is an important safety assessment. The safety review consisted of the overall safety profile of Omegaven (Section 8.2.4) as well as specific safety issues (Section 8.2.5) when used in the context of pediatric patients with PNAC. An integrated analysis of safety, including expanded access use information available to the Agency, is discussed in Section 8.2.11.

Review of the studies was based primarily on the reviewers' independent analyses of the datasets provided by the Applicant, and secondarily on the Applicant's study reports. The tables and analyses presented in this report reflect the independent analysis of the reviewer except where otherwise noted.

Data Sources

The CSRs, protocols, SAPs, Statistical Analysis System (SAS) transport datasets in Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) format, SAS codes, and dataset reviewer's guides for the two studies were submitted electronically. The network path for the original submissions is \\cdsesub1\evsprod\NDA210589\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pn\5351-stud-rep-contr. The network paths for the analysis datasets in the

original submission are \\cdsesub1\evsprod\NDA210589\0003\m5\datasets\omeg-034-ip3\analysis\adam\datasets and \\cdsesub1\evsprod\NDA210589\0003\m5\datasets\omeg-035-ip3\analysis\adam\datasets.

The following gender and age-standardized growth charts were used in the analysis:

- Fenton for preterm infants (https://www.ucalgary.ca/fenton/2013chart)
- World Health Organization (WHO) for 0-2 years (http://www.who.int/childgrowth/en/)
- Center for Disease Control (CDC) 2-20 years (https://www.cdc.gov/growthcharts/).

For nutritional efficacy, references were made to the fatty acid metabolism: caloric value of fatty acids and energy calculations for complete oxidation of fatty acids via known biochemical pathways.[40]

Data and Analysis Quality

In general, the data submitted by the Applicant to support the efficacy and safety of Omegaven for the proposed indication were acceptable. Observations regarding the data quality are as follows:

- The SDTM and ADaM datasets for Study 34 and Study 35 in the original submission contained combined datasets for both studies. On January 16, 2018, the Applicant provided trial-specific SDTM and ADaM datasets as a response to an information request dated January 11, 2018.
- The ADaM datasets that the Applicant submitted on January 16, 2018, were inconsistent with the inclusion of population flag variables. For example, in both studies, the adverse events analysis dataset (ADAE) contained only the safety population flag variable and did not contain the PP and PM population flag variables. The primary analysis dataset (ADANT) contained the PP and PM population flag variables and did not contain the safety population flag variable.
- The ADaM datasets did not contain clearly defined flag variables for identifying whether a patient met the primary and secondary endpoints.

[40] Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter 17 and 22).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant conducted two investigator-initiated studies, Study 34 (NCT00910104) and Study 35 (NCT00738101), whose objectives were to evaluate the growth of pediatric patients with PNAC who were treated with Omegaven or Intralipid; compare the effect of Omegaven and Intralipid on the course of PNAC in pediatric patients; and demonstrate the safety of Omegaven in pediatric patients with PNAC. Patients prospectively enrolled in the studies were diagnosed with PNAC and treated with Omegaven at a goal dose of 1 g/kg/day until PNAC resolved.

The following sections contain study descriptions which were mostly extracted directly from the Applicant's CSRs.

8.1.1. Investigator-Initiated Trials (Study 34 and Study 35)

Overview and Objective

The primary objectives of Study 34, conducted as protocol 05-04-048 "Cholestasis Reversal: Efficacy of IV Fish Oil" under IND 73488, were initially as follows:

- To determine the safety profile of the intravenous omega-3 fatty acid solution (Omegaven)
- To determine if established PN associated liver disease can be reversed or its progression halted by using a parenteral fat emulsion prepared from fish oil as measured by normalization of serum levels of hepatic enzymes and bilirubin
- To compare the serial changes in serum essential fatty acid profiles over the course of therapy of intravenous fat emulsions containing primarily omega-3 fatty acids.

The primary objective of Study 35 evolved over time. It began under Protocol H-21344, whose primary objective was to determine the short-term safety and obtain preliminary data related to the short-term efficacy of a novel intravenous lipid preparation in the management of infants with cholestasis who have a high risk of death or needing transplant. The primary objective of Protocol H-23365 was to provide a mechanism for critically ill infants with PN-associated cholestasis to receive Omegaven for compassionate-use situations for which there are no satisfactory alternative treatments.

Initially, the study was conducted as Protocol H-21344 under IND 73488 (Applicant: Dr. Mark Puder, BCH), titled as "Use of a Novel Intravenous Fat Preparation in the Management of Infants with Parenteral Nutrition-Associated Cholestasis" and began as a pilot open-label trial evaluating 15 patients. Available data from matched infants of similar diagnosis, age and total bilirubin (2 matched historical controls for each patient in this study) were planned to be used as a comparator in lieu of placebo controls.

By 7/16/2008, the study was transitioned to Protocol H-23365 under IND 102843 (Applicant: Dr. Steven Abrams, TCH), titled as "Compassionate Use of an Intravenous Fat Emulsion Comprised of Fish Oil in the Treatment of Parenteral Nutrition Induced Liver Injury in Infants."

Historical controls from 1999 to 2011 were patients who received Intralipid according to the standard of care at the study site. Due to a relatively low number of HC patients from BCH who could be matched to Omegaven-treated patients, HC patients from TCH and University of California Los Angeles (UCLA) were also used in the study.

In the final post-hoc SAP for Study 34 and Study 35, objectives to support the efficacy and safety of Omegaven as a nutritional source of calories were as follows:

- Evaluate the growth of pediatric patients with PNAC who are treated with Omegaven or Intralipid
- Compare the effect of Omegaven and Intralipid on the course of PNAC in pediatric patients
- Demonstrate the safety of Omegaven in pediatric patients with PNAC.

The original studies were designed by the investigator as an open-label trial to show the safety and preliminary efficacy of Omegaven in terms of resolution of PNAC; however, given the subsequent change in the proposed indication from treatment of PNAC to a nutritional indication in patients with PNAC, the current commercial Applicant, FK, used the data from this study to support Omegaven as a source of calories and fatty acids in the target population.

Protocol Amendments

Study 34 and Study 35 protocol amendments are in Appendix Section 16.5.1 and 16.5.2.

Note that for both Study 34 and Study 35, the HC comparator arm data, study objectives, and endpoints were all generated post-hoc. The original proposal to use Andorsky et al. historical controls was abandoned for a more acceptable contemporaneous matched HC cohort from 3 institutions (i.e., BCH, TCH and UCLA). The quality of HC matching (i.e., the algorithm and outcome) was adequate given the limitations of the available retrospective data (see Appendix Section 16.9).

Despite the measures to mitigate bias (i.e., HC matching algorithm, third-party data collection, etc.), the decision to start Omegaven was under the context of compassionate use from original investigator-initiated protocols, and selection bias in the HC cohort cannot be fully eliminated.

Statistical literature notes that although HC groups may be considered 'acceptable' according to certain criteria, HC groups must still be regarded as potentially biased or unreliable.[41] Inconsistencies in the evaluation of a therapy's effect, inconsistencies in the quality of patients, and variation among investigators can interfere with a comparison to historical controls.

Additionally, Study 34 and Study 35 were not designed to demonstrate non-inferiority (NI) or superiority of Omegaven compared to Intralipid.

Statistical Analysis Plan

Both Study 34 and Study 35 were initially designed to assess the efficacy and safety of Omegaven as a treatment for PNALD in pediatric patients, and not as evidence of a nutritional indication. After the change to the proposed nutritional indication, significant changes were implemented in the SAP finalized on September 30, 2016. Details regarding the modified SAP are in Appendix Section 16.6.

The SAP was finalized 3 years after the data lock occurred; consequently, Study 34 and Study 35 are ultimately post-hoc analyses of retrospectively collected data with a HC comparator group. Therefore, it is important to note analysis limitations in the two studies.

First, in both studies, a lack of comparability between the Omegaven and HC groups could have resulted in confounding biases. The Applicant's protocol indicated that the main limitation of results from Study 34 and Study 35 was a lack of comparability. Two notable concerns in the Study 34 and Study 35 protocols were: a) several health care standards and reporting systems changed, and possibly improved, during the period in which HC patients were enrolled; and b) Omegaven-treated patients may have had more advanced PNALD than HC patients, since the Omegaven-treated patients were enrolled under a compassionate-use protocol. Also, biases in endpoint estimates could have resulted from missing data, since more missing data were expected to occur in HC patients than in Omegaven-treated patients. The Applicant also noted that it was possible that patients who received Omegaven were scrutinized somewhat more carefully because of perceived risks associated with treating patients under an IND.

Second, ANCOVA model assumptions may not have been met given the study design of Study 34 and Study 35. For example, in a study with a quasi-experimental design that lacks random treatment assignment, covariate measurement error can create bias in adjusted ANCOVA means, and this measurement error can reduce statistical power.[42] Covariate measurement error may exist since the Omegaven and HC groups differed in time period, and as noted in Section 8.2.3, weight, body height/length, and head circumference were not consistently recorded. Another ANCOVA assumption is that each treatment group is a simple random

[41] Pocock SJ. The combination of randomized and historical controls in clinical trials. Journal of chronic diseases. 1976 Mar 1;29(3):175-88.
[42] Owen SV, Froman RD. Uses and abuses of the analysis of covariance. Research in Nursing & Health. 1998 Dec;21(6):557-62.

sample from its population. This assumption is not met since Study 34 and Study 35 were not prospectively designed with a random treatment assignment. Additionally, the ANCOVA assumption that residuals are normally and independently distributed with zero mean and a common variance did not hold in all cases in the two studies, and small sample sizes in Study 35 may contribute to the violation of this assumption.[43]

Compliance with Good Clinical Practices

The Applicant attests that the studies were conducted in full accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guidance (E6) and any applicable national and local laws and regulations (e.g., Code of Federal Regulations [CFR] Title 21, Part 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies of medicinal products for human use).

Patient Characteristics for Study 34

8.1.2.1 Patient Disposition

A total of 141 patients at BCH were treated with Omegaven and screened for enrollment into Study 34. Of these 141 patients, 128 were retained in the safety population, including 37 patients in the compassionate-use group. There were 59 HC patients included in the safety population, including all 47 HC patients from BCH, 6 patients from TCH, and 6 patients from UCLA. The PP population comprised 91 Omegaven-treated patients and 52 HC patients. The PM population comprised 52 Omegaven-treated patients and 26 HC patients.

In the PP and PM populations, greater proportions of Omegaven-treated patients than HC patients completed the study. Among patients who were weaned from PN, more Omegaven-treated patients than HC patients were weaned after achieving resolution of PNAC, regardless of study population.

Across study populations, the most common reasons for patient discontinuation from the study prior to resolution of PNAC were death, liver transplantation, and being lost to follow-up. The most common reasons for patient discontinuation after resolution of PNAC were death, being lost to follow-up, and the resumption of soybean oil-based lipid emulsion dosing.

Table 6 summarizes patient disposition by treatment group for this study.

[43] Lawson A. Rank analysis of covariance: Alternative approaches. The Statistician. 1983 Sep 1:331-7.

Table 6. Patient Disposition by Population for Study 34

	Safety Population		PP Population		PM Population	
Patient status	**Omegaven N = 128 n (%)**	**HC N = 59 n (%)**	**Omegaven N = 91 n (%)**	**HC N = 52 n (%)**	**Omegaven N = 52 n (%)**	**HC N = 26 n (%)**
Completed study	**89 (69.5)**	**37 (62.7)**	**70 (76.9)**	**33 (63.5)**	**44 (84.6)**	**15 (57.7)**
Weaned from PN[a]	67 (52.3)	36 (61.0)	56 (61.5)	32 (61.5)	37 (71.2)	14 (53.8)
With resolution of PNAC	49 (38.3)	3 (5.1)	42 (46.2)	3 (5.8)	29 (55.8)	1 (3.8)
Without resolution of PNAC	18 (14.1)	33 (55.9)	14 (15.4)	29 (55.8)	8 (15.4)	13 (50.0)
Reached data cutoff date[b]	22 (17.2)	n/a	14 (15.4)	n/a	7 (13.5)	n/a
With resolution of PNAC	22 (17.2)	0	14 (15.4)	0	7 (13.5)	0
Without resolution of PNAC	0	0	0	0	0	0
Discontinued study prior to resolution of PNAC	**23 (18.0)**	**18 (30.5)**	**13 (14.3)**	**17 (32.7)**	**5 (9.6)**	**9 (34.6)**
Death	8 (6.3)	8 (13.6)	5 (5.5)	8 (15.4)	3 (5.8)	4 (15.4)
Liver transplantation	6 (4.7)	6 (10.2)	4 (4.4)	6 (11.5)	0	5 (19.2)
Lost to follow-up	4 (3.1)	4 (6.8)	3 (3.3)	3 (5.8)	2 (3.8)	0
Adverse event	2 (1.6)	0	1 (1.1)	0	0	0
Other	2 (1.6)	0	0	0	0	0
Resumption of soybean oil-based lipid dosing	1 (0.8)	n/a	0	n/a	0	n/a
Discontinued study after resolution of PNAC	**16 (12.5)**	**4 (6.8)**	**8 (8.8)**	**2 (3.8)**	**3 (5.8)**	**2 (7.7)**
Death	6 (4.7)	1 (1.7)	1 (1.1)	0	0	0
Lost to follow-up	6 (4.7)	0	6 (6.6)	0	3 (5.8)	0
Resumption of soybean oil-based lipid dosing	3 (2.3)	n/a	0	n/a	0	n/a
Physician decision	1 (0.8)	0	1 (1.1)	0	0	0
Unknown	0	2 (3.4)	0	2 (3.8)	0	2 (7.7)
Other	0	1 (1.7)	0	0	0	0

Source: Study 34 CSR Table 6 (p. 103)

[a] A patient was considered to be weaned from PN after 30 consecutive days of receiving no PN.

[b] The data cutoff date was June 30, 2012. This was not applicable for HC patients since they were all treated prior to the availability of Omegaven under the institution's IND.

8.1.2.2 Demographic and Baseline Anthropometric and Clinical Characteristics

There were more males than females in both the safety and PP populations, regardless of treatment group. In the PM population, there were equal numbers of male and female Omegaven-treated patients, but more male than female HC patients.

Most patients were White, regardless of study population; however, some patients in each study population did not provide information for race (i.e., race was unknown).

Most patients did not have information for ethnicity (i.e., ethnicity was unknown). For those patients with ethnicity information, there were proportionally more Hispanic/Latino HC patients than Hispanic/Latino Omegaven-treated patients, regardless of study population.

Omegaven-treated patients tended to be older (chronological age) at baseline, regardless of study population.

In the PM population, Omegaven-treated patients tended to have a higher body weight at birth than HC patients, but a lower height/length and head circumference.

Table 7 summarizes demographic characteristics by treatment group for this study.

Table 7. Demographic Characteristics for Study 34

	Safety Population		PP Population		PM Population	
Category Statistic	**Omegaven N = 128**	**HC N = 59**	**Omegaven N = 91**	**HC N = 52**	**Omegaven N = 52**	**HC N = 26**
Sex, n (%)						
Male	71 (55.5)	35 (59.3)	53 (58.2)	31 (59.6)	26 (50.0)	16 (61.5)
Female	57 (44.5)	24 (40.7)	38 (41.8)	21 (40.4)	26 (50.0)	10 (38.5)
Race, n (%)						
White	75 (58.6)	27 (45.8)	51 (56.0)	27 (51.9)	31 (59.6)	18 (69.2)
Black or African American	13 (10.2)	9 (15.3)	10 (11.0)	6 (11.5)	5 (9.6)	2 (7.7)
Asian	4 (3.1)	2 (3.4)	3 (3.3)	1 (1.9)	3 (5.8)	1 (3.8)
Native Hawaiian or other Pacific Islander	1 (0.8)	0	1 (1.1)	0	1 (1.9)	0
Unknown	35 (27.3)	21 (35.6)	26 (28.6)	18 (34.6)	12 (23.1)	5 (19.2)
Ethnicity, n (%)						
Hispanic or Latino	5 (3.9)	9 (15.3)	3 (3.3)	9 (17.3)	2 (3.8)	8 (30.8)
Not Hispanic or Latino	4 (3.1)	5 (8.5)	4 (4.4)	4 (7.7)	1 (1.9)	4 (15.4)
Unknown	119 (93.0)	45 (76.3)	84 (92.3)	39 (75.0)	49 (94.2)	14 (53.8)
Chronological age at baseline (weeks)						
n	128	59	91	52	52	26
Mean (SD)	38.6 (97.84)	9.0 (11.34)	15.0 (11.80)	9.8 (11.81)	11.3 (7.53)	10.2 (8.07)
Median	13.5	5.0	11.0	6.0	9.0	8.5
Range	3 – 761	0 – 62	3 – 64	0 – 62	3 – 42	1 – 41
Gestational age at baseline (weeks)						
n	125	59	91	52	52	26
Mean (SD)	31.1 (4.75)	32.4 (4.76)	31.2 (4.73)	32.4 (4.69)	31.6 (4.53)	31.4 (4.25)
Median	32.0	33.0	32.0	33.0	33.0	31.0
Range	24 – 41	23 – 41	24 – 41	23 – 41	24 – 39	23 – 40
Body weight at birth (kg)						
n	111	54	87	48	50	23
Mean (SD)	1.63 (0.914)	1.73 (0.835)	1.68 (0.910)	1.74 (0.824)	1.80 (0.929)	1.53 (0.714)
Median	1.43	1.65	1.50	1.65	1.75	1.47
Range	0.5 – 4.2	0.5 – 3.9	0.5 – 4.0	0.5 – 3.9	0.5 – 3.8	0.5 – 3.1
Body height/length at birth (cm)						
n	56	31	47	25	29	15
Mean (SD)	38.8 (6.00)	39.7 (6.07)	38.9 (6.08)	40.0 (6.23)	39.3 (5.75)	40.4 (6.18)
Median	38.8	39.0	39.0	39.0	39.0	42.0
Range	29 – 50	29 – 52	29 – 50	29 – 52	30 – 49	29 – 48
Head circumference at birth (cm)						
n	56	32	47	25	29	15
Mean (SD)	27.1 (4.00)	28.8 (4.26)	27.2 (4.07)	29.0 (4.16)	27.7 (4.14)	28.7 (4.05)
Median	27.1	29.5	27.3	29.5	28.0	29.5
Range	20 – 35	21 – 36	20 – 35	21 – 36	22 – 35	21 – 35

Source: Study 34 CSR Table 7 (p. 107)

Baseline Anthropometric and Clinical Characteristics

Although Omegaven-treated patients tended to weigh more than HC patients at baseline, regardless of study population, they had a lower median age-adjusted body weight. Omegaven-treated patients tended to have a greater body height/length at baseline compared to HC patients, regardless of study population. In the PM population, Omegaven-treated patients had a greater median age-adjusted height/length at baseline than HC patients. Omegaven-treated patients also tended to have a greater head circumference at baseline compared to HC patients, regardless of the study population. In the PM population, median age-adjusted head circumference was higher for the Omegaven-treated patients at baseline compared to HC patients.

Table 8 summarizes baseline anthropometric characteristics by treatment group for this study.

Table 8. Baseline Anthropometric Characteristics for Study 34

	Safety Population		PP Population		PM Population	
Measurement characteristic	**Omegaven N = 128**	**HC N = 59**	**Omegaven N = 91**	**HC N = 52**	**Omegaven N = 52**	**HC N = 26**
Body weight at baseline (kg)						
n	126	57	91	50	52	26
Mean (SD)	4.63 (4.637)	3.00 (1.663)	3.60 (1.775)	3.11 (1.688)	3.34 (1.469)	3.17 (1.343)
Median	3.63	2.70	3.17	2.74	3.03	2.74
Range	0.9 – 36.8	0.8 – 8.3	0.9 – 10.0	0.8 – 8.3	0.9 – 6.8	1.3 – 6.1
Age-adjusted body weight at baseline (Z-score)						
n	122	57	91	50	52	26
Mean (SD)	-1.73 (1.541)	-1.39 (1.253)	-1.65 (1.556)	-1.46 (1.276)	-1.43 (1.356)	-1.40 (1.478)
Median	-1.75	-1.31	-1.50	-1.43	-1.45	-1.20
Range	-5.2 – 2.3	-5.6 – 1.0	-5.2 – 2.3	-5.6 – 0.8	-3.9 – 2.3	-5.6 – 0.8
Body height/length at baseline (cm)						
n	113	41	83	37	48	24
Mean (SD)	52.8 (15.98)	46.4 (6.41)	49.7 (8.32)	46.7 (6.51)	48.7 (6.75)	47.7 (6.55)
Median	49.5	46.0	49.0	46.5	49.0	46.8
Range	33 – 152	34 – 62	34 – 73	34 – 62	34 – 63	38 – 62
Age-adjusted body height/length at baseline (Z-score)						
n	108	41	82	37	47	24
Mean (SD)	-2.05 (2.022)	-1.76 (1.390)	-1.87 (1.720)	-1.68 (1.394)	-1.47 (1.635)	-1.74 (1.338)
Median	-1.96	-1.82	-1.81	-1.80	-1.57	-2.10
Range	-8.3 – 8.1	-4.2 – 1.0	-5.7 – 2.2	-4.2 – 1.0	-5.7 – 2.2	-3.5 – 0.4
Head circumference at baseline (cm)						
n	106	41	79	35	47	21
Mean (SD)	34.4 (5.34)	32.4 (4.48)	33.8 (4.76)	32.7 (4.25)	33.7 (3.94)	32.7 (3.31)
Median	34.5	32.8	34.0	32.8	33.5	32.8
Range	24 – 49	24 – 44	24 – 43	24 – 44	24 – 43	27 – 40
Age-adjusted head circumference at baseline (Z-score)						
n	104	41	78	35	46	21
Mean (SD)	-1.70 (1.436)	-1.00 (1.513)	-1.62 (1.430)	-1.02 (1.603)	-1.23 (1.337)	-1.43 (1.736)
Median	-1.57	-1.19	-1.48	-1.19	-1.19	-1.32
Range	-5.1 – 2.1	-6.0 – 2.1	-5.1 – 2.1	-6.0 – 2.1	-4.4 – 2.1	-6.0 – 1.6

Source: Study 34 CSR Table 8 (p. 109)

Most patients did not present with sepsis at baseline and, although the incidence of sepsis at baseline was consistently higher in Omegaven-treated patients than HC patients, the proportions of patients with sepsis at baseline were relatively similar between groups.

Proportionally fewer Omegaven-treated patients had an abdominal wall defect as an underlying surgical condition, regardless of study population. Proportionally more Omegaven-treated patients than HC patients had necrotizing enterocolitis as an underlying surgical condition in the safety and PP populations; the opposite was true in the PM population. Notable proportions of patients had "other" underlying surgical conditions in both groups, regardless of study population; few patients had both abdominal wall defects and necrotizing enterocolitis.

In the safety and PP populations, Omegaven-treated patients had notably higher median DBil, AST, and ALT levels at baseline compared to HC patients. In the PM population, median DBil and ALT levels at baseline were similar between groups, and median AST levels were higher in HC patients compared to Omegaven-treated patients. The similar median DBil levels between groups at baseline were a result of the matching process.

Table 9 summarizes baseline clinical characteristics by treatment group for this study.

Table 9. Baseline Clinical Characteristics for Study 34

	Safety Population		PP Population		PM Population	
Measurement statistic	**Omegaven N = 128**	**HC N = 59**	**Omegaven N = 91**	**HC N = 52**	**Omegaven N = 52**	**HC N = 26**
Presence of sepsis, n (%)						
Yes	33 (25.8)	14 (23.7)	22 (24.2)	11 (21.2)	12 (23.1)	5 (19.2)
No	95 (74.2)	45 (76.3)	69 (75.8)	41 (78.8)	40 (76.9)	21 (80.8)
Underlying surgical condition, n (%)						
Abdominal wall defect	19 (14.8)	17 (28.8)	16 (17.6)	17 (32.7)	9 (17.3)	8 (30.8)
Necrotizing enterocolitis	39 (30.5)	13 (22.0)	28 (30.8)	11 (21.2)	13 (25.0)	8 (30.8)
Both[a]	3 (2.3)	1 (1.7)	2 (2.2)	1 (1.9)	1 (1.9)	1 (3.8)
Other	60 (46.9)	20 (33.9)	40 (44.0)	18 (34.6)	27 (51.9)	8 (30.8)
Unknown	7 (5.5)	8 (13.6)	5 (5.5)	5 (9.6)	2 (3.8)	1 (3.8)
DBil (mg/dL)						
n	128	59	91	52	52	26
Mean (SD)	7.00 (4.544)	3.75 (2.297)	6.58 (3.719)	3.79 (2.398)	4.79 (2.317)	4.64 (2.337)
Median	5.80	2.70	5.80	2.60	3.90	4.05
Range	2.0 – 28.5	2.0 – 12.8	2.0 – 19.2	2.0 – 12.8	2.0 – 10.8	2.0 – 10.4
AST (µkat/L)						
n	123	38	88	33	49	16
Mean (SD)	3.09 (2.928)	1.75 (2.149)	3.00 (2.725)	1.90 (2.270)	2.58 (2.602)	2.57 (2.012)
Median	2.30	0.88	2.13	1.32	1.58	2.14
Range	0.3 – 14.5	0.2 – 10.3	0.3 – 14.5	0.2 – 10.3	0.3 – 14.5	0.4 – 8.0
ALT (µkat/L)						
n	128	57	91	50	52	26
Mean (SD)	2.29 (2.276)	1.17 (1.637)	2.22 (2.114)	1.28 (1.720)	1.95 (2.218)	1.73 (1.963)
Median	1.51	0.52	1.43	0.58	1.07	1.06
Range	0.1 – 14.8	0.1 – 8.5	0.1 – 11.6	0.1 – 8.5	0.1 – 11.6	0.1 – 8.5

Source: Study 34 CSR Table 9 (p. 111)
[a] Abdominal wall defect and necrotizing enterocolitis.

8.1.3. Patient Characteristics for Study 35

8.1.3.1 Patient Disposition

A total of 61 patients at TCH were treated with Omegaven and screened for enrollment into Study 35. Of these 61 patients, all 61 were retained in the safety population. There were 26 HC patients included in the safety population, including 15 patients from TCH who could be matched to Omegaven-treated patients at either BCH or TCH, as well as 6 patients from BCH and 5 patients from UCLA. The PP population comprised 60 Omegaven-treated patients and 24 HC patients. The PM population comprised 30 Omegaven-treated patients and 15 HC patients.

Proportionally more HC patients than Omegaven-treated patients completed the study, regardless of study population. Among patients who were weaned from PN, more Omegaven-treated patients than HC patients were weaned after achieving resolution of PNAC, regardless of study population.

Across study populations, the most common reasons for patient discontinuation from the study prior to resolution of PNAC were death and liver transplantation. The most common reasons for patient discontinuation after resolution of PNAC were resumption of soybean oil-based lipid emulsion dosing and "unknown" reasons.

Table 10 summarizes patient disposition by treatment group for this study.

Table 10. Patient Disposition by Population for Study 35

	Safety Population		PP Population		PM Population	
Patient status	**Omegaven N = 61 n (%)**	**HC N = 26 n (%)**	**Omegaven N = 60 n (%)**	**HC N = 24 n (%)**	**Omegaven N = 30 n (%)**	**HC N = 15 n (%)**
Completed study	**32 (52.5)**	**18 (69.2)**	**32 (53.3)**	**17 (70.8)**	**16 (53.3)**	**9 (60.0)**
Weaned from PN[a]	29 (47.5)	17 (65.4)	29 (48.3)	16 (66.7)	13 (43.3)	8 (53.3)
With resolution of PNAC	17 (27.9)	5 (19.2)	17 (28.3)	4 (16.7)	8 (26.7)	3 (20.0)
Without resolution of PNAC	12 (19.7)	12 (46.2)	12 (20.0)	12 (50.0)	5 (16.7)	5 (33.3)
Reached data cutoff date[b]	3 (4.9)	n/a	3 (5.0)	n/a	3 (10.0)	n/a
With resolution of PNAC	3 (4.9)	0	3 (5.0)	0	3 (10.0)	0
Without resolution of PNAC	0	0	0	0	0	0
Discontinued study prior to resolution of PNAC	**14 (23.0)**	**8 (30.8)**	**13 (21.7)**	**7 (29.2)**	**6 (20.0)**	**6 (40.0)**
Death	9 (14.8)	4 (15.4)	9 (15.0)	3 (12.5)	4 (13.3)	2 (13.3)
Liver transplantation	1 (1.6)	4 (15.4)	1 (1.7)	4 (16.7)	0	4 (26.7)
Lost to follow-up	1 (1.6)	0	1 (1.7)	0	0	0
Adverse event	1 (1.6)	0	1 (1.7)	0	1 (3.3)	0
Other	1 (1.6)	0	0	0	0	0
Resumption of soybean oil-based lipid dosing	1 (1.6)	n/a	1 (1.7)	n/a	1 (3.3)	n/a
Discontinued study after resolution of PNAC	**15 (24.6)**	**0**	**15 (25.0)**	**0**	**8 (26.7)**	**0**
Resumption of soybean oil-based lipid dosing	9 (14.8)	0	9 (15.0)	n/a	6 (20.0)	0
Unknown	4 (6.6)	0	4 (6.7)	0	2 (6.7)	0
Death	1 (1.6)	0	1 (1.7)	0	0	0
Liver transplantation	1 (1.6)	0	1 (1.7)	0	0	0

Source: Study 35 CSR Table 5 (p. 92)

[a] A patient was considered to be weaned from PN after 30 consecutive days of receiving no PN.

[b] The data cutoff date was June 30, 2012.

8.1.3.2 Demographic and Baseline Anthropometric and Clinical Characteristics

There were more males than females in the safety and PM populations, regardless of treatment

group. In the PP population, there was an equal number of male and female HC patients, but more male than female Omegaven-treated patients.

Most patients were White, regardless of study population; however, some HC patients in each study population did not have information for race (i.e., race was unknown).

Most patients reported ethnicity as Hispanic or Latino, regardless of study population; however, some HC patients in each study population did not have information for ethnicity (i.e., ethnicity was unknown).

Omegaven-treated patients tended to be older at baseline, regardless of study population. The investigator's protocol noted that other methods to address PNAC were to be attempted prior to enrollment in the study and the administration of Omegaven.[44] In contrast, HC patients were enrolled (retrospectively) as soon as their DBil level was > 2 mg/dL.

Median body weight, body height, and head circumference at birth were higher in HC patients compared to Omegaven-treated patients, regardless of study population.

Table 11 summarizes demographic characteristics by treatment group for this study.

[44] This was specified as an inclusion criterion, but not collected in the submitted database.

Table 11. Demographic Characteristics for Study 35

	Safety Population		PP Population		PM Population	
Category statistic	**Omegaven N = 61**	**HC N = 26**	**Omegaven N = 60**	**HC N = 24**	**Omegaven N = 30**	**HC N = 15**
Sex, n (%)						
Male	38 (62.3)	14 (53.8)	38 (63.3)	12 (50.0)	16 (53.3)	8 (53.3)
Female	23 (37.7)	12 (46.2)	22 (36.7)	12 (50.0)	14 (46.7)	7 (46.7)
Race, n (%)						
White	44 (72.1)	18 (69.2)	43 (71.7)	17 (70.8)	18 (60.0)	9 (60.0)
Black or African American	10 (16.4)	3 (11.5)	10 (16.7)	2 (8.3)	6 (20.0)	2 (13.3)
Asian	3 (4.9)	0	3 (5.0)	0	3 (10.0)	0
Unknown	4 (6.6)	5 (19.2)	4 (6.7)	5 (20.8)	3 (10.0)	4 (26.7)
Ethnicity, n (%)						
Hispanic or Latino	32 (52.5)	14 (53.8)	31 (51.7)	13 (54.2)	15 (50.0)	6 (40.0)
Not Hispanic or Latino	27 (44.3)	5 (19.2)	27 (45.0)	4 (16.7)	14 (46.7)	2 (13.3)
Unknown	2 (3.3)	7 (26.9)	2 (3.3)	7 (29.2)	1 (3.3)	7 (46.7)
Chronological age at baseline (weeks)						
n	61	26	60	24	30	15
Mean (SD)	10.3 (8.07)	5.7 (3.41)	10.4 (8.10)	5.8 (3.44)	9.0 (5.17)	5.6 (4.00)
Median	7.0	5.0	7.5	5.0	7.0	5.0
Range	2 – 41	0 – 13	2 – 41	0 – 13	4 – 24	0 – 13
Gestational age at baseline (weeks)						
n	61	26	60	24	30	15
Mean (SD)	30.0 (4.89)	31.9 (4.92)	30.0 (4.87)	31.9 (4.99)	29.9 (4.58)	32.6 (4.69)
Median	29.0	33.0	28.5	33.0	29.0	34.0
Range	23 – 38	22 – 38	23 – 38	22 – 38	24 – 38	25 – 38
Body weight at birth (kg)						
n	58	26	57	24	29	15
Mean (SD)	1.47 (0.876)	1.73 (0.873)	1.45 (0.866)	1.74 (0.896)	1.49 (0.857)	1.85 (0.875)
Median	1.06	1.70	1.01	1.70	1.12	1.76
Range	0.5 – 3.1	0.4 – 3.1	0.5 – 3.1	0.4 – 3.1	0.5 – 3.1	0.5 – 3.0
Body height/length at birth (cm)						
n	51	20	51	19	27	10
Mean (SD)	37.7 (6.54)	38.7 (6.73)	37.7 (6.54)	38.8 (6.90)	38.5 (6.48)	39.9 (7.24)
Median	36.5	39.4	36.5	40.0	38.0	42.0
Range	28 – 48	27 – 48	24 – 48	27 – 48	29 – 48	27 – 48
Head circumference at birth (cm)						
n	49	21	49	20	27	11
Mean (SD)	26.5 (4.40)	27.6 (4.66)	26.5 (4.40)	27.7 (4.77)	26.8 (4.70)	28.0 (4.64)
Median	25.1	28.0	25.1	28.5	25.5	28.0
Range	19 – 36	20 – 35	19 – 36	20 – 35	19 – 34	21 – 35

Source: Study 35 CSR Table 6 (p. 96)

Baseline Anthropometric and Clinical Characteristics

Median body weight and median age-adjusted body weight were similar for Omegaven-treated patients and HC patients at baseline, regardless of study population. Median body height/length was lower for Omegaven-treated patients than HC patients at baseline in the safety and PP population and similar for Omegaven-treated and HC patients at baseline in the PM population. Omegaven-treated patients had a lower median age-adjusted height/length at baseline than HC patients. Median head circumference was similar for Omegaven-treated patients and HC patients at baseline, regardless of study population. Omegaven-treated patients had a lower median age-adjusted head circumference at baseline than HC patients.

Table 12 summarizes baseline anthropometric characteristics by treatment group for this study.

Table 12. Baseline Anthropometric Characteristics for Study 35

	Safety Population		PP Population		PM Population	
Measurement characteristic	**Omegaven N = 61**	**HC N = 26**	**Omegaven N = 60**	**HC N = 24**	**Omegaven N = 30**	**HC N = 15**
Body weight at baseline (kg)						
n	61	25	60	23	30	14
Mean (SD)	2.94 (1.577)	2.70 (1.176)	2.94 (1.590)	2.72 (1.162)	2.84 (1.284)	2.80 (0.998)
Median	2.83	2.90	2.80	2.90	2.92	2.90
Range	0.8 – 9.0	0.7 – 5.4	0.8 – 9.0	0.7 – 5.4	0.9 – 5.5	1.1 – 4.2
Age-adjusted body weight at baseline (Z-score)						
n	61	25	60	23	30	14
Mean (SD)	-1.32 (1.059)	-1.16 (1.118)	-1.32 (1.068)	-1.15 (1.166)	-1.11 (0.847)	-1.32 (1.308)
Median	-1.11	-1.04	-1.08	-1.03	-0.97	-0.97
Range	-4.1 – 0.4	-4.3 – 0.8	-4.1 – 0.4	-4.3 – 0.8	-2.7 – 0.4	-4.3 – 0.2
Body height/length at baseline (cm)						
n	60	17	59	15	29	6
Mean (SD)	45.8 (8.32)	45.1 (7.50)	45.8 (8.38)	45.1 (7.76)	45.1 (6.91)	46.4 (7.67)
Median	45.6	47.0	45.5	47.0	46.0	46.3
Range	33 – 70	31 – 55	33 – 70	31 – 55	34 – 59	37 – 55
Age-adjusted body height/length at baseline (Z-score)						
n	60	17	59	15	29	6
Mean (SD)	-1.91 (1.265)	-1.51 (1.306)	-1.92 (1.275)	-1.50 (1.303)	-1.78 (1.224)	-1.44 (1.506)
Median	-1.75	-1.52	-1.76	-1.52	-1.74	-1.45
Range	-6.1 – 0.4	-3.9 – 0.8	-6.1 – 0.4	-3.9 – 0.8	-4.0 – 0.3	-3.9 – 0.8
Head circumference at baseline (cm)						
n	58	17	57	15	29	6
Mean (SD)	31.8 (4.77)	31.7 (5.44)	31.7 (4.77)	31.9 (5.31)	31.3 (4.60)	32.4 (4.50)
Median	32.5	33.0	32.4	33.0	32.5	33.0
Range	23 – 46	21 – 39	23 – 46	21 – 39	23 – 40	26 – 39
Age-adjusted head circumference at baseline (Z-score)						
n	58	17	57	15	29	6
Mean (SD)	-1.52 (1.410)	-0.96 (1.633)	-1.55 (1.396)	-0.87 (1.682)	-1.75 (1.240)	-0.73 (1.175)
Median	-1.59	-1.22	-1.60	-1.22	-1.67	-0.75
Range	-4.5 – 3.0	-3.1 – 2.9	-4.5 – 3.0	-3.1 – 2.9	-4.5 – 0.3	-2.4 – 0.9

Source: Study 35 CSR Table 7 (p. 98)

Most patients did not present with sepsis at baseline; however, the incidence of sepsis at baseline was consistently higher in HC patients than Omegaven-treated patients, regardless of study population.

Proportionally fewer Omegaven-treated patients had an abdominal wall defect as an underlying surgical condition, regardless of study population. Proportionally more Omegaven-treated patients than HC patients had necrotizing enterocolitis as an underlying surgical condition, regardless of study population. Notable proportions of patients had "other" underlying surgical conditions in both groups, regardless of study population. Only 1 HC patient in the safety and PP populations had both abdominal wall defects and necrotizing enterocolitis.

In the safety and PP populations, Omegaven-treated patients had higher median DBil, AST, and ALT levels at baseline compared to HC patients; the difference between groups was more pronounced for DBil in both populations. In the PM population, Omegaven-treated patients had higher median AST and ALT levels at baseline compared to HC patients; however, DBil levels were similar between the 2 groups. The similar median DBil levels between groups at baseline was a result of the matching process.

Table 13 summarizes baseline clinical characteristics by treatment group for this study.

Table 13. Baseline Clinical Characteristics for Study 35

	Safety Population		PP Population		PM Population	
Measurement statistic	**Omegaven N = 61**	**HC N = 26**	**Omegaven N = 60**	**HC N = 24**	**Omegaven N = 30**	**HC N = 15**
Presence of sepsis, n (%)						
Yes	10 (16.4)	6 (23.1)	9 (15.0)	5 (20.8)	4 (13.3)	3 (20.0)
No	51 (83.6)	20 (76.9)	51 (85.0)	19 (79.2)	26 (86.7)	12 (80.0)
Underlying surgical condition, n (%)						
Abdominal wall defect	10 (16.4)	8 (30.8)	10 (16.7)	7 (29.2)	6 (20.0)	5 (33.3)
Necrotizing enterocolitis	18 (29.5)	3 (11.5)	18 (30.0)	3 (12.5)	8 (26.7)	2 (13.3)
Both[a]	0	1 (3.8)	0	1 (4.2)	0	0
Other	25 (41.0)	7 (26.9)	24 (40.0)	7 (29.2)	12 (40.0)	4 (26.7)
Unknown	8 (13.1)	7 (26.9)	8 (1.3)	6 (25.0)	4 (13.3)	4 (26.7)
DBil (mg/dL)						
n	61	26	60	24	30	15
Mean (SD)	6.73 (4.488)	3.86 (1.759)	6.70 (4.516)	3.85 (1.830)	4.26 (2.190)	4.00 (2.122)
Median	5.80	3.35	5.70	3.25	3.35	3.40
Range	2.1 – 23.9	2.0 – 9.0	2.1 – 23.9	2.0 – 9.0	2.1 – 10.8	2.0 – 9.0
AST (µkat/L)						
n	47	16	46	16	23	10
Mean (SD)	3.02 (3.392)	2.03 (1.924)	3.04 (3.426)	2.03 (1.924)	1.96 (1.358)	1.43 (1.205)
Median	2.20	1.95	2.21	1.95	1.78	0.87
Range	0.5 – 20.7	0.4 – 8.0	0.5 – 20.7	0.4 – 8.0	0.5 – 6.6	0.4 – 3.7
ALT (µkat/L)						
n	49	23	48	22	23	13
Mean (SD)	2.04 (1.761)	1.50 (1.765)	2.05 (1.778)	1.51 (1.805)	1.50 (1.163)	1.09 (0.949)
Median	1.45	1.17	1.44	1.04	1.32	0.80
Range	0.2 – 8.5	0.2 – 8.5	0.2 – 8.5	0.2 – 8.5	0.2 – 4.8	0.2 – 3.4

Source: Study 35 CSR Table 8 (p. 100)
[a] Abdominal wall defect and necrotizing enterocolitis.

8.1.4. Study 34 Results

In the PM population, the treatment group effect in the ANCOVA model was not statistically significant at the three prespecified time points for the three anthropometric endpoints (change from baseline in age-adjusted body weight, change from baseline in age-adjusted body height/length, and change from baseline in age-adjusted head circumference). Results in this primary analysis suggest that for the three endpoints, when adjusting for the baseline value, there was no significant difference in mean change from baseline between the Omegaven and HC groups during the three time periods. Sample sizes for both treatment groups at the EOETP time point were too small to allow for reasonable comparisons.

In this population, for most patients with evaluable endpoint data, the EOITP time point occurred at week 8 or earlier, and the EOS time point occurred at week 20 or earlier.

ANCOVA model results for the three anthropometric endpoints are shown in Table 14 through Table 16. Mean changes from baseline in age-adjusted values over time are shown in Figure 3 through Figure 5. Efficacy endpoint results were confirmed by the statistical reviewer.

Table 14. Applicant's Primary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Weight (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=77)**	**EOETP (N=35)**	**EOS (N=71)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0116	0.0348	0.0071
Treatment group	0.6037	0.1548	0.9686
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.33 [-0.69, 0.03]	0.09 [-0.43, 0.62]	-0.05 [-0.51, 0.41]
Historical control	-0.16 [-0.68, 0.35]	1.67 [-0.47, 3.82]	-0.07 [-0.69, 0.56]
Difference	-0.16 [-0.79, 0.46]	-1.58 [-3.79, 0.63]	0.02 [-0.76, 0.79]

Source: Study 34 CSR Table 15 (p. 120)
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 3. Mean Change from Baseline in Age-adjusted Body Weight Over Time in Study 34 (PM Population)

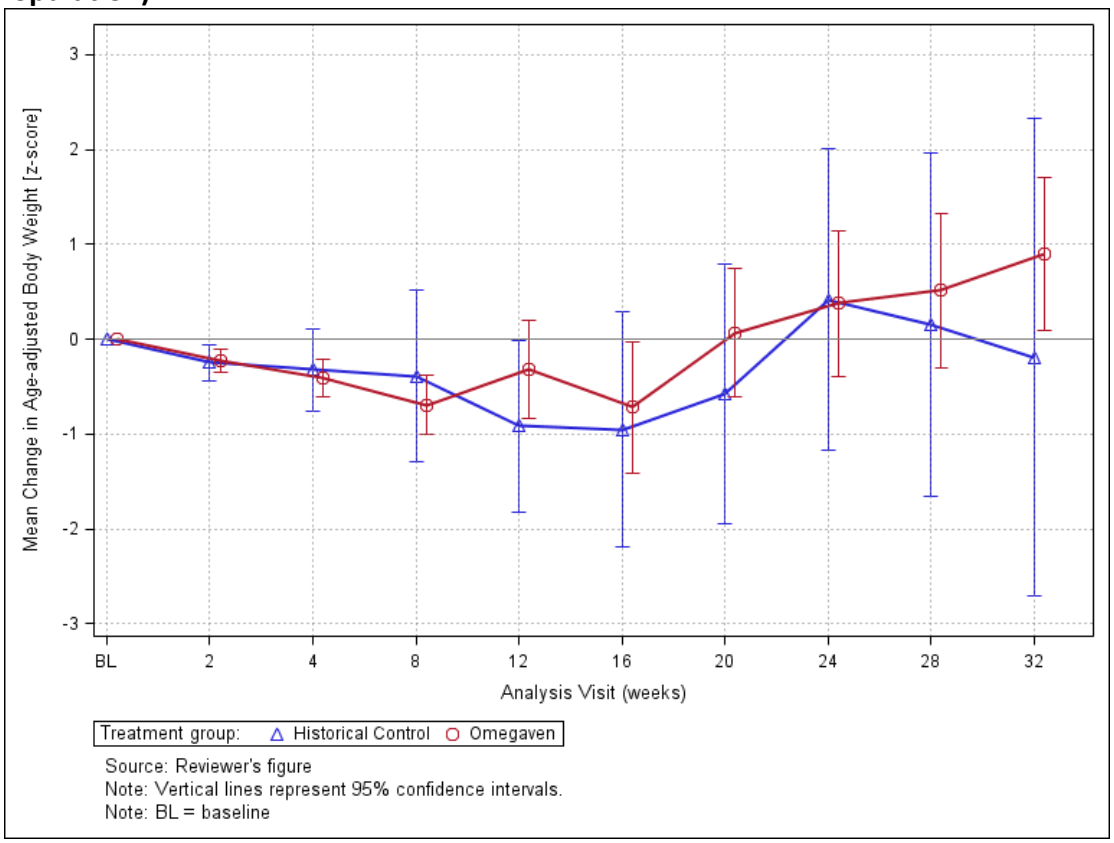


Table 15. Applicant's Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Height/Length (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=63)**	**EOETP (N=29)**	**EOS (N=58)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.1713	0.2522	0.2013
Treatment group	0.1560	0.9614	0.5724
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.16 [-0.49, 0.17]	-0.36 [-0.96, 0.24]	-0.31 [-0.74, 0.11]
Historical control	-0.60 [-1.11, -0.08]	-0.28 [-3.52, 2.96]	-0.53 [-1.16, 0.10]
Difference	0.44 [-0.17, 1.05]	-0.08 [-3.38, 3.22]	0.22 [-0.55, 0.98]

Source: Study 34 CSR Table 20 (p. 131)
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 4. Mean Change from Baseline in Age-adjusted Body Height/Length Over Time in Study 34 (PM Population)

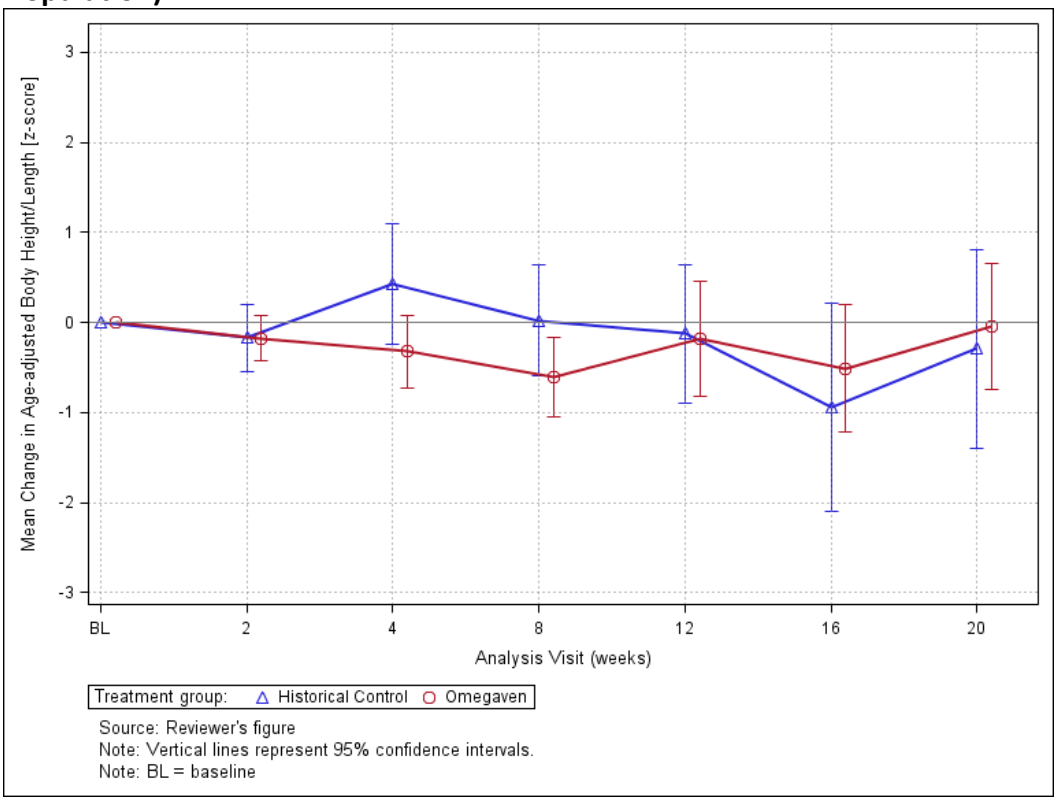
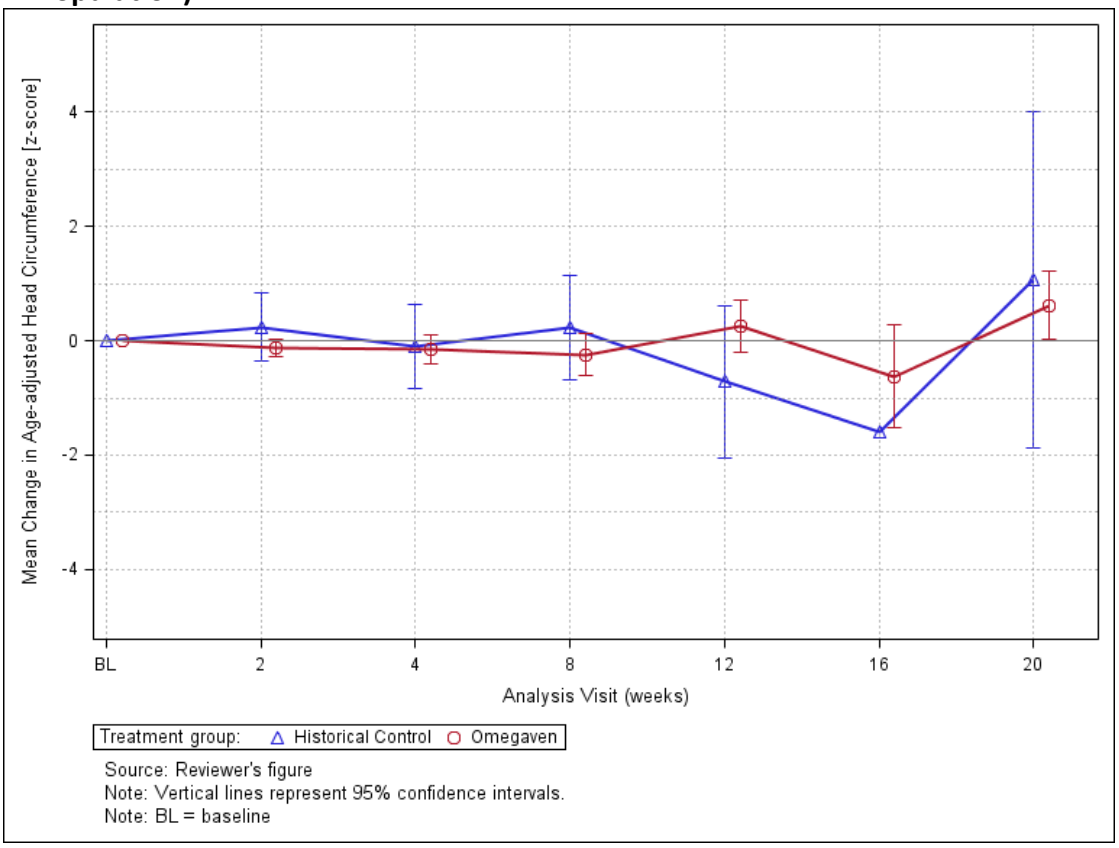


Table 16. Applicant's Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Head Circumference (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=59)**	**EOETP (N=26)**	**EOS (N=51)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0383	0.2436	0.1202
Treatment group	0.4951	0.6147	0.5141
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.02 [-0.34, 0.30]	0.15 [-0.34, 0.63]	0.00 [-0.44, 0.43]
Historical control	-0.25 [-0.82, 0.33]	-0.46 [-2.89, 1.96]	-0.28 [-0.99, 0.43]
Difference	0.23 [-0.43, 0.88]	0.61 [-1.86, 3.08]	0.27 [-0.56, 1.11]

Source: Study 34 CSR Table 25 (p. 141)
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 5. Mean Change from Baseline in Age-adjusted Head Circumference Over Time in Study 34 (PM Population)



The reviewer conducted additional efficacy analyses for the three anthropometric endpoints. An evaluation of the endpoint results using the FM population (derived by DB VII as described in Appendix Section 16.9) was conducted to compare endpoint results with the Applicant's (see Appendix Section 16.7.1.1). An evaluation of the endpoint results at additional time points was conducted to ascertain patients' growth independent of the liver endpoints in the Applicant's primary analysis (see Appendix Sections 16.7.1.2 and 16.7.1.3).

8.1.5. Study 35 Results

In the PM population, the treatment group effect in the ANCOVA model was marginally statistically significant in favor of the HC patients at the EOITP time point for the primary endpoint of change from baseline in age-adjusted body weight (p-value = 0.0470), as shown in Table 17. For most patients in the PM population who were evaluable at the EOITP time point (29/42 patients), the EOITP time point occurred at week 4 or earlier; 6 HC patients evaluable at the EOITP time point had an EOITP visit at week 20 or later. Mean changes from baseline in age-adjusted body weight were lower for the Omegaven group from week 2 through week 16, and were higher than the HC group from week 20 to week 28, as shown in Figure 6. The ANCOVA least squares mean difference in age-adjusted body weight and the estimate's 95% CI at the EOITP time point were -0.92 (-1.83, -0.01). This result was affected by the 6 HC patients who had an EOITP visit at week 20 or later, since those patients had the largest change from baseline values, which ranged from 1.48 to 5.13. As described in Appendix Section 16.7.2.2, when weight was evaluated at the weekly analysis visits up to week 12, the treatment group effect was not statistically significant.

The treatment group effect was statistically significant in favor of the Omegaven-treated patients at the EOITP and EOS time points for the secondary endpoint of change in age-adjusted head circumference (p-value = 0.0185 and p-value = 0.0354, respectively), as shown in Table 19. For most patients in the PM population who were evaluable at the EOITP time point (25/33 patients), the EOITP time point occurred at week 4 or earlier. For most patients in the PM population who were evaluable at the EOS time point (23/31 patients), the EOS time point occurred at week 12 or earlier. However, at each of the EOITP and EOS time points, only 4 HC patients were evaluable. Small sample sizes at these time points limit the conclusions that can be drawn from these analyses. Mean changes in age-adjusted head circumference for the Omegaven group were the same as or higher than the HC group from week 2 to week 20, as seen in Figure 8. The ANCOVA least squares mean difference in age-adjusted head circumference and the estimate's 95% CI at the EOITP and EOS time points were 0.96 (0.17, 1.75) and 1.15 (0.08, 2.21), respectively.

Mean age-adjusted head circumference values for Omegaven-treated patients were lower compared to HC patients from baseline through week 12, and mean age-adjusted head circumference increased in Omegaven-treated patients and exceeded that of HC patients by approximately week 16 in both populations.

The treatment group effect was not statistically significant at the other prespecified time points for the three anthropometric endpoints. Sample sizes for both treatment groups at the EOETP time point were too small to allow for reasonable comparisons.

ANCOVA model results for the three anthropometric endpoints are shown in Table 17 through Table 19. Mean changes from baseline in age-adjusted values over time are shown in Figure 6 through Figure 8. Efficacy endpoint results were confirmed by the statistical reviewer.

Table 17. Applicant's Primary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Body Weight (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=42)**	**EOETP (N=21)**	**EOS (N=43)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.1917	0.5677	0.3645
Treatment group	0.0470	0.5876	0.1477
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.50 [-0.98, -0.01]	-0.45 [-1.40, 0.50]	-0.48 [-1.10, 0.15]
Historical control	0.42 [-0.34, 1.19]	-1.02 [-2.98, 0.94]	0.35 [-0.59, 1.29]
Difference	-0.92 [-1.83, -0.01]	0.57 [-1.61, 2.75]	-0.83 [-1.95, 0.30]

Source: Study 35 CSR Table 14 (p. 109)
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 6. Mean Change from Baseline in Age-adjusted Body Weight Over Time in Study 35 (PM Population)

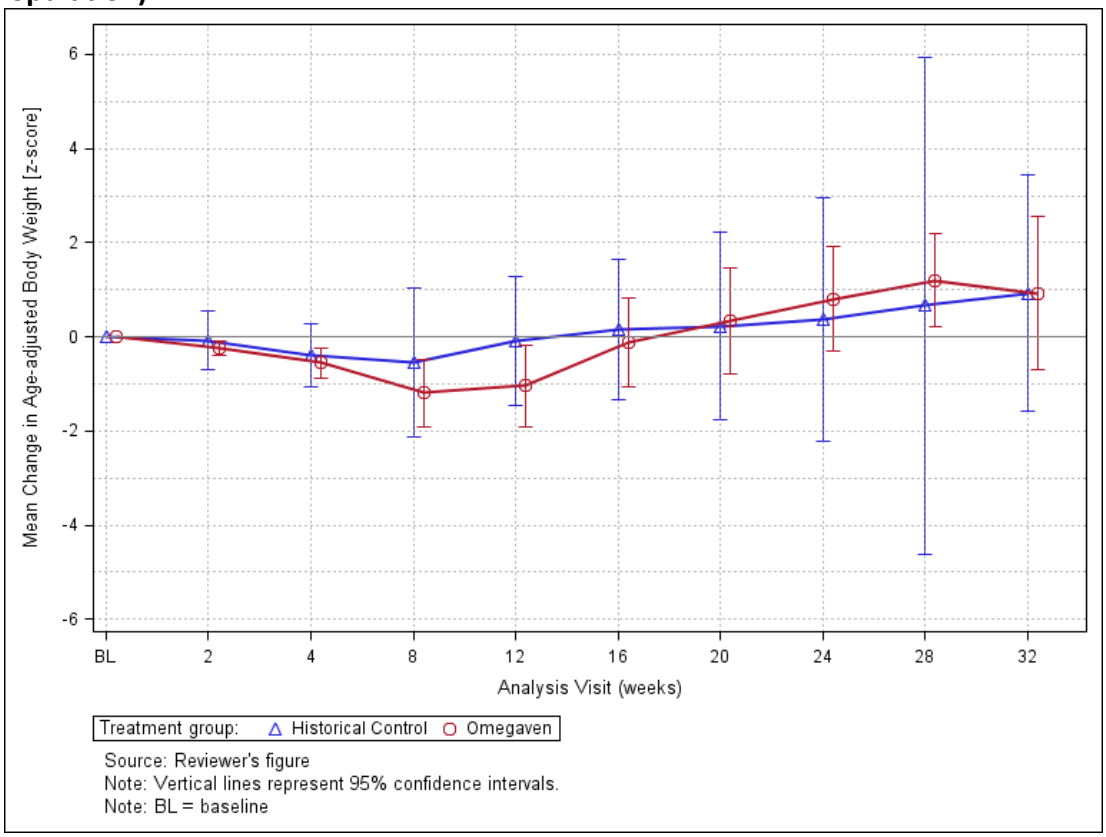


Table 18. Applicant's Secondary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Body Height/Length (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=33)**	**EOETP (N=19)**	**EOS (N=33)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.8918	0.4905	0.5963
Treatment group	0.1525	0.9368	0.1299
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.46 [-0.90, -0.02]	-0.58 [-1.40, 0.23]	-0.45 [-1.00, 0.10]
Historical control	-1.37 [-2.56, -0.18]	-0.68 [-3.16, 1.79]	-1.65 [-3.13, -0.17
Difference	0.91 [-0.36, 2.18]	0.10 [-2.53, 2.73]	1.20 [-0.37, 2.78]

Source: Study 35 CSR Table 19 (p. 119)
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 7. Mean Change from Baseline in Age-adjusted Body Height/Length Over Time in Study 35 (PM Population)

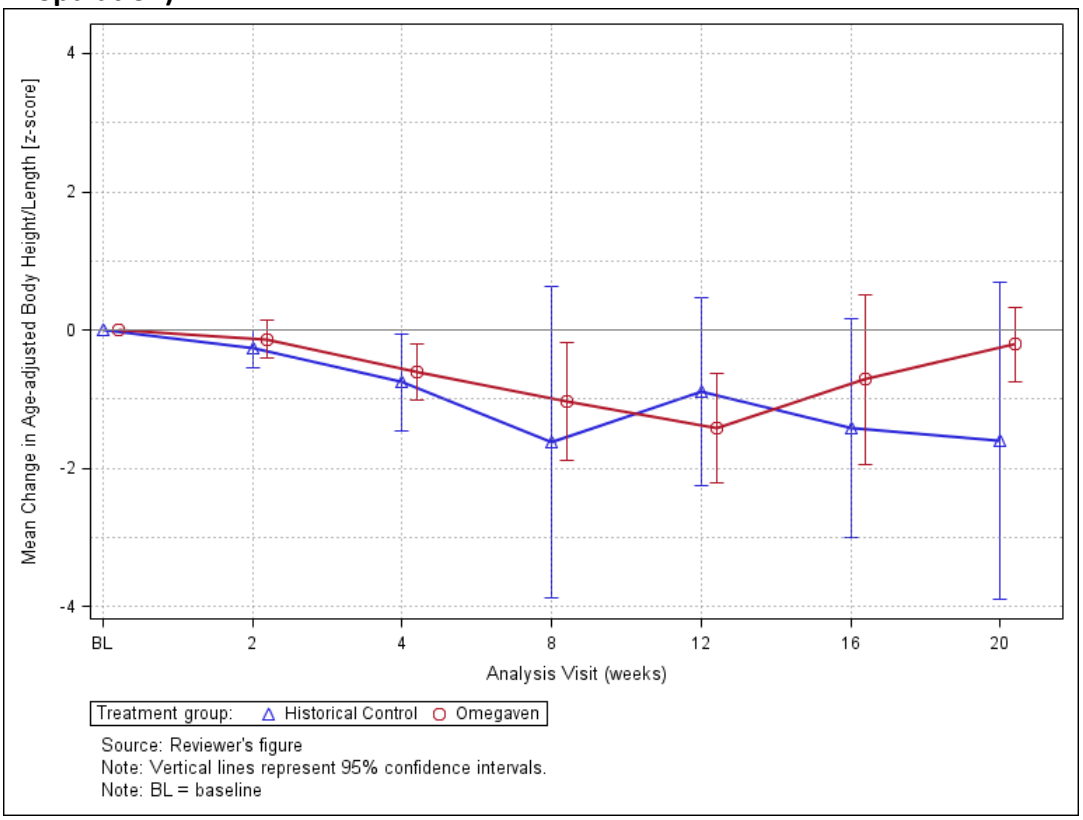
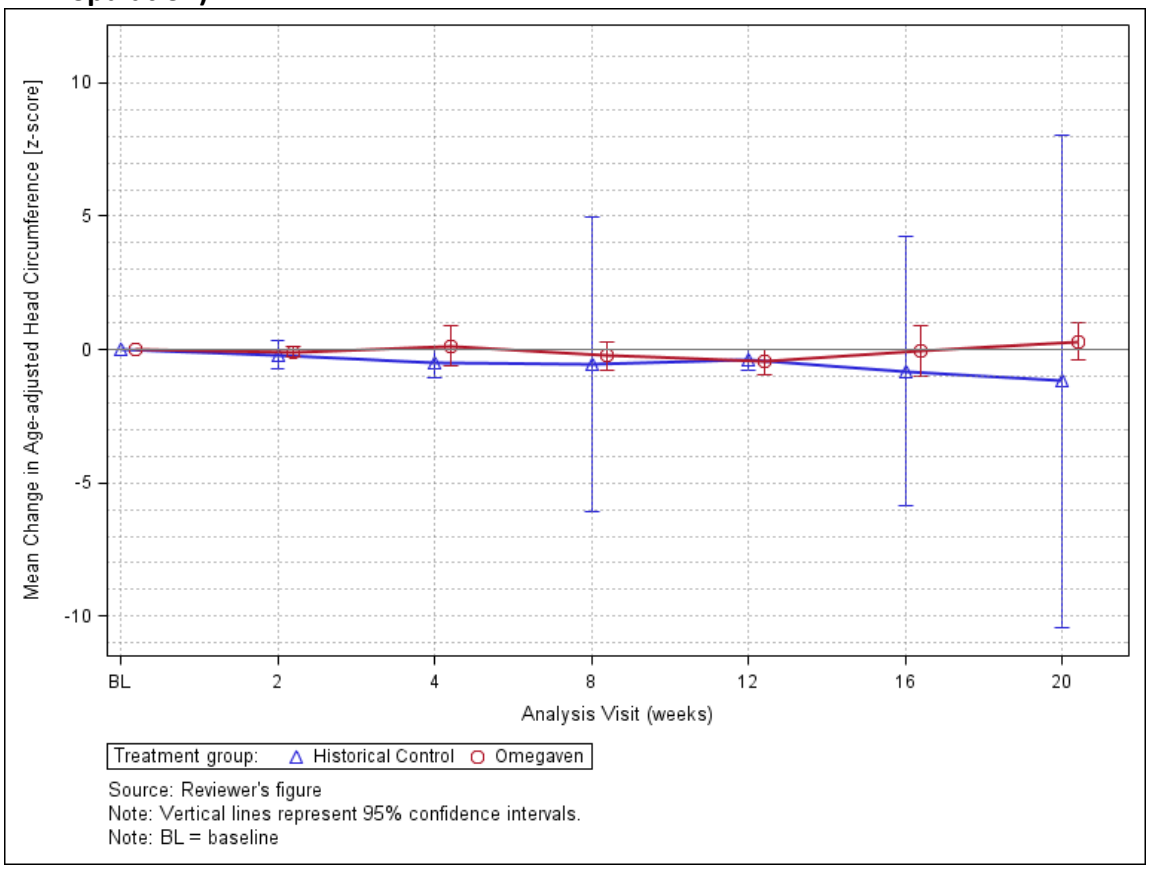


Table 19. Applicant's Secondary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Head Circumference (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=33)**	**EOETP (N=17)**	**EOS (N=31)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.4148	0.1963	0.3283
Treatment group	0.0185	0.1157	0.0354
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	0.04 [-0.23, 0.30]	0.23 [-0.33, 0.79]	0.11 [-0.26, 0.48]
Historical control	-0.92 [-1.66, -0.19]	-1.05 [-2.58, 0.48]	-1.04 [-2.02, -0.05]
Difference	0.96 [0.17, 1.75]	1.28 [-0.36, 2.91]	1.15 [0.08, 2.21]

Source: Study 35 CSR Table 24 (p. 129)
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 8. Mean Change from Baseline in Age-adjusted Head Circumference Over Time in Study 35 (PM Population)



The same additional efficacy analyses of the three anthropometric endpoints that were conducted for Study 34 were also conducted for Study 35 (see Appendix Section 16.7.2).

8.1.6. Additional Efficacy Considerations

Analysis Time Points

The prespecified analysis time points were based on ROPNAC (DBil < 2 mg/dL), the original efficacy endpoint for treatment of PNAC indication, which was somewhat arbitrary for growth assessment for a nutritional indication as source of calories. The duration of time patients remained in the various study periods differed significantly, e.g., HC patients had a longer time (37 days for Omegaven-treated vs. 103 days for HC) in the initial treatment period. Therefore, a comparison of growth at "analysis visits" (i.e., ROPNAC or EOITP) is confounded by duration of absolute time to grow within that study period; the comparison of growth over time irrespective of the defined "analysis visits" verified similar efficacy results (see Appendix Section 16.7).

Dose

Of note, HC patients received a higher PN lipid dose (3 g/kg/day) than the Omegaven-treated

patients (1 g/kg/day), and therefore more PN calories.[45] Omegaven-treated patients received comparable calories by compensating with increased non-lipid macronutrients (e.g., dextrose and protein) calories. Initial decline in growth was more pronounced for Omegaven-treated patients, but overall, Omegaven-treated patients achieved comparable growth across the two studies.

Subpopulations

Across both trials, female patients achieved better catch-up growth and time to reach full enteral feeds (secondary efficacy endpoint) than males; this corresponds with the well-documented gender disparity in premature infants. Other demographic patterns in the studies echoed those in published literature: patients with underlying necrotizing enterocolitis did worse than those patients with abdominal wall defect, and extremely low birth weight (ELBW) and very low birth weight (VLBW) infants did worse than LBW and NBW infants, as would be expected.

Earlier versions of the protocol and the expanded access programs had mandated confirmation of PNAC by at least 2 consecutive cholestatic DBil levels; whereas the to-be-labeled PNAC population will be identified by a single DBil > 2 mg/dL. The integrated efficacy analysis showed that those patients with baseline DBil < 5 mg/dL did better than those with baseline DBil ≥ 5 mg/dL, suggesting a potential advantage to initiating Omegaven earlier (i.e., as soon as DBil levels reach > 2 mg/dL).

Concurrent Enteral Nutrition

Concurrent enteral nutrition (Table 20) was a significant confounder for the efficacy evaluations using anthropometric measurements, and growth for individual patients treated with Omegaven as an exclusive lipid source (i.e., 0 g/kg/day of enteral lipid intake) was assessed. Patients treated with Omegaven as their exclusive lipid source achieved age-appropriate growth as compared to the gender- and age-standardized Fenton,[46] World Health Organization (WHO),[47] and Center for Disease Control (CDC)[48] growth charts (see Appendix 16.8): for those patients followed for > 12 months, anthropometric measurements for weight, height and head circumference crossed percentiles and demonstrated appropriate symmetric extrauterine catch-up growth even on Omegaven as an exclusive source of lipid intake.

[46] https://www.ucalgary.ca/fenton/2013chart
[47] http://www.who.int/childgrowth/en/
[48] https://www.cdc.gov/growthcharts/

Table 20. Concurrent Enteral Nutrition, Efficacy Population

Study		Omegaven	Historical Control
034 BCH		N=52	N=26
	Exclusive PN (0% EN)	6 (12%)	0
	Concomitant EN	46 (88%)	100%
	% of calories provided as EN Median (Min – Max)	24% (1 – 53%)	25% (0.4-68%)
035 TCH		N=30	N=15
	Exclusive PN (0% EN)	6 (20%)	1
	Concomitant EN	24 (80%)	14 (93%)
	% of calories provided as EN Median (Min – Max)	21% (1-75%)	12% (3-40%)

Source: S. Seo

8.1.7. Integrated Assessment of Effectiveness

Although Study 34 and Study 35 were not adequately designed to demonstrate noninferiority or superiority of Omegaven to the soybean oil comparator, the two studies support Omegaven as a source of calories and fatty acids in pediatric patients with PNAC.

Nutritional efficacy was assessed by biomarkers of lipid metabolism, anthropometric indices (body weight, length/height and head circumference), and/or mean changes in fatty acid parameters. The changes in median age-adjusted body weight (Z-scores) over time for Omegaven-treated patients appeared similar to those for HC patients. In both the Omegaven and HC groups, there was an initial decline in all growth parameters (weight, height/length, head circumference) over the initial weeks of treatment, followed by catch-up growth and more age-appropriate values through the remainder of the study.

In addition, to assess age appropriate growth in PNAC patients where Omegaven was the exclusive lipid source, we compared the study data to gender- and age-standardized Fenton and WHO growth charts. We determined that Omegaven can provide nutritional calories and fatty acids to adequately support growth in pediatric patients with PNAC.

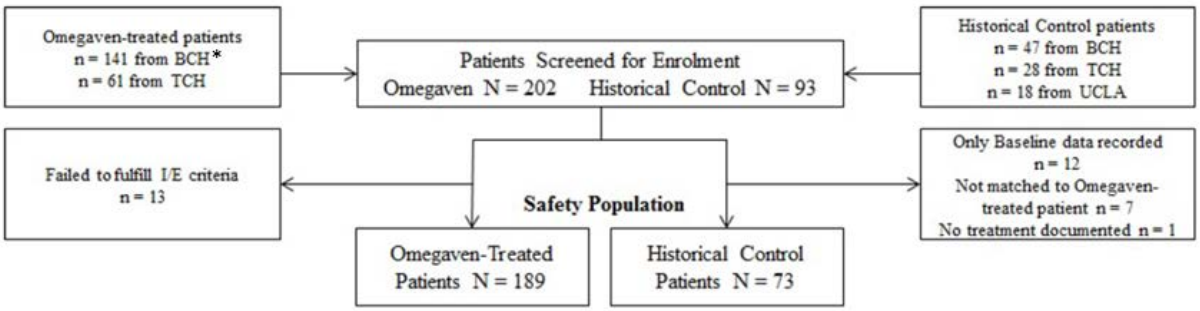
8.2. Review of Safety

Safety Review Approach

The safety review focuses on the population of patients with PNAC, defined as DBil $\geq$ 2 mg/dL who received at least one dose of study drug in the open-labelled trials OMEG-034-IP3 and OMEG-035-IP3 from 2007-2012 (Figure 9). The available limited safety database of expanded access patients treated with Omegaven under the two respective original intermediate size expanded access IND73488 and IND 102843 from 2012-2017 was reviewed separately.

Expanded access information from other single-patient and intermediate size INDs was reviewed separately.

Figure 9. Integrated Safety Population from Pivotal Trials



Source: Integrated Summary of Safety
*Of the 141 Omegaven-treated patients from BCH, 128 were included in the Safety Population, which included 37 patients who were in the Compassionate-Use Group (a subgroup of patients who were treated with Omegaven although they did not fulfill all of the study's enrollment criteria).

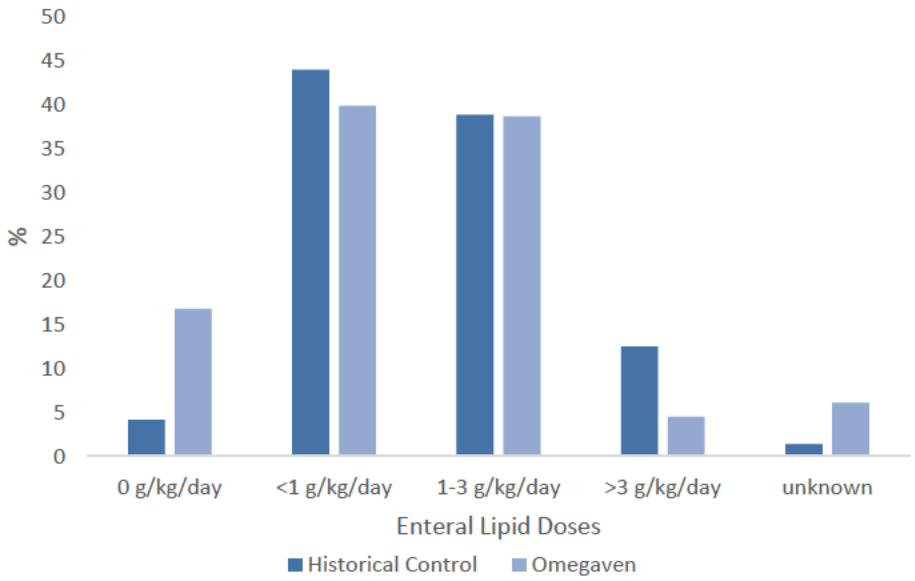
Review was based primarily on this reviewer's independent analysis of the datasets provided by the Applicant, and secondarily on the Applicant's study report. The tables and analyses presented in this review reflect the independent analysis of the reviewer except where otherwise noted. Narratives of patients with serious adverse events were reviewed.

A priori, essential fatty acid deficiency or EFAD was a concern in the evaluation of omega-3 predominant lipid emulsions. Due to the investigator reported clinical experience of resolution of PNAC with Omegaven use, and the origins of the development program under the treatment paradigm for the PNALD indication (Section 2. Regulatory History), a composite safety endpoint evaluating liver function was prespecified for the safety analysis. The composite liver safety endpoints and EFAD are discussed in detail in sections 8.2.5.1 and 8.2.5.2, respectively, under Analysis of Submission-Specific Safety Issues. Other class labeling safety issues such as bleeding, fat overload syndrome and pleural effusions were also reviewed and discussed in Section 8.2.5 to evaluate their relevance for inclusion in the Omegaven product label.

While there were no specific safety signals that have emerged in the Omegaven program, due to the nonrandomized study design and inherent limitations of using historical controls, there were several confounders that impacted the safety analyses. There were significant imbalances between the two groups: more patients in the treatment arm of the safety population were smaller, more premature at birth, older in chronological age, had worse baseline LFTs at entry, and had complications of prematurity (i.e., bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity, patent ductus arteriosus, sepsis, etc). During the trial, 78% and 95% of Omegaven treated and HC patients,

respectively, received median 21% and 23% of calories from concurrent enteral nutrition.[49] Given that enteral nutrition could play a role in blunting the detection of safety signals arising from an unbalanced or suboptimal nutrient source (i.e., EFAD), analyses stratified by enteral lipid dose subgroups (Table 21) are presented and discussed where relevant.

Table 21. Percentage of Patients in Each Subgroup by Enteral Lipid Doses, Integrated Safety Population (Omegaven N=178, Historical Control N=72)*



Source: S. Seo
*11 Omegaven-treated patients and 1 HC patient excluded from figure due to missing enteral nutrition information

8.2.2. Review of the Safety Database

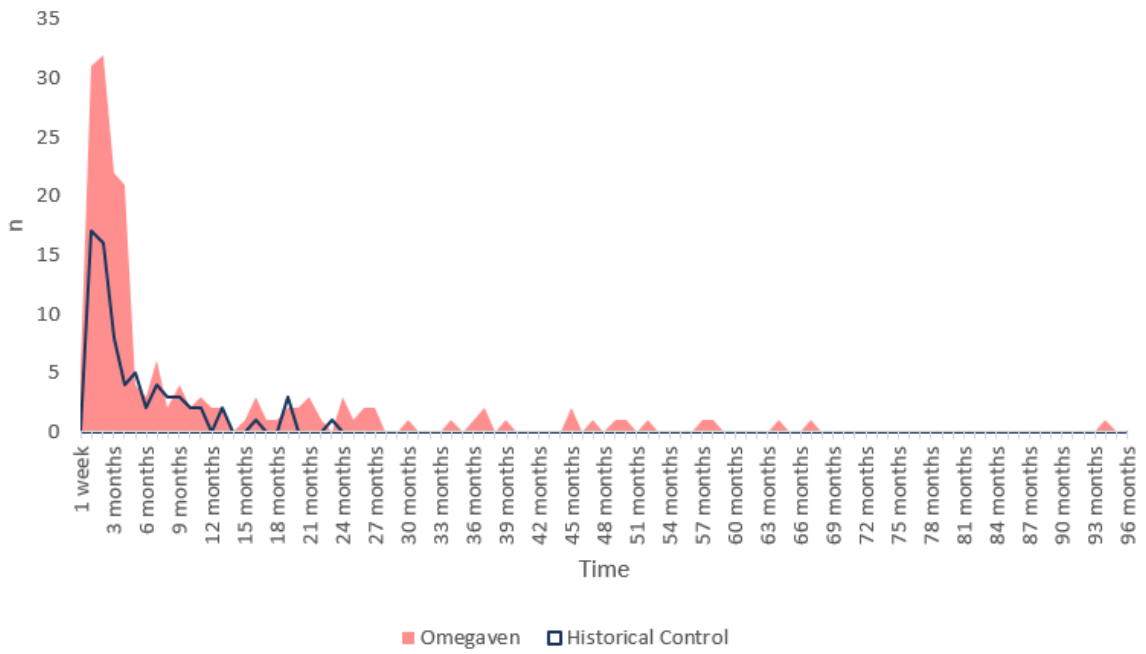
Overall Exposure

Overall, 189 patients were exposed to at least one dose of Omegaven, 90 for up to 3 months, 34 for up to 6 months, 13 for up to twelve months, 19 for up to 24 months, and 22 patients with extended treatment with more than 2 years of exposure (Figure 10). Median duration of Omegaven treatment in the safety population was 13.5 weeks (min 3days, max 7.8 years).

Overall, total patient years of exposure and duration of treatment were longer in the Omegaven arm than the HC arm.

[49] The enteral nutrition was not standardized during the prospective open-label trial, and > 70% of enteral data were missing in the extended treatment period.

Figure 10. Relative Distribution of Duration of Exposure, Integrated Safety Population



Source: S. Seo

From a safety perspective, the longer duration of exposure in the treatment arm would favor the HC arm which had a shorter treatment duration.

Relevant characteristics of the safety population:

The safety database generally was less-balanced between the Omegaven and HC arms than in the PM efficacy population. Omegaven-treated patients were older (by both chronological and post menstrual age), more premature at birth, had smaller birthweight, and worse baseline liver function (**Table 22**).

Due to the inclusion of the compassionate use group in the safety population, there were 8 patients who were > 2 years of age at enrollment, including a 15-year old. Inclusive of the additional compassionate use patients from BCH, and the available data under expanded access use from 2012-2017, the safety database was generalizable to the target U.S. pediatric population with respect to baseline characteristics.

The underlying surgical condition information was collected in broad categories which limited analysis and generalizability. The length of bowel in short bowel syndrome, and duration and extent of intestinal failure were not well characterized in the database.

Table 22. Baseline Characteristics, Safety Population

	Historical Control (N=73)	Omegaven (N=189)
Sex		
Female	30 (41)	80 (42)
Male	43 (59)	109 (58)
Race		
White	37 (51)	119 (63)
Black	11 (15)	23 (12)
Asian	2 (3)	7 (4)
Other	0 (0)	1 (1)
Unknown	23 (32)	39 (21)
Ethnicity		
Hispanic	19 (26)	37 (20)
Non-Hispanic	8 (11)	31 (16)
Unknown	46 (63)	121 (64)
Site		
BCH	47 (64)	128 (68)
TCH	15 (21)	61 (32)
UCLA	11 (15)	0 (0)
Infants at birth		
Gestational age - weeks	32 ± 4.8	31 ± 4.8
Birthweight - g	1706 ± 85	1574 ± 90
Extremely Low Birthweight	17 (25)	69 (40)
Very Low Birthweight	13 (19)	26 (15)
Low Birthweight	24 (35)	42 (25)
Infants at start of treatment		
Chronological age - days	61 ± 72	209 ± 571
median	41	76
interquartile range	41	104
Post menstrual age - weeks	40 ± 12	52 ± 46
median	38	41
interquartile range	9	16
Sepsis	19 (26)	43 (23)
Underlying Surgical Condition		
Abdominal wall defects	19 (26)	29 (15)
Necrotizing Enterocolitis	15 (20)	57 (30)
Both	2 (3)	3 (2)
Other	23 (32)	85 (45)
Unknown	14 (19)	15 (8)
Baseline Liver Function		
Direct Bilirubin ≥5 mg/dL	16 (22)	108 (57)
GGT Elevations	13 (62)	134 (80)
Liver Enzymes Elevations	10 (22)	71 (42)

Source: S. Seo, ISSSAFL ADSL.xpt

Consistent with the imbalance in baseline demographics, the Omegaven-treated patients had increased incidence in all medical history SOCs. With the exception of hypertriglyceridemia, where HC patients had higher incidence, and for baseline pulmonary comorbidities, where the incidence was more balanced between the two groups, the Omegaven-treated patients had higher incidence of co-morbid conditions (**Table 23**).

Table 23. Summary of Medical History at Baseline, Integrated Safety Population

	Historical Control (n = 73)	**Omegaven** (n=189)
Parenteral nutrition associated liver disease	21 (29)	125 (66)
Chronic hepatic failure	1 (1)	2 (1)
Necrotising colitis	26 (36)	89 (47)
Hypertriglyceridaemia	7 (9)	14 (7)
Respiratory Distress Syndrome	30 (41)	80 (42)
Bronchopulmonary dysplasia	6 (8)	37 (20)
Pulmonary haemorrhage	2 (3)	9 (5)
Pulmonary hypertension	4 (5)	13 (7)
Pulmonary interstitial emphysema syndrome	2 (3)	6 (3)
Patent ductus arteriosus	26 (36)	87 (46)
Patent ductus arteriosus repair	5 (7)	34 (18)
Anemia	56 (1)	173 (92)
Thrombocytopenia	28 (38)	119 (63)
Sepsis	32 (44)	145 (77)
Intraventricular haemorrhage	10 (14)	50 (26)
Intraventricular haemorrhage neonatal	2 (3)	15 (8)
Retinopathy of prematurity	11 (15)	58 (31)
Developmental delay	2 (3)	7 (4)
Failure to thrive	3 (4)	15 (8)

Source: S. Seo. ISSSAFL ADMH.xpt.

Of note is the recall bias and inconsistencies within the retrospective database. The study enrollment criteria for all patients in the safety population required a diagnosis of PNAC, and the expected rates of PNAC should have been 100% in both arms. While all patients enrolled qualified as having PNAC, the actual rates based upon medical history were 66% and 29% for Omegaven-treated and HC groups, respectively. The database is more robust for the Omegaven group for both medical history as well as adverse events. There are also apparent inconsistencies across datasets, such as the rate of sepsis in Table 22 (from ADSL.xpt) and Table 23 (ADMH.xpt).

There was limited information regarding prior Intralipid exposure (Table 24): no information was provided for HC patients, and prior Intralipid dose data for just the 7 days prior to initiation of Omegaven were collected.

Table 24. Prior Intralipid Dose

	Historical Control (N=73)	Omegaven (N=189)
Prior Intralipid Dose		
< 2 g/kg/day	NR	96 (68)
>= 2 g/kg/day	NR	46 (32)
Intralipid Dose Minimization		
No	73 (100)	166 (88)
Yes	0	23 (12)
Prior Intralipid Dose (g/kg/day)		
Mean (SD)	NR	1.5 ± 0.8
Median (min-max)	NR	1.2 (0-3)
Prior Intralipid Dose Duration (days)		
Mean (SD)	NR	6 ± 2
Median (min-max)	NR	7 (1-7)

Source: S. Seo. ADSL.xpt

While the HC patients were selected and matched for the efficacy analysis, the safety population is comprised of unmatched patients, and the HC group cannot be considered as an entirely adequate active control for comparative analyses. However, the significant imbalances in demographics, baseline status, and duration of exposure favor the HC group.

Adequacy of the safety database:

The overall extent of exposure in the safety database with respect to number of patients and duration of treatment is adequate for review, given the rarity of the disease.[50] It is important to note that the HC group is an unmatched concurrent active control group which was added post-hoc to a non-randomized open-labelled trial, and is a suboptimal comparator with imbalances in exposure and baseline characteristics, as discussed above. In general, although the safety population was not sufficiently matched to provide adequate information for labeling purposes, the HC data are adequate to inform the safety of Omegaven.

The database is essentially a retrospective study and is limited by the post-hoc nature of the analysis plan and retrospective data collection. Information regarding subtle yet important safety signals, such as biochemical and clinical EFAD, may not have been optimally collected, and may have been potentially obscured by neonatal comorbid conditions.

[50] O'Connell, A Priser. Clinical trial safety population size: analysis of drug approvals for rare and common indications by FDA Center for Drug Evaluation and Research. Expert Opinion on Orphan Drugs 2 (9) 2014.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality submitted was adequate to perform a complete review of the safety of Omegaven. Several information requests were sent to the Applicant during the review of safety to confirm data or clarify minor discrepancies. In collaboration with the Office of Computational Sciences, a data fitness assessment was performed. Key findings included:

- Demographics:
  - 32% of subjects are missing Date/Time of Last Study Treatment (RFXENDTC)
  - 5% of randomized subjects are missing Subject Reference End Date/Time (RFENDTC)
- Laboratory:
  - 28% of baseline observations are missing Standard Results (LBSTRESC)
- Vital Signs:
  - 30% of baseline observations are missing Standard Results (VSSTRESC)
- Adverse Events:
  - 1% and 8% of events are missing start time-point and end time-point, respectively

Categorization of Adverse Events

The Applicant's process for recording, coding, and categorizing AEs met minimum standards, with a few exceptions as noted below. The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols[51] with the caveat that in a neonatal study population, there are no standardized definitions for adverse event categorization and/or assessment of severity of adverse events.

Adverse events were recorded from initial treatment date through the end of the study date. The AE database was essentially based on a retrospective collection from patient's medical records. Discordance between lab results (hypertriglyceridemia, cholestasis, etc), diagnoses (PNAC) and/or AE terms were noted, and incorrect treatment emergent flag assignments for congenital conditions were also noted due to the date of diagnosis following the start of treatment.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0. Verbatim terms were included in the file. The Applicant's translation of verbatim terms to preferred terms was adequate; however, to avoid obscuring potential safety signals due to splitting of preferred terms, 281 of 1181 unique preferred terms were recoded by the reviewer (see Appendix 16.10).

[51] 21 CFR 312.32(a) and 314.80

Routine Clinical Tests

Laboratory assessments were performed at regularly scheduled intervals, and when medically necessary during the trials. (refer to the Monitoring Plan in Appendix 16.4 **Error! Reference source not found.** for details).

There were several deficiencies in routine clinical testing:

- Vital signs were not collected prospectively. While it is assumed that continuous cardiorespiratory monitoring would have been performed for a preterm infant under neonatal intensive care, the data were not collected for analysis.
- Weight, length / height, and head circumference were not consistently recorded, especially for HC patients during the extended treatment period beyond resolution of cholestasis.
- Fatty acid profiles were performed at random, some potentially done during continuous infusion of lipid, for n=127 of the Omegaven-treated group; and not collected at all for the HC group.
- Urinalysis and EKG were not included in routine monitoring, and those data were not collected during the trial.

8.2.4. Safety Results

8.2.4.1 Deaths

A total of 35 patients died in the studies (24/189 patients [13%] in the Omegaven arm and 11/73 patients [15%] in the HC arm). Eight of the 24 (33%) Omegaven-treated patients who died were in the compassionate use group (from BCH).

All reported deaths occurred while on treatment, predominantly during the initial treatment period (17 of 24 in Omegaven-treated patients and 10 of 11 in HC patients) prior to reaching ROPNAC. A summary of patients who died during the pivotal study is provided in Table 25. Omegaven-treated patients who died had an earlier study day at death [median 64 days (range 3-29 days)] than the HC patients [median 215 days (range 29-318)]. Omegaven-treated patients who died were more premature at birth (median gestational age 26 weeks for Omegaven-treated patients vs. 33 weeks for HC patients), had lower age-adjusted body weights at baseline (mean age-adjusted body weight Z-scores of -1.41 Omegaven-treated patients vs. -1.22 HC patients), and had higher DBil levels at baseline (mean DBil 7.81 mg/dL for Omegaven-treated patients vs. 4.6 mg/dL HC patients) compared to HC patients who died.

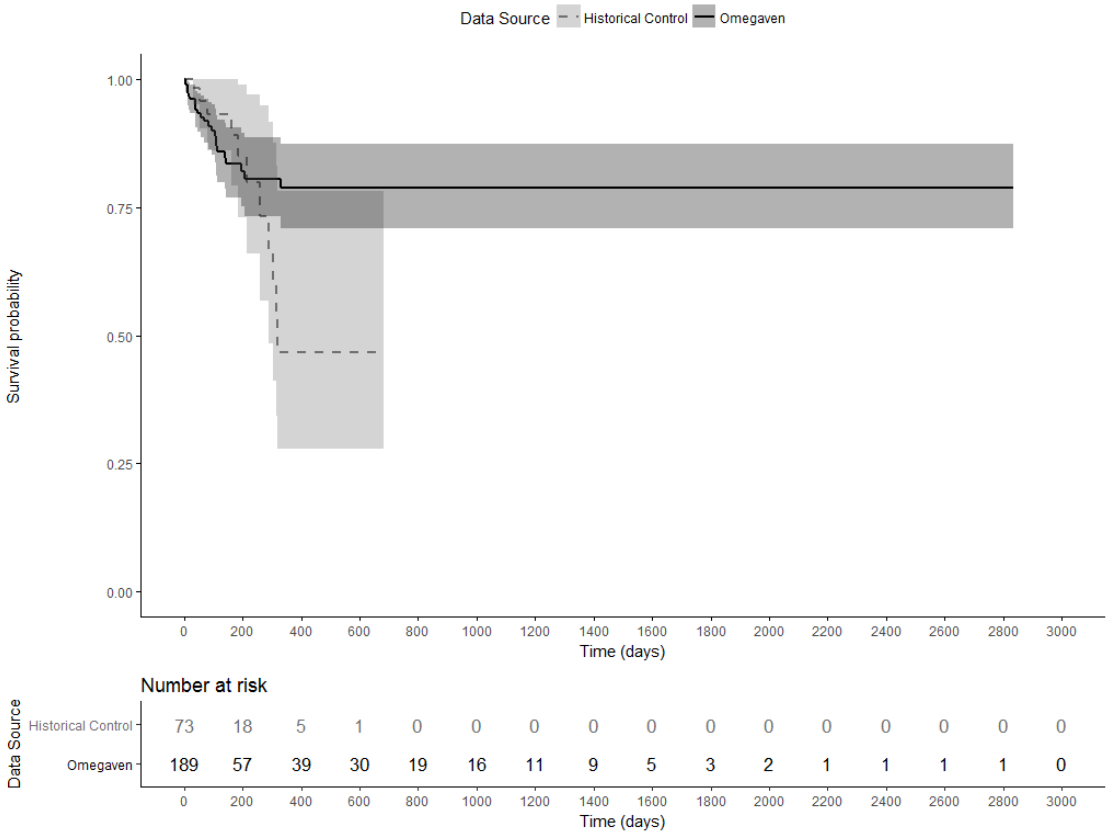
In the Omegaven arm, respiratory and multiorgan failure were reported as the most frequent preferred terms with an outcome of death, (reported in 6 patients each); whereas specific liver related cause of death (“liver failure”, “gastroschisis, liver+renal failure, sepsis”, “end-stage liver disease septic shock”) were more common in the HC arm. There were no Omegaven-treated

patients who experienced fatal SAEs in the SOC of Hepatobiliary Disorders.

The proportion of patients with sepsis at baseline was higher for HC patients who died as compared to Omegaven-treated patients who died, and the HC patients were more likely to have sepsis-associated fatal TEAEs than Omegaven-treated patients who died. None of the SAEs leading to death were considered related to the study treatment by the Applicant.

In the Kaplan-Meier estimates for the time-to-event analysis (Figure 11), the median time to death was estimated to be 45.4 weeks [95% CI: 23.1, 44.9] for HC patients, but a median time of death for Omegaven-treated patients could not be estimated because survival exceeds 50% throughout the duration of the study.

Figure 11. Kaplan-Meier Estimates for Time to Death - Integrated Safety Population



Source: R.Jung

Table 25. Summary of Deaths - All Patients, Integrated Safety Population

Patient #	Treatment Group	Gender	Gestational Age at Birth (weeks)	Birthweight (g)	Age at Enrollment	Study Day at Death	MedDRA Preferred Term	Related AE?
(b) (6)	Omegaven	F	26	620	150 days	Day 85	Respiratory Failure	N
	Omegaven	M	25	724	73 days	Day 3	Dependence on Respirator	N
	Omegaven	F	34	1420	121 days	Day 192	Multiple organ dysfunction syndrome	N
	Omegaven	M	24	490	73 days	Day 145	Multiple organ dysfunction syndrome	N
	Omegaven	M	35	2470	274 days	Day 329	Respiratory Failure Cardiac Arrest	N N
	Omegaven	M	27	940	37 days	Day 11	Cardiopulmonary Failure	N
	Omegaven	F	29	1190	195 days	Day 138	Death	Unk
	Omegaven	F	35		282 days	Day 37	Haemorrhage	N
	Omegaven	M	25		73 days	Day 45	Respiratory Failure	N
	Omegaven	F	26	830	55 days	Day 114	Respiratory Failure	N
	Omegaven	F	40		218 weeks	Day 208	Death	Unk
	Omegaven	F	25	740	195 days	Day 3	Multiple organ dysfunction syndrome	Unk
	Omegaven	M	24	625	69 days	Day 108	Enterobacter Infection Pulmonary Hypertension	N N
	Omegaven	F	31		170 days	Day 14	Acute Kidney Injury	N
	Omegaven	M	26	675	64 days	Day 38	Circulatory Collapse	N
	Omegaven	F	28	1105	41 days	Day 55	Respiratory Failure	N
	Omegaven	M	28	665	119 days	Day 39	Multiple organ dysfunction syndrome Cardiac Arrest	N N
	Omegaven	F	23	595	30 days	Day 94	Metabolic Acidosis	N
	Omegaven	M	30	1120	37 days	Day 68	Cardiopulmonary Failure	N
	Omegaven	F	24	529	66 days	Day 11	Multiple Organ Dysfunction Syndrome	N
	Omegaven	F	29	840	128 days	Day 21	Cardiac Arrest	N
	Omegaven	M	25	650	33 days	Day 98	Multiple Organ Dysfunction Syndrome	N
	Omegaven	M	24	590	34 days	Day 16	Respiratory Failure	N
	Omegaven	F	26	610	54 days	Day 111	Cardiopulmonary Failure	N
	Historical Control	M	32	1230	27 days	Day 75	Cardiopulmonary Failure	N
	Historical Control	M	36	2290	5 days	Day 317	Cardiac Arrest	N
	Historical Control	M	28	519	98 days	Day 10	Respiratory Failure	Unk
	Historical Control	M	40	3130	34 days	Day 257	Hepatic Function Abnormal Chronic Hepatic Failure Pneumonia Enterococcal Sepsis Enterobacter Sepsis Respiratory Distress Respiratory Failure	Y Y Y N N N N N
	Historical Control	F	36	2420	173 days	Day 285	Cardiac Arrest	N
	Historical Control	M	32		19 days	Day 183	Respiratory Failure Dependence on Respirator Hepatic Failure	N N Y
	Historical Control	M	28	925	67 days	Day 314	Staphylococcal Sepsis	N
	Historical Control	F	38	3055	72 days	Day 53	Hepatic Failure Sepsis Bradycardia	N N N
	Historical Control	M	36	2194	56 days	Day 160	Arrhythmia	N
	Historical Control	M	33	1560	66 days	Day 304	Respiratory Failure Septic Shock	N N
	Historical Control	M	27	1031	135 days	Day 215	Cardiopulmonary Failure	N

Source: S. Seo

The incidence of death reported in the pivotal study (data through June 30, 2012) was 11% and 16% for BCH and TCH, respectively. Since the enrollment cut-off date (June 30, 2011) and data cut-off date (June 30, 2012), under the expanded access INDs at the two sites from 2012-2017, there were 8 and 25 additional deaths reported from BCH and TCH, respectively (Table 26).

Including the 35 deaths included in the NDA submission (Table 25), the cumulative incidence of death from 2005 through December 2017 was 8% and 14% at BCH and TCH, respectively.

In contrast, the published mortality rate for infants who develop PNAC with DBil level ≥2.5mg/dL was 49% in 2005[52] and for infants with Dbil level >10mg/dL was 38% in 2010.[53] In 2012, the Pediatric Intestinal Failure Consortium[54] reported a cumulative incidence of death and intestinal transplant of 27% and 26%, respectively, in preterm infants with intestinal failure. All reported deaths in this population are attributed to complications of end-stage liver disease including sepsis, hemorrhage, and the ultimate progression to multi-organ failure.

[52] Spencer AU, Neaga A, West B, Safran J, Brown P, Btaiche I, Kuzma-O'Reilly B, Teitelbaum DH. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg. 2005;242(3):403-9; discussion 9-12.
[53] Willis TC, Carter BA, Rogers SP, Hawthorne KM, Hicks PD, Abrams SA. High rates of mortality and morbidity occur in infants with parenteral nutrition-associated cholestasis. JPEN J Parenter Enteral Nutr. 2010;34(1):32-7.
[54] Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. The Journal of pediatrics. 2012;161(4):723-8.e2.

Table 26. Summaries of Death Under Expanded Access (IND73,488 and IND102,634) from 2012-2017

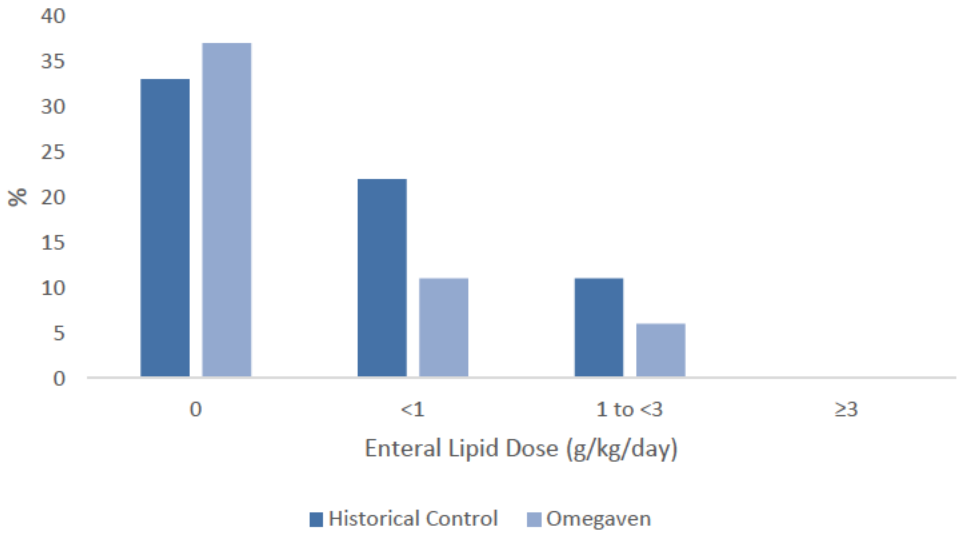
Patient #	Site	Gender	Date of Birth	Date of Death	Primary Cause of Death	Gestational Age at Birth (weeks)	DBil at Baseline (mg/dL)	Age at Enrollment	Study Day at Death	Related AE?
	(b) (6)	M		(b) (6)	Respiratory Failure Sepsis	37	23	136 days	24 days	N
		M			Respiratory Failure	26	>20	55 days	6 days	N
		M			Multisystem Organ Failure	29		5 months	20 days	N
		M			Sepsis and Respiratory Failure	26		6 months	119 days	N
		M			Multisystem Organ Failure	24		2 months	197 days	N
		F			Multisystem Organ Failure			9 months	44 days	N
		F			Pneumonia	28			236 days	N
		M			Gram Negative Sepsis	24	9.3	2 months	70 days	N
		M			Multisystem Organ Failure Sepsis		12.3	27 days	9 days	N
		M			IVH and Respiratory Failure		3.6	25 days	7 months	N
		M			Sepsis Congenital Heart Disease		6.9	35 days	33 days	N
		F			Multisystem Organ Failure	23	3.7	60 days	5 months	N
		M			NEC totalis		4.3	71 days	21 days	N
		M			Sepsis Multisystem Organ Failure	26	14.7	31 days	136 days	N
		F			Pneumothorax	23	4.2	18 days	13 days	N
		F			IVH and Sepsis		4.9	55 days	30 days	N
		M			End stage Renal Disease Respiratory Failure	34	7.8	29 days	38 days	N
		M			Multisystem Organ Failure	24	11.9	18 days	6 days	N
		F			Multisystem Organ Failure Sepsis		3.6	43 days	5 days	N

(b) (6)		(b) (6)						
	M		Sepsis and Congenital Cardiac Disease		3.2	42 days	99 days	N
	M		Pulmonary Vein Stenosis	23	1.5	206 days	196 days	N
	F		Respiratory Distress Syndrome Intraventricular Hemorrhage Hypotension Fungal Infection	23	8.7	35 days	5 days	N
	M		Heart Failure Fungal Sepsis		9.9	71 days	3 days	N
	M		Liver Failure Intestinal Failure Adrenal Insufficiency	26	3.3	138 days	94 days	N
	M		Multisystem Organ Failure Sepsis	31	9.4	39 days	18 days	N
	M		Multisystem Organ Failure	34	8.1	36 days	28 days	N
	F		Multisystem Organ Failure Myeloproliferative disorder	37	6.2	34 days	148 days	N
	F		NEC totalis	24	4.7	34 days	1 day	N
	M		Sepsis	27	17.8		5+ days	N
	M		Cardiac Insufficiency Pulmonary Insufficiency		6.1	116 days	71 days	N
	F		Multisystem Organ Failure	29	4	52 days	81 days	N
	M		Multisystem Organ Failure Congenital Cardiac Anomalities	term	2.4	183 days	2 weeks	N

BCH: Boston Children's Hospital, TCH: Texas Children's Hospital, DBil: Direct Bilirubin
Source: S. Seo. Generated from 120-Day Safety Update

As expected, mortality rates were higher in the exclusive parenteral lipid source subgroups in both arms, and correlated with lower rates with increasing enteral nutrition to no deaths in the subgroup on ≥ 3 g/kg/day of enteral lipids. In the exclusive parenteral lipid source subgroup, Omegaven-treated patients had a slightly higher rate of death, 37% (n=11) vs. 33% (n=1) than the historical controls.

Figure 12. Death Rates by Enteral Lipid Dose Subgroups, Integrated Safety Population



Source: S. Seo. ADSL.xpt. ADNURAW.xpt. ADAE.xpt.

Summary. After the review of the patient narratives, the reported deaths appeared to be the result of events related to prematurity and complications of underlying disease and likely not related to the study drug. The apparent lack of fatal SAEs in the Hepatobiliary Disorders SOC for Omegaven treatment arm is notable; however, there was a higher incidence of multiorgan failure as a cause of death in the treatment arm which is a nonspecific "catch-all" term that often includes liver failure among concurrent multiple other organ dysfunctions. Given the extreme prematurity and underlying PNAC, both conditions already associated with high morbidity and mortality, it is difficult to isolate and implicate causality in the setting of a "noisy" background.

The Applicant's conclusion that during the initial treatment with Omegaven, there may be a lower risk of death than in HC patients who received the soybean oil-based lipid comparator, seems reasonable. However, there was no long-term safety information following end of treatment, and mortality beyond the parenteral nutrition treatment period (i.e., EOETP) was not assessed, which is a significant limitation.

8.2.4.2 Serious Adverse Events

Serious adverse events that were more common in the Omegaven group than in the HC group included Bradycardia, Apnea, Temperature Instability, and psychiatric disorders (). Overall, 154 (81%) Omegaven-treated patients and 60 (82%) HC patients had treatment emergent serious adverse events, and more serious adverse events occurred in the HC arm than in the Omegaven arm.

Table 27. Summary of Treatment-Emergent Serious Adverse Events Occurring in at Least 2% patients in Any Pooled Group - All Patients

	Historical Control (n=73)	Omegaven (n=189)
Infections and infestations	**49 (67%)**	**102 (54%)**
Bacterial Infection	29 (40%)	65 (34%)
Sepsis	31 (42%)	63 (33%)
Infection NOS	22 (30%)	56 (30%)
Viral Infection	2 (3%)	11 (6%)
Fungal Infection	7 (10%)	6 (3%)
Respiratory, thoracic and mediastinal disorders	**32 (44%)**	**72 (38%)**
Dependence on respirator	13 (18%)	34 (18%)
Respiratory failure	11 (15%)	25 (13%)
Apnea	6 (8%)	20 (11%)
Chronic Lung Disease	2 (3%)	7 (4%)
Pneumothorax	5 (7%)	5 (3%)
Respiratory Distress	7 (10%)	5 (3%)
Pulmonary oedema	4 (5%)	3 (2%)
Gastrointestinal disorders	**34 (47%)**	**66 (35%)**
Vomiting	6 (8%)	13 (7%)
Diarrhoea	4 (5%)	9 (5%)
Intestinal perforation	3 (4%)	7 (4%)
Haematochezia	4 (5%)	6 (3%)
Gastrointestinal haemorrhage	3 (4%)	5 (3%)
Abdominal distension	2 (3%)	5 (3%)
Short-bowel syndrome	3 (4%)	4 (2%)
Necrotising colitis	8 (11%)	3 (2%)
Abdominal compartment syndrome	4 (5%)	3 (2%)
Metabolism and nutrition disorders	**24 (33%)**	**46 (24%)**
Hypokalaemia	5 (7%)	13 (7%)
Feeding intolerance	9 (12%)	12 (6%)
Dehydration	5 (7%)	8 (4%)
Electrolyte imbalance	4 (5%)	5 (3%)
Hypoglycemia	3 (4%)	5 (3%)
Acidosis	2 (3%)	5 (3%)
Hyperkalaemia	5 (7%)	4 (2%)

General disorders and administration site conditions	**12 (16%)**	**37 (20%)**
Temperature Instability	3 (4%)	17 (9%)
Multiorgan Failure	1 (1%)	10 (5%)
Blood and lymphatic system disorders	**21 (29%)**	**35 (19%)**
Anaemia	12 (16%)	18 (10%)
Thrombocytopenia	9 (12%)	14 (7%)
Coagulopathy	5 (7%)	7 (4%)
Cardiac disorders	**14 (19%)**	**33 (17%)**
Bradycardia	9 (12%)	24 (13%)
Cardiac Arrest	4 (5%)	7 (4%)
Investigations	**14 (19%)**	**21 (11%)**
Oxygen saturation decreased	8 (11%)	12 (6%)
Bacterial Infection	6 (8%)	4 (2%)
Injury, poisoning and procedural complications	**14 (19%)**	**17 (9%)**
Stoma complication	3 (4%)	6 (3%)
Product issues	**8 (11%)**	**16 (8%)**
Device complications	8 (11%)	16 (8%)
Renal and urinary disorders	**17 (23%)**	**16 (8%)**
Acute kidney injury	5 (7%)	7 (4%)
Renal failure	4 (5%)	7 (4%)
Nervous system disorders	**7 (10%)**	**15 (8%)**
Vascular disorders	**18 (25%)**	**15 (8%)**
Hypotension	10 (14%)	5 (3%)
Hepatobiliary disorders	**16 (22%)**	**14 (7%)**
Hepatic failure	12 (16%)	6 (3%)
Eye disorders	**2 (3%)**	**8 (4%)**
Retinopathy of prematurity	1 (1%)	6 (3%)
Psychiatric disorders	**2 (3%)**	**7 (4%)**

Source: S. Seo, ADAE.xpt

No specific safety signals were identified for Omegaven. The serious adverse events with higher incidence in the Omegaven-treated patients were consistent with underlying prematurity. Although numbers are small, the multiorgan failure rate in the treatment arm, was higher than the HC arm. Consistent with the SAE profile, the rate was the highest in the exclusive Omegaven group (Table 28).

Table 28. Multiorgan Failure Rates by Lipid Emulsion Exposure, Integrated Safety Population

	Historical Control N=73		Omegaven N=189	
Total	2 (3)		11 (6)	
Enteral Lipid Dose Subgroups				
0 g/kg/day	(n=3)	0	(n=30)	3 (10%)
< 1g/kg/day	(n=32)	2 (6%)	(n=71)	5 (7%)
1 - <3g/kg/day	(n=28)	0	(n=69)	3 (4%)
≥ 3g/kg/day	(n=9)	0	(n=8)	0

Source: S. Seo

Multiorgan failure is a nonspecific term indicating concurrent multiple organ dysfunctions and systemic illness. While it may be implausible to specifically implicate Omegaven (or any single agent) as a causative agent, especially in this group of patients with underlying critical illness, because multiorgan failure indicates a constellation of organ dysfunctions worsening to organ failure, it is not possible to fully agree with the Applicant's views that Omegaven has made no contributions. Of note, the analysis and specific causality assessment is confounded by the fact that Omegaven-treated patients were more premature with higher liver indices at baseline.

8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

The TEAEs that led to permanent discontinuation of study drug administration in the 3 (2%) Omegaven-treated patients (coagulopathy, intestinal hemorrhage, device related infection, and Staphylococcal infection) were severe in intensity. The 3 (4%) HC patients had hepatic failure and *Escherichia coli* urinary tract infection. The HC patients who discontinued reported more AEs than the Omegaven patients who discontinued.

Table 29. Adverse Events Leading to Discontinuation, by System Organ Class

	Historical Control (n=73)	Omegaven (n=189)
Patients with at least 1 AE leading to discontinuation	**3(4)**	**3(2)**
Infections and infestations	**1 (1)**	**1 (<1)**
Bacterial Infection	1 (1)	1 (<1)
Infection NOS	0	1 (<1)
Blood and lymphatic system disorders	**1 (1)**	**1 (<1)**
Coagulopathy	0	1 (<1)
Iron deficiency anaemia	1 (1)	0
Gastrointestinal disorders	**1 (1)**	**1 (<1)**
Anorectal disorder	1 (1)	0
Intestinal haemorrhage	0	1 (<1)
General disorders and administration site conditions	**2 (3)**	**0**
Temperature Instability	2 (3)	0
Cardiac disorders	**1 (1)**	**0**
Tachycardia	1 (1)	0
Hepatobiliary disorders	**1 (1)**	**0**
Hepatic failure	1 (1)	0
Investigations	**1 (1)**	**0**
Bacterial Infection	1 (1)	0
Liver palpable	1 (1)	0
Metabolism and nutrition disorders	**1 (1)**	**0**
Breast milk substitute intolerance	1 (1)	0
Dehydration	1 (1)	0
Hypernatraemia	1 (1)	0
Weight gain poor	1 (1)	0
Renal and urinary disorders	**1 (1)**	**0**
Hydronephrosis	1 (1)	0
Respiratory, thoracic and mediastinal disorders	**1 (1)**	**0**
Cough	1 (1)	0
Pulmonary congestion	1 (1)	0

Source: S. Seo (ADAE.xpt. ISSSAFFL.TRTEMFL.AEACN.)

8.2.4.4 Significant Adverse Events

The following adverse events of special interest (AESIs) were investigated by the Applicant: TEAEs in the SOCs of Infections and Infestations and Metabolism and Nutrition Disorders; TEAEs associated with catheter-site reactions; TEAEs potentially associated with anemia and bleeding disorders, allergic/anaphylactic reactions to study drug, or fever; and TEAEs of

chills and tremor. Proportionally more HC patients than Omegaven-treated patients experienced events in each of the AESI categories, except for events potentially associated with allergic/anaphylactic reactions to study drug (e.g., allergy to chemical).

AEs that meet the ICH E3 guidance criteria of significant AEs (i.e., ≥ Grade 3 by CTCAE that do not meet the definition of a serious AE), shown in Table 46, are similar to those associated with SAEs (Section 8.2.4.2) and TEAEs (Section 8.2.4.5). Bacterial infection, cellulitis, and stoma complication rates, which are conditions not uncommon to the population with the underlying comorbities of prematurity, PNAC and intestinal failure, were higher in the Omegaven-treated group.

8.2.4.5 Treatment Emergent Adverse Events and Adverse Reactions

Table 30. Common Adverse Events (≥20%), Safety Population

	Historical Control (n=73)	Omegaven (n=189)
Bacterial Infection	40 (55)	104 (55)
Vomiting	32 (44)	87 (46)
Infection NOS	38 (52)	81 (43)
Temperature Instability	39 (53)	76 (40)
Agitation	25 (34)	67 (35)
Respiratory failure	31 (42)	66 (35)
Bradycardia	24 (33)	66 (35)
Sepsis	34 (47)	64 (34)
Abdominal distension	28 (38)	46 (24)
Dependence on respirator	23 (32)	45 (24)
Stoma complication	18 (25)	44 (23)
Fungal Infection	21 (29)	42 (22)
Tachycardia	21 (29)	41 (22)
Acidosis	28 (38)	38 (20)
Diarrhoea	23 (32)	38 (20)
Apnea	14 (19)	38 (20)
Hypotension	22 (30)	37 (20)

Source: S. Seo
Preferred terms are sorted by descending order of incidence for the Omegaven-treated group.

Due to the imbalance in concurrent enteral nutrition and the potential for this to confound safety analyses, it is important to explore adverse events stratified by concurrent enteral lipid doses (Table 31). Among patients who were on exclusive parenteral source of lipids, overall, HC patients had more adverse events than the Omegaven-treated patients, but the numbers were few (n=3) in the HC group.

Table 31. Adverse Events (≥10%) by Concurrent Enteral Nutrition, System Organ Class

	Exclusive PN Lipids		Concurrent Enteral Lipids	
	Historical Control (n=3)	Omegaven (n=30)	Historical Control (n=69)	Omegaven (n=148)
Patients with at least 1 event, N (%)	3 (100)	30 (100)	67 (97)	147 (99)
Gastrointestinal disorders	2 (67)	21 (70)	56 (84)	126 (86)
Respiratory, thoracic and mediastinal disorders	2 (67)	23 (77)	57 (85)	113 (77)
Infections and infestations	3 (100)	24 (80)	55 (82)	106 (72)
Metabolism and nutrition disorders	3 (100)	19 (63)	55 (82)	93 (63)
Investigations	3 (100)	22 (73)	51 (76)	89 (61)
General disorders and admin site conditions	3 (100)	21 (70)	54 (81)	90 (61)
Cardiac disorders	1 (33)	20 (67)	43 (64)	78 (53)
Psychiatric disorders	1 (33)	17 (57)	32 (48)	73 (50)
Skin and subcutaneous tissue disorders	1 (33)	12 (40)	34 (51)	68 (46)
Blood and lymphatic system disorders	2 (67)	14 (47)	43 (64)	59 (40)
Injury, poisoning and procedural complications	3 (100)	12 (40)	34 (51)	61 (41)
Vascular disorders	1 (33)	13 (43)	38 (57)	59 (40)
Hepatobiliary disorders	3 (100)	13 (43)	44 (66)	42 (29)
Eye disorders	1 (33)	7 (23)	24 (36)	48 (33)
Renal and urinary disorders	2 (67)	8 (27)	30 (45)	44 (30)
Nervous system disorders	2 (67)	9 (30)	31 (46)	42 (29)
Congenital, familial and genetic disorders	1 (33)	5 (17)	18 (27)	41 (28)
Musculoskeletal and connective tissue disorders	1 (33)	3 (10)	17 (25)	16 (11)
Product issues	1 (33)	2 (7)	13 (19)	16 (11)
Reproductive system and breast disorders	0	3 (10)	9 (13)	11 (7)
Endocrine disorders	0	3 (10)	8 (12)	3 (2)

Source: S. Seo, ADAE.xpt
System organ classes are sorted by descending order of overall incidence. Patients are counted only once within each system organ class category.

More TEAEs were reported in the exclusive PN lipids groups for both the HC and Omegaven group, likely because inability to tolerate enteral feed correlates with severity of comorbid conditions. SOCs where Omegaven had a higher incidence than historical controls in both subgroups were gastrointestinal disorders and psychiatric disorders. SOCs where the exclusive Omegaven lipid source patients had a higher incidence of AEs were respiratory, thoracic and mediastinal disorders, cardiac disorders, skin and subcutaneous tissue disorders, and vascular disorders.

The concurrent enteral lipid group was further classified as < 1g/kg/day, 1-3 g/kg/day, and > 3g/kg/day. This subgroup analysis of TEAEs revealed no notable difference, and there were no specific enteral lipid dose dependent safety signals.

8.2.4.6 Laboratory Findings

Overall, improvements in hepatic function parameters were observed in Omegaven-treated patients compared to HC patients. This is reviewed in detail in conjunction with discussion of the composite liver safety endpoint in Section 8.2.5.1 Parenteral Nutrition Associated Cholestasis.

Due to the limitations of the clinical trial design, while the favorable safety profile for Omegaven-treated patient is reassuring, it is impossible to distinguish whether the safety benefits are due to the product (i.e., decreased omega-6), due to the absence of hepatotoxic ingredients (i.e., phytosterol), due to transition to enteral feeds, or a combination of these factors.

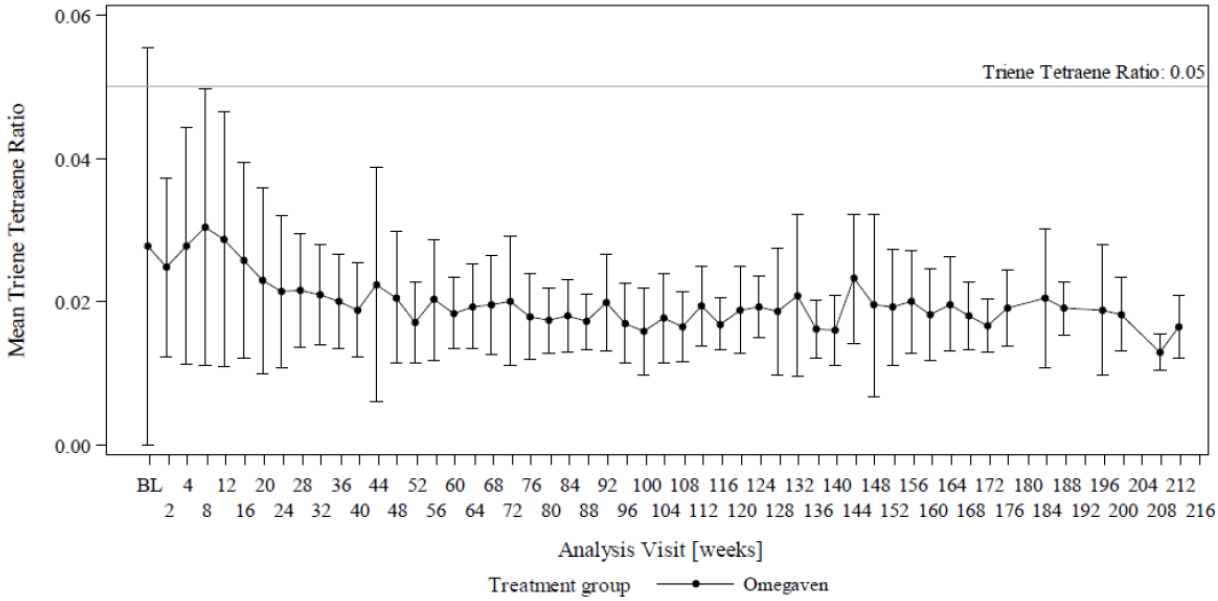
Other notable findings include no evidence of hyperglycemia despite the Omegaven-treated patients receiving a higher percentage of calories from the Dextrose component of TPN due to the lower parenteral lipid dose. Hematology parameters showed no evidence of coagulopathies with stable platelets, international normalized ratio, activated partial thromboplastin time, and fibrinogen levels. Albumin and prealbumin levels remained stable and more favorable when compared to historical controls. Mean triglyceride values showed a decrease over time for Omegaven-treated patients, with more stable levels during treatment compared to the HC patients throughout the available observation period.

There was a paucity of data available for other lipid metabolism parameters (i.e., total, HDL, LDL, and VLDL cholesterol), which is a significant limitation. Given the small sample size, especially for HC patients, a comparative analysis is limited.

Overall, the changes in fatty acid parameters, obtained from Omegaven-treated patients from BCH (n = 127) over time reflected the fatty acid compositions of the lipid emulsions administered (See Section 6, Figure 2).

The mean triene:tetraene (T:T) ratio was only evaluated in Omegaven-treated patients in the study conducted at BCH (Figure 13). The mean values displayed include no less than 6 patients and may include a maximum of 53 patients. It was a random sampling, sometimes with co-administration of lipid infusion and concurrent enteral nutrition. The mean T:T ratio remained stable from 0.021 at baseline to 0.023 at EOITP, 0.018 at EOETP and 0.02 at EOS. The T:T ratios over time showed a downward trend until week 40, after which point most mean T:T ratios were ≤0.02. See further discussion of T:T ratios and risk of EFAD in Section 8.2.5.2.

Figure 13. Mean T:T Ratio Over Time, Omegaven-Treated Patients in the Safety Population of the Boston Study



Only time points with at least 6 patients with nonmissing data are displayed. Plot shows arithmetic mean values ± 1 standard deviation. BL=Baseline
Source: ISS Figure 22

There were 41 (30%[55]) patients who had at least one abnormal T:T ratio of >0.05 during the study, irrespective of the major analysis timepoints. Overall those patients who had abnormal T:T ratios were those who did not advance in enteral feeds (0 to <1g/kg/day enteral lipid dose), and those who had concurrent co-morbidities or TEAEs. Individual patients with abnormal T:T ratios are discussed in Section 8.2.5.2.

The lack of fatty acid profile information from the HC arm is a significant deficiency of this submission. While the overall mean T:T ratios remained below biochemical EFAD range, 30% of the patients experienced at least one abnormal T:T ratio during the study, of which clinical significance is yet unknown without long-term developmental assessments. Moreover, the appropriateness of T:T ratio for identification of biochemical EFAD is an open question. (see Section 8.2.5.2).

8.2.4.7 Vital Signs

Vital signs and physical examination findings were not reported. The incidence of TEAEs associated with abnormal vital sign measurements (i.e., pulse rate, respiratory rate, blood pressure, body temperature) were higher in the HC patients overall. The incidence of

[55] 41 of 140 who had T:T ratios available from BCH. The Applicant has reported an incidence rate of abnormal T:T ratio at baseline (8.1%), EOITP (6.4%), EOETP (6%) and EOS (7.1%) which did not account for 22 additional patients with abnormal T:T ratio outside of these specific analysis time points.

bradycardia and apnea were higher in the Omegaven-treated patients.

The failure to capture and report frequent vital sign data is a notable deficiency in the setting of intravenous continuous administration of an investigational parenteral product in the hemodynamically volatile neonatal population. This deficiency in the application precluded an investigation of patterns of vital sign changes during and post-infusion for hemodynamic instability. Apnea and bradycardia events are related more to the degree of prematurity; and while not an unexpected finding for the study population, increased apneas and bradycardias in preterm infants can be loosely correlated with general wellness of the infant. Continuous monitoring should have been performed during administration, and further characterization of the frequency and temporal relationship to the A/B would have been informative.

Neonates and infants <6 months of age, due to immaturity of their immunoglobulin E (IgE)-mediated immunity are likely not able to mount a true type 1 allergic anaphylactic reaction. Rare case reports of severe neonatal anaphylaxis have been reported in the literature[56] due to exposure to antimicrobials, hepatitis B immunoglobulins, vitamin K, and cow's milk based formula; however, the common presenting clinical signs were dermatologic (e.g., urticaria, erythematous rash) and less often with the typical signs consistent with hypersensitivity and/or anaphylaxis (i.e., hypotension, tachycardia, and tachypnea).

8.2.4.8 Electrocardiograms (ECGs)

There was no ECG monitoring performed systematically. A review of preferred terms reported as TEAEs showed a higher incidence of "Arrhythmia[57]" in the HC group (n=7, 10%) compared to the Omegaven-treated patients (n=4, 2%).

8.2.4.9 QT

No dedicated QT study was performed. In general, lipid emulsions are not associated with QT prolongation. Thorough QT studies generally are not required for these clinical development programs.

8.2.4.10 Immunogenicity

Specific immunogenicity was not assessed.

8.2.5. Analysis of Submission-Specific Safety Issues

[56] Handan H T, Nilgun K, Selahattin A, Tulin G Y, Elif O,et al. Meropenem Induced Anaphylactic Shock in a Newborn and Review Of Literature. Acad J Ped Neonatol. 2016; 2(2): 555582.
[57] Regrouped preferred term included all of the following: Arrhythmia, Atrial Flutter, Extrasystoles, Ventricular Extrasystoles, Ventricular Tachycardia, Sinus Arrhythmia, Supraventricular Tachycardia, Ventricular Arrhythmia

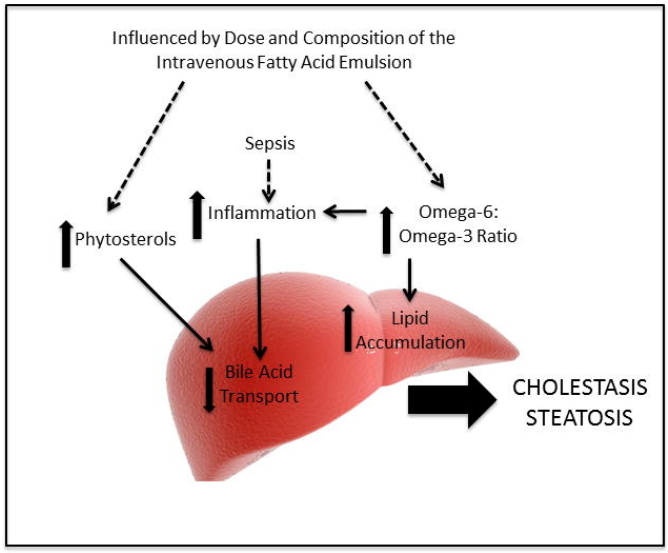
8.2.5.1 Parenteral Nutrition Associated Cholestasis

As discussed in Section 3, Omegaven development began with an investigator initiated expanded access program for treatment of PNAC/PNALD in 2005. However, after unsuccessful attempts to conduct adequately controlled trials to evaluate Omegaven to treat or prevent PNAC, FDA recommended that the Applicant propose a nutritional indication for patients with PNAC where the hepatotoxicity of the product would be evaluated as a safety endpoint.

PNAC is discussed in detail in Section 2. Specifically, there have been widely published theories on the pathogenesis of PNALD (Figure 14), which serve as the basis of the proposed potential mechanism of therapeutic benefit of Omegaven. First, phytosterols (e.g., campesterol, stimgasterol, and sitosterol) are found in plant-based foods and are known to interfere with bile acid transport, resulting in biliary sludge; and because the composition of Omegaven contains no phytosterols, Omegaven has the potential to prevent or reverse PNAC. Second, bile acid transport is regulated by inflammation, and fatty acids can modulate inflammation (i.e., omega-6 fatty acids can produce a cascade of proinflammatory pathways); and because Omegaven contains mainly omega-3 fatty acids, it has the potential to decrease inflammatory mediators and reduce the cholestasis. However, lipid sparing strategies which decrease soybean oil-based lipid alone have also shown to modify the incidence and progression of PNALD.[58,59,60]

[58] Cober MP, Killu G, Brattain A, Welch KB, Kunisaki SM, Teitelbaum DH. Intravenous fat emulsions reduction for patients with parenteral nutrition-associated liver disease. The Journal of pediatrics. 2012;160(3):421-7.
[59] Rollins MD, Ward RM, Jackson WD, Mulroy CW, Spencer CP, Ying J, et al. Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for parenteral nutrition-associated liver disease: a pilot study. Journal of pediatric surgery. 2013;48(6):1348-56.
[60] Sanchez SE, Braun LP, Mercer LD, Sherrill M, Stevens J, Javid PJ. The effect of lipid restriction on the prevention of parenteral nutrition-associated cholestasis in surgical infants. Journal of pediatric surgery. 2013;48(3):573-8.

Figure 14. Proposed etiology of PNALD



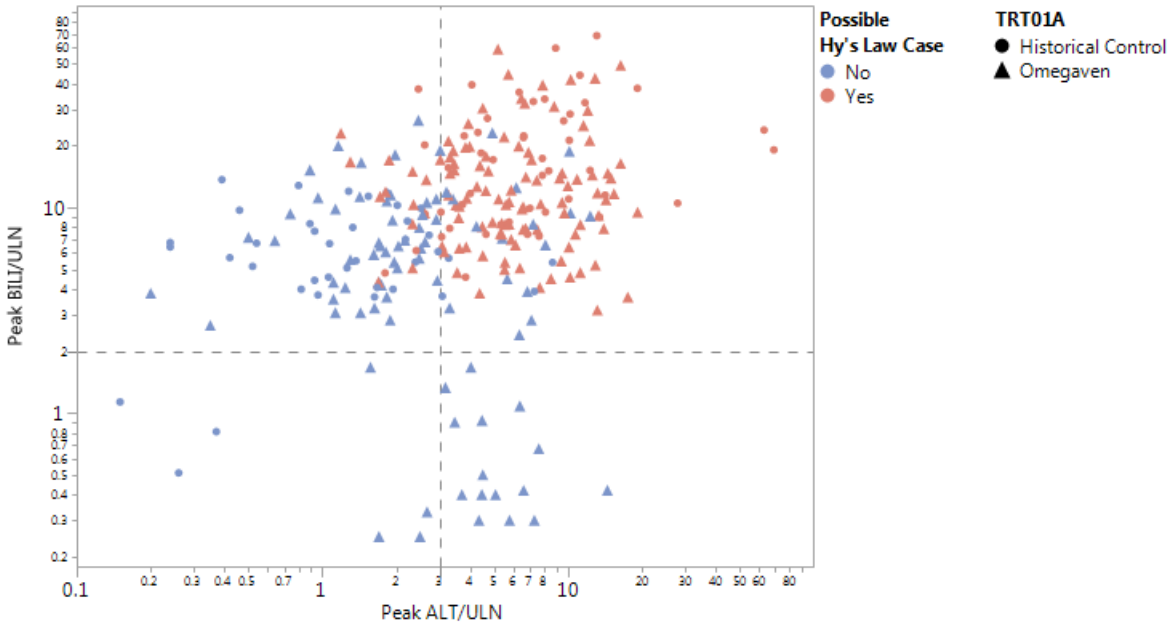
Source: Calkins K et al. *Clinics in perinatology*. 2014;41(2):331-345.

While the Applicant asserts that PNAC, PNALD or IFALD are interchangeable terms, it is important to note that a liver biopsy is required to definitively diagnose the *disease*. Because most physicians will not consider an invasive procedure in the target population, in the absence of liver biopsies, alternative definitions have been developed, based on serum levels of conjugated or direct bilirubin (DBil). PNAC has been considered the preferred term in the absence of a liver biopsy, since a disorder with elevated Dbil is ipso facto "cholestasis" unless there is also a biopsy to document disease. The public consensus on the definition of PNAC was developed at the 2012 FDA Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) workshop, to define PNAC by Dbil level ≥ 2 mg/dL in the absence of other liver disorders in patients with a need for PN for > 2 weeks. Resolution was defined by the return of the Dbil level to < 2 mg/dL.

It is well recognized that histological injury begins soon after PN initiation and may not always correlate with bilirubin concentrations. There has been published evidence that despite normalization of the bilirubin, and hence resolution of cholestasis, there can be progression of severe histological damage.[61] Therefore, in lieu of histological assessments, in addition to the individual liver function tests, a composite liver safety endpoint (DBil <2 mg/dL, [resolution of PNAC] and AST or ALT < 3 x ULN) was evaluated.

[61] Fitzgibbons SC, Jones BA, Hull MA, Zurakowski D, Duro D, Duggan C, et al. Relationship between biopsy-proven parenteralnutrition-associated liver fibrosis and biochemical cholestasis in children with short bowel syndrome. Journal of pediatric surgery. 2010;45(1):95-9; discussion 9.

Figure 15. Hy's Law Plot – Integrated Safety Population



Source: JMP Clinical 6.0. Possible Hy's Law Cases are flagged if ALT or AST >= 3*ULN and BILI >= 2*ULN within 0 Days of ALT/AST peak.

The majority of the patients in the integrated safety population began in the Hy's law quadrant, indicated by the red color in Figure 15, top right panel. The shift table (Table 32) shows that a higher proportion of Omegaven-treated patients than HC patients who achieved the composite liver safety endpoint of Dbil < 2 mg/dL and decrease in AST or ALT to < 3 x ULN at the end of the initial treatment period and at the end of study, regardless of baseline AST or ALT elevation.

Table 32. Number of Patients Who Achieved the Composite Endpoint by ALT and/or AST Elevation at Baseline, Integrated Safety Population

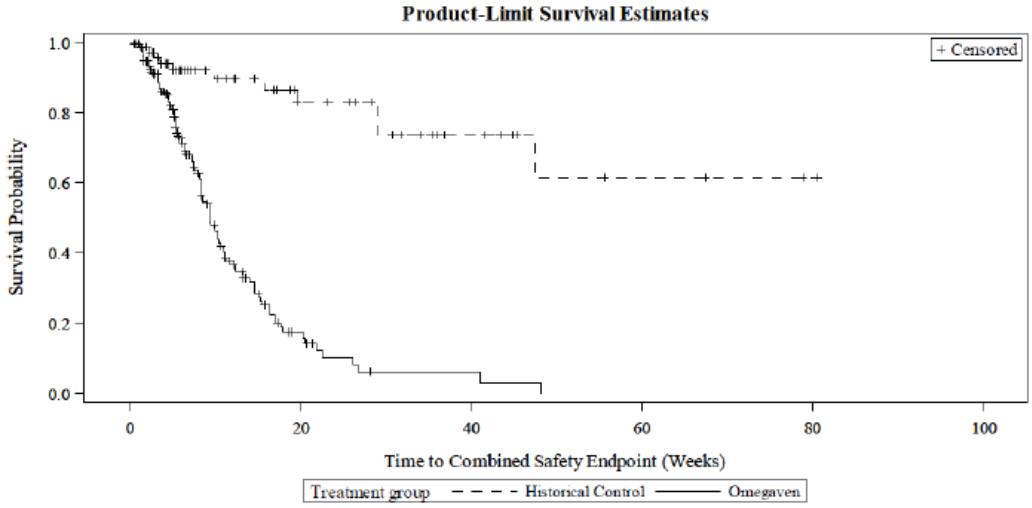
	No Elevation		Any Elevation	
	Historical Control (n=36)	Omegaven (n=99)	Historical Control (n=10)	Omegaven (n=71)
End of Initial Treatment Period	2/36 (6%)	50/99 (51%)	2/10 (20%)	28/71 (40%)
End of Extended Treatment Period	4/4 (100%)	61/65 (94%)	1/1 (100%)	42/43 (98%)
End of Study	4/36 (11%)	61/99 (62%)	3/10 (30%)	43/71 (61%)

ALT=alanine aminotransferase; AST=aspartate aminotransferase
Source: Integrated Summary of Safety

Kaplan-Meier estimates (which censored patients who died or otherwise discontinued the studies prior to achieving the composite liver safety endpoint) indicated that all Omegaven-treated patients would achieve the composite liver safety endpoint by approximately 52 weeks of treatment; at the same time point, the likelihood of a HC patient achieving the composite liver safety endpoint was 39% (Figure 16). In the time-to-event analysis, the estimated median time to achieving the composite liver safety endpoint was 9.3 weeks (95% CI: 8.3, 10.9) for

Omegaven-treated patients, whereas for HC patients, the median time to achieving the composite liver safety endpoint was not reached within the 80-week observation period.

Figure 16. Kaplan-Meier Plots of Time to Achievement of the Composite Endpoint, Integrated Safety Population



Source: Integrated Summary of Safety, Figure 10.8.1.9i

As cholestasis is a surrogate for PNALD, ultimately death (Section 8.2.4.1) or liver transplantation is the clinical outcome of interest in patients with PNALD (Table 33). A total of 28 patients included in the database for the integrated safety analyses were listed for transplant[62], 12 (6%) Omegaven-treated patients and 16 (22%) HC patients. Of these patients, a total of 20 received a transplant[63], 9 (5%) Omegaven-treated patients and 11(15%) HC patients. Of the 8 patients who were listed but were not transplanted, the condition of 3 Omegaven-treated patients (from BCH) improved, to preclude the need for a liver transplant. The median PELD[64] score was higher for Omegaven-treated patients (29, range 8 - 36) as compared to HC patients (18.5, range 5 to 31). All liver transplantations occurred during the initial treatment period except for one that occurred during the extended treatment period in an Omegaven-treated patient.

The Applicant's analysis using the efficacy pair-matched population inflated the results showing a 0% transplant rate in the Omegaven-treated patients vs. 9/41 (22%) HC patients. In the PP population, the liver transplant rate was 6/151 (4%) in the Omegaven group vs. 9/64 (14%) in the HC patients, similar to the rates seen in the safety population. Nonetheless, there was a

[62] 15 patients (10 Omegaven; 5 HC) from BCH, 2 patients (2 Omegaven) from TCH, and 11 HC patients from UCLA
[63] 11 patients from BCH (7 Omegaven, 4 HC), 2 patients from TCH (2 Omegaven), and 7 HC patients from UCLA
[64] PELD score may not necessarily be clinically applicable to SBS patients who often need multivisceral transplant vs. isolated liver transplant, since the PELD score only considers liver function parameters, the patient's true clinical condition would not be reflected. [Shneider BL, Suchy FJ, Emre S. National and regional analysis of exceptions to the pediatric end-stage liver disease scoring system (2003-2004). Liver Transpl. 2006;12(1):40-5.]

lower rate of liver transplantation in the Omegaven-treated patients as compared to the HC patients.

Table 33. Patients Listed for Liver Transplant, Integrated Safety Population

Patient ID	Trial Site	Treatment Group	Trial Start Date	Date Listed	PELD score at listing	Outcome / Date	
	(b) (6)	Omegaven		(b) (6)	21	Improved- no transplant needed	(b) (6)
		Omegaven			32	Transplantation	
		Omegaven				Improved- no transplant needed	
		Omegaven			17	Transplantation	
		Omegaven			21	Transplantation	
		Omegaven			33	Transplantation	
		Omegaven			36	Transplantation	
		Omegaven			29	Improved- no transplant needed	
		Omegaven			30	Transplantation	
		Omegaven			34	Transplantation	
		Omegaven				Transplantation	
		Omegaven			8	Transplantation	
		HC			27	Death: Overwhelming Sepsis	
		HC			17	Transplantation	
		HC			21	Transplantation	
		HC			19	Transplantation	
		HC				Transplantation	
		HC				unknown	
		HC			19	Transplantation	
		HC			28	Transplantation	
		HC			16	Transplantation	
		HC			12	Transplantation	
		HC			17	Transplantation	
		HC			21	Death: End-Stage Liver Disease; Septic Shock	
		HC			10	Transplantation	
		HC			31	Death: Cardiorespiratory Failure	
		HC			18	Transplantation	
		HC			5	ROPNAC 7/2/2007 Death: gastroschisis, respiraotry distress 2/8/2008	

BCH=Boston Children's Hospital; TCH= Texas Children's Hospital; UCLA=University of California at Los Angeles; HC=historical control; PELD=Pediatric End-Stage Liver Disease; ROPNAC=Resolution of PNAC
Source: S.Seo Adapted from Applicant's Response to MCC IR Response 4/16/201

Summary

Several potential mechanisms of action for ROPNAC with Omegaven lipid infusion have been postulated and widely published in the literature, ranging from the lack of the phytosterol

component of soybean oil-based lipid emulsion to reduced omega-6 fatty acid ratio in Omegaven. It is important to note that while the hepatic safety profile favors Omegaven, given that the pivotal non-randomized historically controlled study was not powered and analyzed with the hepatic safety outcomes as prespecified endpoints, these results were considered hypothesis-generating.

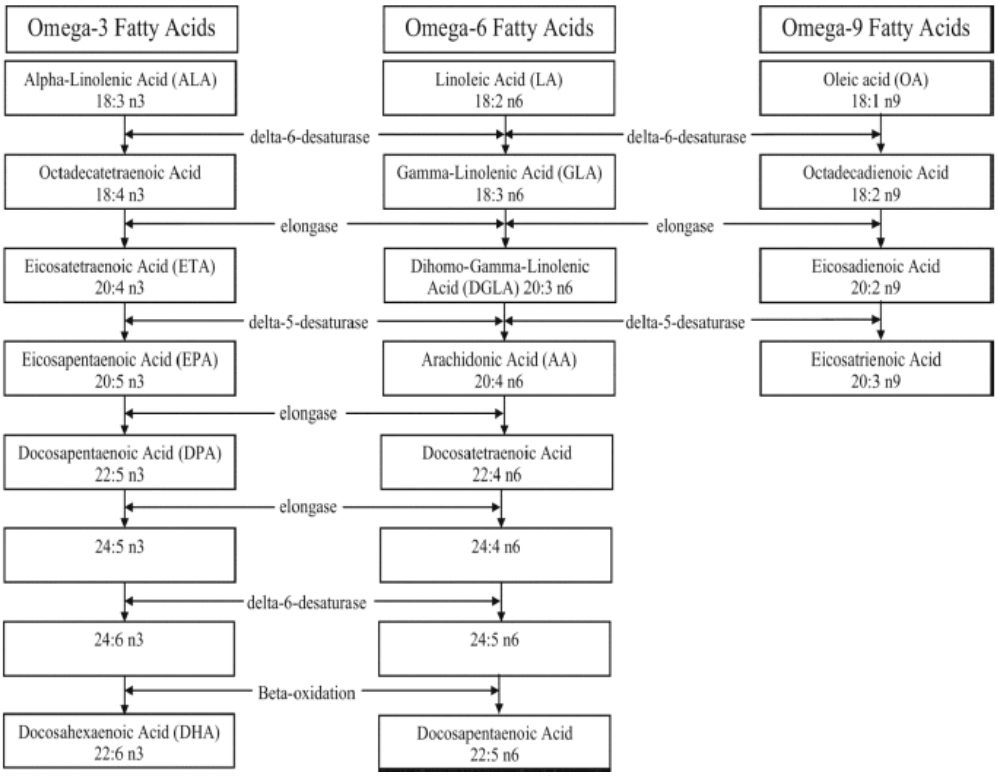
Due to trial design limitations, it is impossible to distinguish whether the safety benefits are due to the product (i.e., decreased omega-6), due to the absence of a hepatotoxic ingredient (i.e., phytosterol), due to transition to enteral feeds, or a combination of factors; and therefore, the indication of "treatment" or "prevention" of PNAC cannot be granted. However, as a source of nutrition for patients with PNAC, the lower hepatotoxicity potential of this product as compared to treatment received by the HC cohort is considered highly favorable from a safety perspective.

8.2.5.2 Essential Fatty Acid Deficiency

Only two specific fatty acids are generally considered to be "essential": alpha linolenic acid (ALA) and linoleic acid (LA). They are both long chain (18-carbon) polyunsaturated fatty acids (LCPUFA) that cannot be synthesized by mammals. ALA is the precursor of the n-3 family of PUFA, in which the first double bond in the molecule is 3 carbons away from the methyl terminus. LA is the precursor of the n-6 PUFA family, in which the first double bond in the molecule is 6 carbons from the methyl terminus. ALA and LA are converted to longer chain, more highly unsaturated fatty acids through enzymatic chain elongation and desaturation (Figure 17).

The downstream metabolites of ALA, i.e., eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), are critical components of cell membranes; and LA is converted to arachidonic acid (ARA) which is both a membrane component and a precursor to potent signaling molecules, i.e., the prostaglandins and leukotrienes. Because these PUFAs are structural components of the highly specialized lipid membranes of the human central nervous system, especially critical to cerebral and retinal development, as well as the immune system, they are particularly important for neonates. Inadequate provision of ALA and LA leads to omega-3 and omega-6 PUFA deficiencies, also referred to as EFAD.

Figure 17. Metabolic Pathway of Polyunsaturated Fatty Acids in Humans



Source: Sponsor submission - Clinical Overview Pg.21[65]

To prevent fatty acid deficiency, the 2008 joint Food and Agriculture Organization of the United Nations (FAO)/ World Health Organization (WHO) recommended dietary intakes of the essential FA as shown in Table 34. Human milk is typically used as a model to define acceptable intakes for fats and fatty acids in early life for normal infants; however, due to the variations seen in the LCPUFA composition of human milk, the absolute amount of lipid intake of specific PUFAs is not known,[66] and direct translation to optimal parenteral requirements is limited.

[65] Vanek VW, Seidner DL, Allen P, Bistrian B, Collier S, Gura K, Miles JM, Valentine CJ, Kochevar M, Novel Nutrient Task Force IFEW, American Society for P, Enteral Nutrition Board of D. A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. Nutr Clin Pract. 2012;27(2):150-92.
[66] Stam J, Sauer PJ, Boehm G. Can we define an infant's need from the composition of human milk? The American journal of clinical nutrition. 2013;98(2):521s-8s.

Table 34. Recommended dietary intakes for fatty acid in infants and children

Fats / FA	Age Group	Measure	Numeric Amount	Level of Evidence[c]
n-6 PUFA				
LA	0-6 mo	AI:	HM composition as %E of total fat	Convincing
	6-12 mo	AI:	3 - 4.5%E	Convincing
	6-12 mo	U-AMDR:	<10%E	Probable
	12-24 mo	AI:	3 - 4.5%E	Convincing
	12-24 mo	U-AMDR:	<10%E	Probable
AA	0-6 mo	AI:	0.2-0.3%E[a]	Convincing
n-3 PUFA				
ALA	0-6 mo	AI:	0.2-0.3%E[a]	Convincing
	6-12 mo	AI:	0.4-0.6%E	Probable
	6-12 mo	U-AMDR:	<3%E	Probable
	12-24 mo	AI:	0.4-0.6%E	Probable
	12-24 mo	U-AMDR:	<3%E	Probable
DHA	0-6 mo	AI:	0.1-0.18%E[a]	Convincing
	0-6 mo	U-AMDR:	<0.75%E[b]	Convincing
	6-12 mo	AI:	10-12 mg/kg	Probable
	12-24 mo	AI:	10-12 mg/kg	Probable
EPA + DHA	2-4 yr	AI:	100 - 150 mg	Probable
	4-6 yr	AI:	150 - 200 mg	Probable
	6-10 yr	AI:	200 - 250 mg	Probable

FA= fatty acid, LA=linoleic acid, AA=arachidonic acid, ALA=alpha-linolenic acid, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, HM=human milk, AI=adequate intake, %E= percent of energy, U-AMDR=upper level of acceptable macronutrient distribution range.

[a] The amounts are expressed as %E in order to be consistent with the other values in the table. However, based on human milk composition, the amounts for AA and ALA would be expressed as 0.4-0.6%FA and for DHA as 0.2-0.36%FA. This conversion assumes that half of the energy in human milk comes from fat.

[b] There is no upper value within the human milk composition.

[c] Four levels of evidence identified and ranked as Convincing, Probable, Possible, Insufficient

To prevent EFAD, an intake of LA is recommended at 4-5% of total calories, and ALA at 1% of total calories.

Source: Adapted from Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition (10-14 November 2008, WHO, Geneva) http://www.who.int/nutrition/topics/FFA_interim_recommendations/en/

Preterm infants, particularly infants with short bowel syndrome (SBS) with decreased fat stores, and with insignificant oral / enteral nutrient absorption and low parenteral lipid intake are at high risk for EFAD. ELBW infants are particularly vulnerable to insufficient lipid supply because significant in utero fat accretion does not occur until the third trimester.[67] Specific EFA requirements for preterm infants with IFALD / PNAC who remain dependent on parenteral nutrition are not known at this time.

Clinical EFAD

[67] Brunzell JD, Hazzard WR, Porte D, Jr, Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. J Clin Invest. 1973;52:1578–85.

EFAD in adults leads to a recognizable EFAD syndrome of which dermatological manifestations are the most prominent. The adult form is easily reversible; however, EFAD in infants may have more far-reaching and possibly permanent consequences for neurological development.[68] EFAD may be present at birth in premature infants, but most commonly develops over a 72-hour period of deprivation. The clinically apparent manifestations of fatty acid deficiency in premature infants are mainly due to omega-6 fatty acid deficiency (i.e., scaly dermatomes, inflamed skin, decreased skin pigmentation, poor wound healing, decreased growth, hepatic steatosis, hematologic disturbances [see Section 8.2.5.3 Bleeding / Coagulopathy], and diminished immune system status or increased susceptibility to infections) because signs of omega-3 fatty acid deficiency (i.e., reduced visual acuity, increased stereotyped behavior and altered learning, and exploratory and aggressive behavior) are difficult to detect in premature infants clinically.[69,70,71]

The composition of Omegaven is mainly n-3, predominantly EPA and DHA with trivial ALA, LA and ARA levels. *A priori*, there was a concern for EFAD given the lack of omega-6 PUFAs in the product. In the safety database, there were no patients with a clinical diagnosis of EFAD. Diagnosis of clinical EFAD requires a high index of suspicion since the constellation of EFAD symptoms could be hidden under isolated findings or individual preferred terms. For this reason, FDA's review focused on explorations of TEAEs related to bleeding, ulcers, skin disorders, neurodevelopmental AE preferred terms, and infections; no specific safety signals were identified.

Two concerns remain regarding the lack of clinical EFAD: 1. active comorbidities of prematurity, intestinal failure and liver disease prevalent in the study population could certainly have masked the more subtle clinical manifestations of EFAD during the study, and 2. the longer-term neurocognitive effects of EFAD would not be apparent during the time course of the trial (Median duration of Omegaven treatment in the safety population was 13.5 weeks; min 3 days to max 7.8 years). Neurodevelopmental assessment was not part of the development program for Omegaven (see Section 8.2.8).

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[68] The supply of EFA affects the structural composition of the brain and myelin sheaths in particular. The functional correlates of these biochemical changes induced by malnutrition include alterations in the waking electroencephalographic activity, visual- and auditory-evoked responses, motor and cognitive development, and social abilities. Sleep-wake cycle organization as well as autonomic nervous system functioning during sleep are perturbed by early human malnutrition. Most of these effects are potentiated by other environmental factors that interact with poor diet in defining the adverse consequences.

[69] Salama GS, Kaabneh MA, Almasaeed MN, Alquran MI. Intravenous Lipids for Preterm Infants: A Review. *Clinical Medicine Insights Pediatrics*. 2015;9:25-36.

[70] Hansen AE, Wiese HF, Boelsche AN, et al. Role of linoleic acid in infant nutrition: clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. Pediatrics. 1963;31:171.

[71] Holman RT. Essential fatty acid deficiency. In: Holman RT, editor. Progress in the Chemistry of Fats and Other Lipids. Vol. 9. Oxford: Pergamon Press; 1968. pp. 275–348.

To identify subclinical EFAD, a biochemical definition using Triene: Tetraene (T:T) ratio, determined by Mead acid (n-9): ARA (n-6), has been utilized. The 3 classes of unsaturated fatty acids, n-3, n-6 and n-9 PUFAs compete for the same enzymes, and the enzymes interact with fatty acids in a preferential order of n-3 > n-6> n-9 (Figure 17). Oleic acid (ω9 mono-unsaturated fatty acid) is converted to eicosatrienoic acid (Mead acid) at a significant rate only when insufficient amounts of ALA or LA are present. When ALA and LA are deficient, oleic acid is desaturated and elongated to Mead acid, whereas lesser amounts of n-3 and n-6 downstream metabolites (i.e., ARA and EPA) are synthesized. Therefore, an increased T:T ratio of >0.2, otherwise known as the Holman Index, have historically been used to determine biochemical EFAD. T:T ratio >0.4 is generally accompanied by clinical signs and symptoms of EFAD.
More recently, clinical analytical methods have progressed[72] and the Mayo Medical Laboratories have updated the reference range for the T:T ratios as shown in Table 35. Values above this reference range are now considered indicative of EFAD following the same reasoning Holman applied to his older data. Indeed, recent publications[73] define a T:T ratio of 0.05 across all age groups as mild EFAD and severe EFAD as a T:T ratio at least 0.20.

Table 35. Mayo Medical Laboratories Reference Range for T:T Ratio

Age	T:T Ratio
1-31 days	0.017-0.083
32 days - 17 years	0.013 - 0.050
≥ 18 years	0.010-0.038

Source: Retreived from https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82426

The median T:T ratio of those patients treated with Omegaven in study 34 was 0.02 (interquartile range: 0.01 – 0.03) at baseline and the end of the study (see Section 8.2.4.6). While the overall T:T ratios remained below the Mayo Medical Laboratories reference range for biochemical EFAD, there were 19 cases of abnormal peak T:T ratios at the analysis time points, of whom 9 had abnormal values only at baseline (Table 36). Six patients had an uptrend in the T:T ratio during the study, all of whom had complicated comorbid illnesses and of whom 3 died. All of the abnormal values at the end of study were <0.1, still within the Mayo Medical Laboratories reference ranges (Table 35).

[72] Lagerstedt SA, Hinrichs DR, Batt SM, Magera MJ, Rinaldo P, McConnell JP. Quantitative determination of plasma c8-c26 total fatty acids for the biochemical diagnosis of nutritional and metabolic disorders. Molecular genetics and metabolism. 2001;73(1):38-45.
[73] Cober MP, Teitelbaum DH. Prevention of parenteral nutrition-associated liver disease: lipid minimization. Current opinion in organ transplantation. 2010;15(3):330-3.

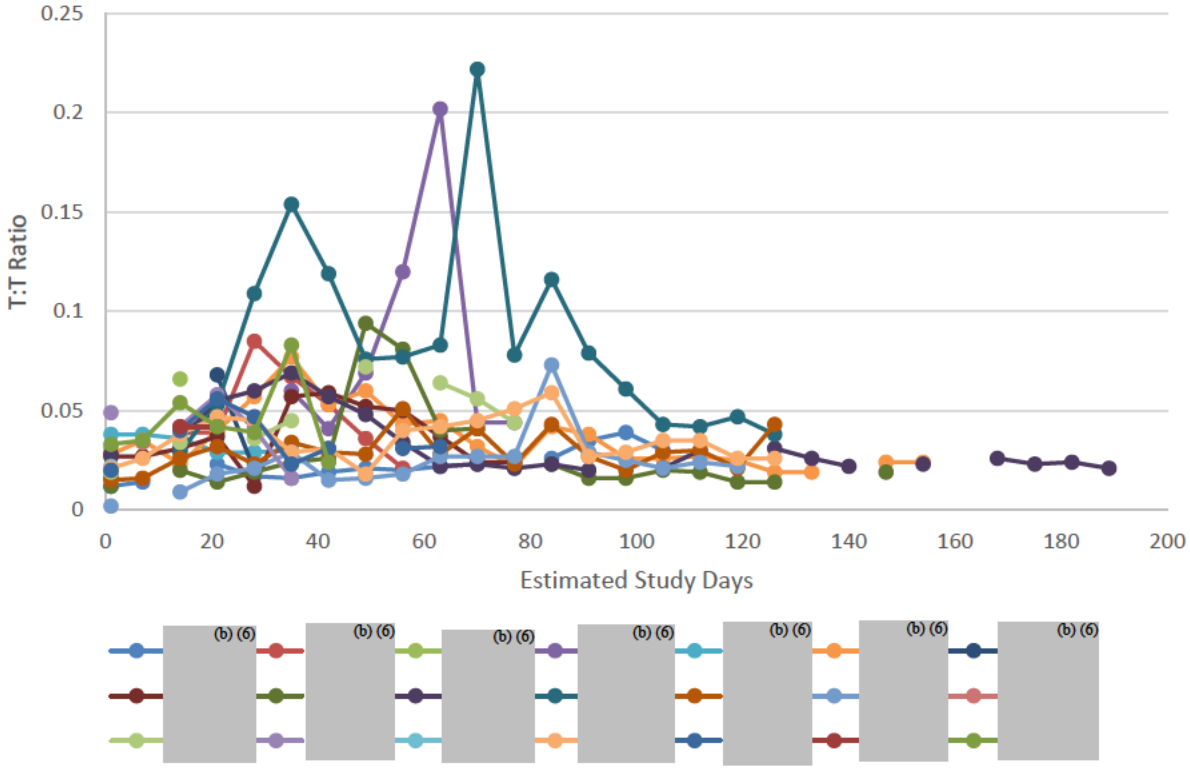
Table 36. Abnormal T:T Ratio at Analysis Time Points, BCH Safety Population (n=140)

Patient	Time Point				Average Enteral Lipid Dose (g/kg/day)	Outcome	Comments:
	Baseline	EOITP	EOETP	EOS			
(b) (6)	0.008	**0.061**	0.032	0.032	1		Respiratory Failure
	0.018	**0.06**	0.032	0.032	1	unknown	
	0.023	**0.081**	N/A	**0.081**	1		5 weeks duration, increased feeding intolerance, vomiting, alkalosis
	0.014	0.022	**0.069**	**0.069**	1		Stable throughout, peak at EOS due to NEC
	0.031	**0.061**	N/A	**0.061**	1	death	Concurrent multiple bacterial infections, death due to MOF
	0.023	0.023	**0.052**	**0.052**	unknown	death	Concurrent renal failure
	0.024	**0.063**	0.034	0.034	1	death	Remained >0.05 for 84 days
	0.011	0.021	**0.07**	**0.07**	1		Steady increasing trend (0.01- 0.043) until study day 102
	0.023	**0.066**	**0.095**	**0.095**	0	death	Remained >0.05 from day 21-137
	0.058	**0.058**	N/A	**0.058**	1		Short duration (<3 days), weaned from TPN, no further follow up
	0.115	0.03	N/A	0.03	0	death	
	0.054	0.026	0.013	0.013	unknown		
	0.162	0.016	N/A	0.016	1	liver transplant	
	0.077	0.018	0.021	0.021	1		
	0.059	0.042	N/A	0.042	1	liver transplant	
	0.055	0.025	N/A	0.025	2		
	0.065	0.026	0.015	0.015	2		
	0.18	0.038	N/A	0.038	0	unknown	
	0.175	0.01	N/A	0.01	unknown	unknown	

Values above >0.05 bolded
EOITP=End of Initial Treatment Period, EOETP = End of Extended Treatment Period, EOS = End of Study
Source: Adapted from ISS Table 103. ADNURAW.xpt, ADAE.xpt, and ADLB.xpt.

There were 21 additional patients identified who had at least one abnormal T:T ratio of > 0.05 during the study (Figure 18), outside of the analysis time points. Ten patients had only one spurious peak T:T ratio value > 0.05; nine had a median of 3 visits (min 2 to max 4 visits) with abnormal ratios during median of 15.5 follow up visits (min 7 to max 25 visits).

Figure 18. Abnormal T:T ratio >0.05 During Study, Study 34 Omegaven-Treated Patients

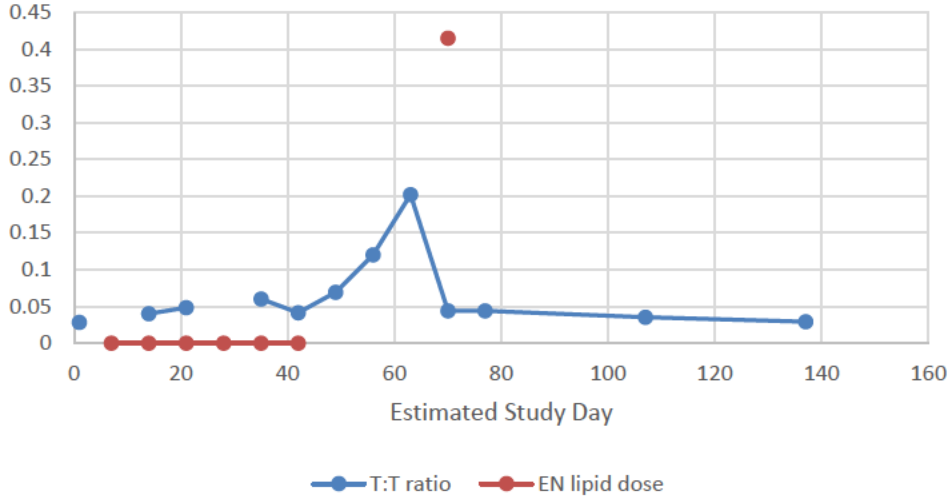


Source: S. Seo. ADLB.xpt.

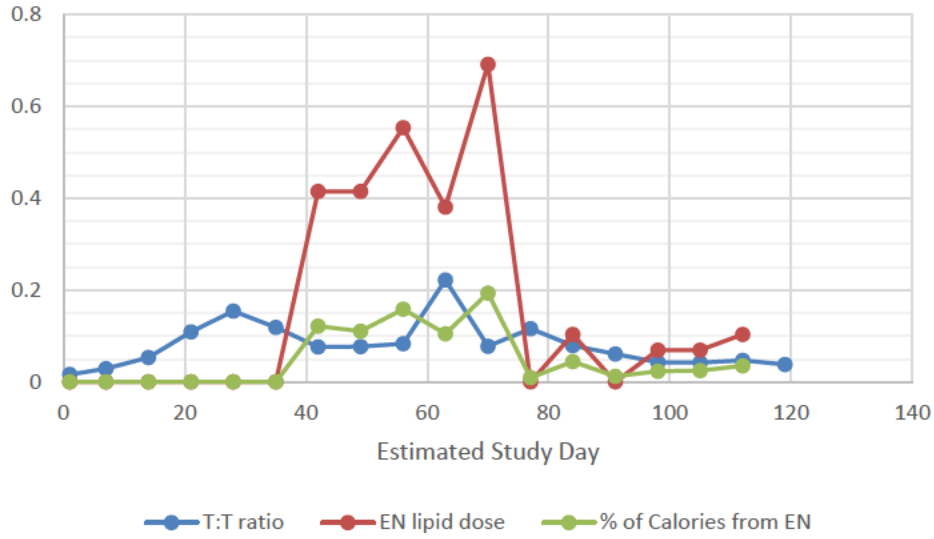
There were 2 patients with T:T ratio >0.2 during the study period (Figure 19), and all resolved to values <0.05 by the end of study. Patient (b) (6) (A) appeared to have a temporally associated clinical set-back starting at approximately Day 47 with cardiac, respiratory and metabolic TEAEs reported through Day 62. Patient (b) (6) (Figure 19B) had 2 peaks in the T:T ratio; the first, temporally associated with TEAEs reported (i.e., respiratory failure, intermittent anasarca, acidosis, and seizures), and the second temporally coincided with advance in enteral feed, which the patient could not tolerate. The patient subsequently remained PN dependent and was maintained on Omegaven for 5 years, in which the T:T ratio remained <0.05 from approximately 100 days through the end of the study (not shown in figure).

Figure 19. Subjects with T:T Ratio > 0.2 during Omegaven Treatment from Study 34

A. T:T ratios with EN lipid dose received over time –Patient (b) (6)



B. T:T ratios with EN lipid dose received over time –Patient (b) (6)



Source: S. Seo. ADNURAW.xpt. ADLB.xpt.

Overall, those patients who had abnormal T:T ratios, both at any time during the study or at specific analysis timepoints, were those who had significant feeding intolerance (i.e., intestinal failure), unable to tolerate enteral feeds beyond 1 g/kg/day enteral lipid dose, and those who had concurrent co-morbidities or TEAEs related to underlying conditions (i.e., infections, sepsis, NEC, etc). Often, the peak T:T ratio occurred during those times that the patients were transitioning between parenteral and enteral nutrition.

The clinical significance of relatively short term peaks of T:T ratios, indicating biochemical EFAD, during treatment is difficult to quantify for both short and long-term risk of EFAD. It is especially

difficult to distinguish the interrelated cause and effect of underlying comorbid conditions and potential biochemical EFAD. Certainly, when these vulnerable patients are challenged clinically, they are more likely to be at risk of abnormal lipid metabolism; and conversely, when subclinical EFAD may be at play, patients may secondarily manifest multiple clinical signs of illness. The absence of T:T ratios from the HC arm is a significant limitation that hinders the interpretation of this biochemical EFAD information. Regardless, it is important to note that the risk of EFAD may exist, probably for all PN-dependent patients, particularly during transitions between parenteral to enteral nutrition.

Furthermore, while the abnormal T:T ratio can be explained or reassured, the applicability of the Holman Index in the context of exclusive omega-3 PUFA nutrition remains an open question. While the disproportionate downstream PUFAs provided parenterally can lead to a false-positive diagnosis of EFAD[74] , the main concern is the potential false-negative results of the Holman Index with the ratio of Mead Acid: ARA remaining relatively stable despite absolute deficiency of the specific n-6 PUFAs. Holman himself cautioned in 1971:

> "The triene:tetraene ratio, although useful as a good rule of thumb, should not be applied arbitrarily…when the chief dietary PUFA is not of the omega-6 family, only the numerator of the ratio is affected and the calculated ratio will not reveal a full picture. The triene:tetraene ratio is valid in most natural dietary situations in which linoleate is the dominant EFA."

In those patients receiving Omegaven as an exclusive lipid source, while the omega-3 PUFAs (i.e., EPA and DHA) may be supplied in abundance, because the ALA and LA are minimally present at approximately (b) (4) of lipid composition of Omegaven, the amount of omega-6 PUFAs (i.e., ARA) and omega-9 PUFAs (i.e., Mead acid) can potentially both become deficient over time leading to arachidonic acid deficiency per se. Hypothetically, if the Mead Acid and ARA, the numerator and the denominator of the T:T ratio, decrease proportionally, the ratio could remain unchanged in the setting of undetectable omega-6 EFAD.

Fatty Acid Profiles

In view of the above, it appears better to obtain a full panel of fatty acids for clinical trials that aim to evaluate the status of fatty acids and essential fatty acids. Average fatty acid levels measured during treatment with Omegaven remained within acceptable ranges. The EPA and DHA levels were high, as expected; and the ARA plasma concentrations remained within normal range throughout the 212 week study period. While the amounts of LA and ALA present in Omegaven are small compared to other soybean oil based lipids emulsions, Omegaven is not devoid of these LCPUFAs and their content may be sufficient to prevent EFAD.

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[74] Gramlich, L., Meddings, L., Alberda, C., Wichansawakun, S., Robbins, S., Driscoll, D. and Bistrian, B. (2015), Essential Fatty Acid Deficiency in 2015. Journal of Parenteral and Enteral Nutrition, 39: 61S-66S.

Table 37. Fatty Acid Profiles for Omegaven-Treated Patients from Study 34

	FA [umol/L]	Ref Range*	Baseline	EOITP	EOETP	EOS
Omega 3	ALA	<1 yr: 10-190 1-17 yr: 20-120	122	59	52	59
	EPA	<1yr: 2- 60 1-17 yr: 8 - 90	170	975	972	965
	DHA	<1 yr: 10 - 220 1-17 yr: 30 - 160	312	1085	956	999
Omega 6	LA	<1 yr: 1000-3300 1-17 yr: 1600 - 3500	2519	1488	1618	1612
	DGLA	<1 yr: 30 - 170 1-17 yr: 60 - 220	120	59	37	45
	ARA	<1 yr: 110 - 1110 1-17 yr: 350 - 1030	752	510	440	466
Omega 9	OLEIC	<1yr: 250-3500 1-17 yr: 350 - 3500	1364	1329	1260	1271
	MEAD	<1 yr: 3 - 24 1-17 yr: 7-30	18	12	9	10
Saturated FA	PALMITIC	<1 yr: 720-3120 1-17 yr: 960-3460	1752	1576	1344	1419
	STEARIC	<1 yr: 270-1140 1-17 yr: 280 - 1170	874	776	689	722
Trans and omega 7	PALMITO	<1 yr: 20 - 1020 1-17 yr: 100-670	473	396	268	322
Branched chain FA	PRIST	≤0.77 ≤1.47	0	1	1	1
T: T Ratio			0.03	0.03	0.02	0.02

FA= Fatty acids, ALA= Alpha linolenic acid, EPA = Eicosapentaenoic acid , DHA = Docosahexaenoic acid, LA = Linoleic acid, DGLA= Homo-gamma-linolenic acid, ARA= Arachidonic acid, EOITP = End of Initial Treatment Period, EOETP= End of Extended Treatment Period, EOS=End of Study
*Reference ranges retrieved from https://www.mayomedicallaboratories.com/test-catalog/Overview/82426
Source: S. Seo, ADLB.xpt.

DHA : ARA ratio

Even though there was no evidence of overt ARA deficiency, there was a decline in the mean ARA concentration during the study (though still within the reference range); and given the significant increase in the DHA content from Omegaven, the median ARA: DHA ratio decreased substantially in Omegaven-treated patients from 4.2 (range 0.19-18.4) at baseline to 0.4 (range 0.16-7.6) by the EOS. This is notable, as results of published studies evaluating the effects of different ratios of omega-6 to omega-3 demonstrate that a proper balance of DHA and ARA is needed for optimal cognitive performance as too much DHA may suppress the benefits

provided by ARA.[75]

In several early clinical studies of infant formula, the provision of high amounts of DHA/EPA without a concomitant supply of ARA has been associated with adverse effects on growth in premature infants.[76,77] Due to the potential for high concentrations of EPA to interfere with the synthesis of AA, which is essential for normal growth, EPA was subsequently removed and ARA was added to DHA-enriched formula. Since 2001, currently available infant formulas in the US contain only ARA and DHA derived from algal or fungal sources, rather than fish oil, and contain levels of ARA and DHA at 140 mg/day and 100 mg/day, respectively, based on worldwide averages of ARA and DHA content in human milk. In fact, all commercially available infant formulas contain preformed ARA at levels equal to or higher than the DHA content in formulas where these LCPUFA are added.

The balance between omega-3 and 6 is complex and not fully understood or characterized in the literature. The available fatty acid profiles from Study 34 show that although ARA decreased over time in Omegaven-treated patients, mean concentrations of ARA were within the normal range, which may suggest that the negligible ARA and LA content of Omegaven may be adequate to maintain normal plasma levels of the PUFAs. However, the impact of the altered DHA to ARA ratio, or relative ARA deficiency, is difficult to assess short-term; and given the importance of ARA in neurocognitive development, a thorough evaluation of long-term neuro-cognitive developmental assessment is warranted.

Additional studies are required that have a prespecified SAP with a comparable placebo or active control arm to assess EFA status as primary or secondary outcomes, using up-to-date clinical analytical methods. Due to the lack of fatty acid profile information in the HC arm, a comparative analysis could not be performed. Also of note, the analysis of the EFAD risk was significantly confounded by the concurrent administration of enteral nutrition and inconsistent sampling of the FA profiles in relation to the continuous lipid infusion. The disproportionate PUFA composition may mask biochemical signs of EFAD, and co-morbid illnesses may mask the clinical signs of EFAD. Lastly, long-term neurodevelopmental assessment is imperative, as discussed above.

8.2.5.3 Bleeding / Coagulopathy

There are theoretical risks of bleeding disorders based on the mechanism of inhibition of arachidonic acid and decreased thromboxane A2 production (a potent promotor of platelet

[75] Hadley KB, Ryan AS, Forsyth S, Gautier S, Salem N. The Essentiality of Arachidonic Acid in Infant Development. *Nutrients*. 2016;8(4):216.
[76] Carlson SE, Cooke RJ, Werkman SH, Tolley EA. First year growth of preterm infants fed standard compared to marine oil n-3 supplemented formula. Lipids. 1992;27(11):901-907.
[77] Carlson SE, Werkman SH, Tolley EA. Effect of long-chain n-3 fatty acid supplementation on visual acuity and growth of preterm infants with and without bronchopulmonary dysplasia. Am J Clin Nutr. 1996;63(5):687-697.

aggregation). There is published evidence that the administration of oral omega-3 supplements to healthy individuals has mild effects on platelet aggregation and, subsequently, bleeding time. For this reason, the trial enrollment criteria excluded patients with prolonged INR > 2 or active bleeding.

In the integrated safety population, there was a lower incidence of TEAE associated with anemia or bleeding disorders in the Omegaven-treated group.

Table 38. Overall Incidence of Bleeding Disorders, Integrated Safety Population

	Historical Control (n=73)	Omegaven (n=189)
Number of Subjects	45 (62%)	79 (42%)
Number of Events	238	191

Source: S. Seo, MAED analysis. ISS ADSL.xpt, AE.xpt

The median INR and activated partial thromboplastin times decreased from baseline to EOS in Omegaven-treated patients, but were prolonged in HC patients. Table 77 of the Applicant's ISS Section 4.5.2.2 summarizing abnormal coagulation parameters over time showed that proportionally more HC patients than Omegaven-treated patients had high INR, high aPTT, and low fibrinogen during the study, and at each analysis timepoint. There were no significant anemia, hemolysis or coagulopathy noted in the Omegaven-treated patients in the safety database.

Under the expanded access INDs, one spontaneous investigator safety report included a case of a 6 month-old patient with PNAC who required multiple RBC transfusions with abnormal peripheral RBC smears (e.g., evidence of spur cells and hemolysis) while receiving Omegaven. The hematology consultant at the institution recommended stopping Omegaven, the investigational product, "which may have resulted in an unusual finding of hemolysis in a susceptible individual." With an intravenous infusion, an immediate effect on the membrane lipid composition of circulating blood cells and endothelial cells may be expected. *In vitro*, fish-oil has been shown to interact with the outer hemileaflet of the erythrocyte membrane and affect membrane functions, although the effect was negligible at the pharmacological concentrations expected from clinically relevant dosing.[78]

Lastly, in the European postmarket safety database, a case of massive hemorrhage following a routine central catheter change in a 9-month old infant while on treatment with Omegaven as the exclusive source of lipid has been reported and is discussed in detail in Section 8.2.10.

[78] Fischler L, Meredith DO, Reinhart WH. Influence of a parenteral fish-oil preparation (Omegaven) on erythrocyte morphology and blood viscosity in vitro. Clinical hemorheology and microcirculation. 2003;28(2):79-88.

8.2.5.4 Fat Overload Syndrome

In the event of an overdose, fat overload syndrome can occur, which is a rare condition that results from the excess accumulation of lipids in the serum, characterized by hyperlipidemia, fever, fat infiltration, hepatomegaly with or without jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorder, hemolysis and reticulocytosis, abnormal liver parameters, and coma, which resolve when the lipid infusion is discontinued.
There were no cases of fat overload syndrome in the safety database, and none of the laboratory profiles (Section 8.2.4.6) indicated any individuals with laboratory signs of fat overload syndrome. Particularly, the mean triglyceride levels over time showed decreases in these values for Omegaven-treated patients through week 16, at which point they remained relatively stable throughout the remainder of the observation period.

8.2.5.5 Pleural Effusion

Deaths of preterm infants reported in the literature with a finding of intravascular fat accumulation in the lungs subsequently resulted in the boxed warning of soybean oil-based lipids, and is now included as lipid emulsion class labeling. Pleural and pericardial effusion was reviewed to determine the appropriateness of the boxed warning for Omegaven, specifically to evaluate the level of evidence to exempt Omegaven labeling from the class boxed warning.

There is no published report of pleural effusion specifically associated with Omegaven use.[79] Almost all the reported deaths[80] were in infants who received 100% soybean oil-based lipid emulsion at an infusion rate well above the recommended maximum rate of 0.15 g/kg/hr in preterm and low birthweight infants who have poor clearance of intravenous lipid emulsions. Due to the compositional differences between Omegaven and soybean oil-based lipid (i.e., PUFA contents and phytosterol, etc.), and due to the proposed maximum dosing infusion rate of 0.15 g/kg/hr of Omegaven, it is plausible that the risk of pleural effusions may also be different between the two types of lipid emulsions; however, biochemical or mechanistic evidence of this differential risk is lacking at this time.

In the submitted safety database, there were 3 cases of pericardial effusion and 28 cases of pleural effusion (Table 39). None of the cases were fatal, and the HC group had a higher incidence than the Omegaven treatment group. Given the small size of the safety database, and the lack of consistent autopsy findings from all deaths seen in the trials and across the expanded access use, this result simply indicates that pleural and pericardial effusion do occur in this population, and the differential rates do not necessarily provide sufficient evidence that this risk is mitigated by the omega-3 rich fish oil.

[79] From postmarketing experience outside of US, and expanded access SPI and intermediate size INDs.
[80] Levene MI, Wigglesworth JS, Desai R. Pulmonary fat accumulation after intralipid infusion in the preterm infant. Lancet (London, England). 1980;2(8199):815-8.

Table 39. Incidence of Pericardial and Pleural Effusions, Integrated Safety Population

	Historical Control (n=73)	Omegaven (n=189)
Pericardial Effusion	**1 (1%)**	**2(1%)**
mild	1 (1%)	2(1%)
Pleural Effusion	**15 (14%)**	**13 (8%)**
mild	6 (8%)	5 (3%)
moderate	8 (11%)	5 (3%)
severe	1 (1%)	3 (2%)

Source: S. Seo. ADAE.xpt

Some have postulated that the etiology of the pleural effusion of TPN extravasate may be more related to mechanical injury (i.e., structural perforation) from central venous catheters rather than the lipid infusion. More recent autopsy findings of 5 neonatal cases of pericardial effusion and cardiac tamponade revealed that the effusions developed as a result of myocardial wall permeation by hyperosmotic TPN contents with intralipid infusion, and suggest submicroscopic injury to the endothelium and/or endocardial lining.[81] Given that the osmolality and osmolarity of Omegaven ((b) (4) mosm/kg and 273 mOsmol/L, respectively), and Intralipid® 20% (350 mOsmol/kg, representing 260 mOsmol/L of emulsion, respectively) are similar, the expected rate of pleural effusion would also be similar.

The Applicant also asserts that the lipid accumulation is an artefact associated with a delay in the collection and processing of tissue samples at autopsy. Extravasation of TPN was identified in 21% of acquired effusions from an 18 year retrospective study report.[82] Furthermore, in the clinical experience of the primary reviewer, clinically significant accumulation of lipid continues to be a true phenomenon in the neonatal population, not a mere antiquated autopsy artefact. In fact, it may be a more widespread endotheliopathy rather than an isolated or localized pulmonary finding.[83,84]

Even though the hypertriglyceridemia incidence was lower in the Omegaven group (Section 8.2.4.6), there is inadequate evidence to definitively conclude that the risk of lipid-induced endotheliopathy and pleural or pericardial effusions is different for Omegaven lipid emulsion.

[81] Warren M, Thompson KS, Popek EJ, Vogel H, Hicks J. Pericardial effusion and cardiac tamponade in neonates: sudden unexpected death associated with total parenteral nutrition via central venous catheterization. Annals of clinical and laboratory science. 2013;43(2):163-71.
[82] Barbosa M, Rocha G, Flôr-de-Lima F, Guimarães H. Neonatal pleural effusions in a Level III Neonatal Intensive Care Unit. J Pediatr Neonat Individual Med. 2015;4(1):e040123.
[83] Schulz PE, Weiner SP, Haber LM, et al. Neurologic complications from fat emulsion. Ann Neurol. 1994 May;35(5):628-630.
[84] Haber LM, Hawkins EP, Seilheimer DK, Saleem A. Fat overload syndrome. An autopsy study with evaluation of the coagulopathy. American journal of clinical pathology. 1988;90(2):223-7.

Given the small size of the safety database, and the lack of mechanistic proof of differential risk between Omegaven vs. soybean oil-based lipids, there is inadequate evidence or justification to warrant a removal of the class boxed warning for death in preterm infants due to intravascular effusion of lipids.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Demographic subgroups, by chronological age, PMA category at baseline, gestational age at birth, birth-weight category, gender, race and ethnicity, underlying surgical condition, DBil category at baseline (<5 mg/dL and ≥5 mg/dL) and GGT category at baseline were examined for differential safety signals. Many of the subgroups had small numbers of patients for adequate comparative analyses. Overall, none of the subgroup analyses conducted identified any subgroups or types of patients in whom the safety of Omegaven would be different than that observed in the larger integrated safety database of patients treated with Omegaven.

8.2.8. Specific Safety Studies/Clinical Trials

Neurodevelopmental endpoints were not specifically evaluated during the development program. The Applicant submitted supportive publications, and suggests that the head circumference data obtained from the pivotal studies can be used as a simple gauge of neurological development screening during infancy and early childhood.[85] The evidence from 2 supportive publications suggests that Omegaven-treated patients are not at a higher risk of neurological or cognitive impairment compared to patients who receive a soybean oil-based lipid emulsion.

Investigators at BCH conducted a small separate study[86] in neonates and infants who had a baseline DBil < 1.0 mg/dL, gastrointestinal disease requiring surgical intervention, and were expected to be PN-dependent for ≥ 21 days.[87] Patients were randomly assigned to receive Omegaven or a soybean oil-based lipid comparator. Motor, cognitive, and language skills were assessed at 6 and 24 months using Bayley Scales of Infant and Toddler Development (3rd edition), and parents completed the Parent Report of Children's Abilities questionnaire that assessed verbal and nonverbal cognition at 24 months. There were no differences between

[85] Holden KR. Heads you win, tails you lose: measuring head circumference. Dev Med Child Neurol. 2014;56(8):705.
[86] Prevention Trial under BCH IND – Full Clinical Hold. Analysis of available data.
[87] Nehra D, Fallon EM, Potemkin AK, Voss SD, Mitchell PD, Valim C, Belfort MB, BellingerDC, Duggan C, Gura KM, Puder M. A comparison of 2 intravenous lipid emulsions: interim
analysis of a randomized controlled trial. JPEN J Parenter Enteral Nutr. 2014;38(6):693-701.

groups using either of these assessments (Table 40), and mean Bayley scores of the patients examined were similar to the expected population mean (100 ± 15).

Table 40. Neurodevelopmental Outcomes Reported in a Study by Nehra et al.

Test Time Point Endpoint	Soybean Oil-Based Lipid	Omegaven	p-Value
Bayley Scores of Infant Development, median [interquartile range] (n)			
6 months			
Cognitive	105 [100, 105] (5)	100 [95, 100] (6)	0.08
Language	97 [94, 106] (5)	94 [91, 97] (5)	0.43
Motor	97 [97, 103] (5)	94 [79, 103] (5)	0.55
24 months			
Cognitive	95 [85, 115] (6)	93 [88, 98] (4)	0.76
Language	106 [91, 118] (5)	111 [100, 121] (4)	0.56
Motor	99 [88, 103] (6)	101 [94, 109] (4)	0.76
Parent Report of Children's Abilities - Revised, median [interquartile range] (n)			
24 months			
Nonverbal cognition	26 [25, 28] (5)	29 [23, 33] (4)	1
Linguistic skills	33 [29, 92] (5)	77 [64, 99] (4)	0.3
Parent Report Composite Score	59 [52, 120] (5)	98 [87, 125] (4)	0.3

Source: Adapted from Nehra 2014

In another study, patients who received Omegaven were compared to a historical cohort of patients with PNAC who did not receive Omegaven and were matched by gestational age and gender; patients were analyzed for follow-up growth and neurodevelopment.[88] Body weight, body length, fronto-occipital circumference, and language were comparable at 12 months. The cognitive and motor tests revealed a significantly poorer outcome in the Omegaven group compared to a historical cohort at 6 and 12 months ($p < 0.01$). However, a logistic regression analysis adjusting for gestational age, length of hospital stay, and treatment determined that length of hospital stay was an independent risk factor for severe cognitive, language, and motor delays. Since the mean length of hospital stay for Omegaven-treated patients (218 days) was significantly longer than that for patients in the historical cohort (88 days; $p < 0.01$), an additional analysis was performed by matching Omegaven-treated patients to patients in the historical cohort whose length of hospital stay was > 100 days. In this analysis, the differences in cognitive, motor, and language tests essentially disappeared by 12 months.

While there were no differences identified for mean changes from baseline in age-adjusted head circumference at any of the major time points in the integrated PM population, the

[88] Sorrell M, Moreira A, Green K, Jacob R, Tragus R, Keller L, Quinn A, McCurnin D, Gong A, El Sakka A, Mittal N, Blanco C. Favorable Outcomes of Preterm Infants With Parenteral Nutrition-associated Liver Disease Treated With Intravenous Fish Oil-based Lipid Emulsion. J Pediatr Gastroenterol Nutr. 2017;64(5):783-8.

sample size for HC patients, especially by the end of the EOETP, was too small to allow for comparison. At baseline, proportionally more Omegaven-treated patients than HC patients had head circumferences that were considered low-for-age irrespective of the study population.

The supportive evidence from publications reporting neurodevelopmental assessments by Nehra et al. and Sorrell et al. were both small with an n of 11 and 13, respectively. The populations examined in these studies were not generalizable to the to-be-marketed indication population. In addition, the Bayley Scores of Infant Development at 24 months may be insufficient to fully assess the long-term neurocognitive development in this population.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not assessed.

Human Reproduction and Pregnancy

Clinical studies on the use of Omegaven in pregnant women have not been conducted. Two cases involving the off-label use of Omegaven in pregnant women without any associated adverse reactions have been reported to the Applicant:

• A female patient (unknown age), pregnant in the 4th week was prescribed Omegaven for immune therapy to prevent miscarriage. No adverse reaction was reported.
• A female patient (unknown age) in the first trimester of pregnancy received Omegaven as part of off-label use, but reported no adverse reaction during administration.

Pediatrics and Assessment of Effects on Growth

Growth was assessed as the primary efficacy endpoint in Omegaven studies. Longterm growth was not evaluated – the majority of the patients had 2-3 months of treatment and follow up.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The highest administered dose of Omegaven occurred at an infusion rate of 5 g/kg/hr, which was a >33-fold increase from the recommended infusion rate of 0.15 g/kg/hr. In the 3 cases of accidental overdose during the expanded access use, there were no signs of fat overload syndrome including respiratory distress, coagulopathy or fever.

Drug abuse potential, withdrawals and rebound effects are not applicable to the product.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

European Postmarket Experience

Outside of the US, Omegaven has been marketed for adult patients as supplemental lipid parenteral nutrition. Since 1998 through April 2017, 112 adverse drug reactions (ADRs) in 57 patients were reported from spontaneous/authority reports or from the literature. The SOCs with the most (>10) ADRs were General Disorders and Administration Site Conditions (39 ADRs in 28 patients) and Gastrointestinal Disorders (13 ADRs in 9 patients). The most common ADRs were fever (10 ADRs), chills (9 ADRs), and shivering (5 ADRs). 4 ADRs of vomiting, pyrexia, hypersensitivity reaction, headache, and rash were reported.

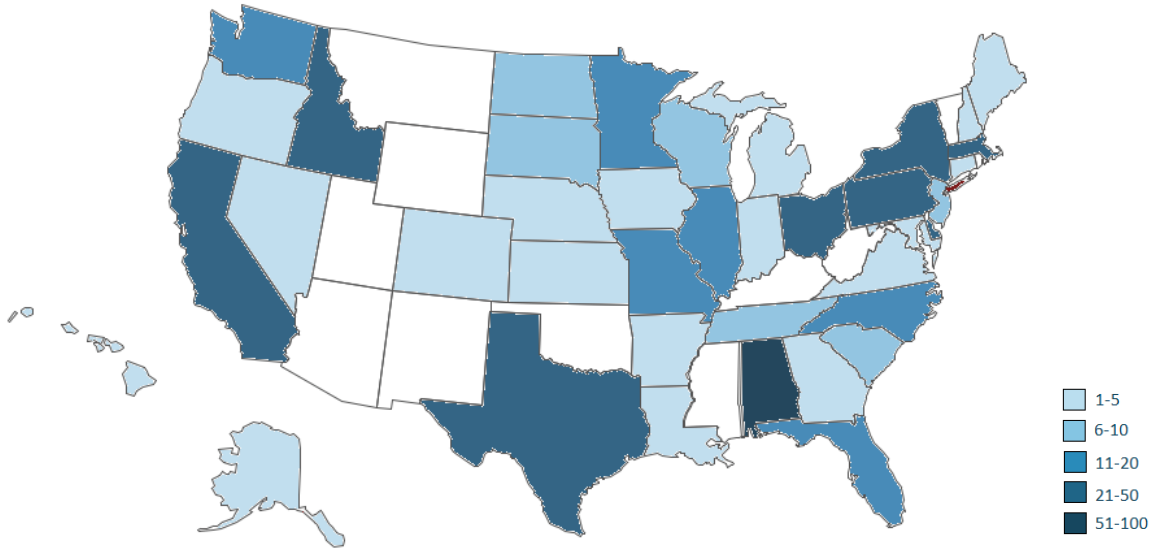
A total of 33 serious ADRs in 18 patients were identified from spontaneous reports (6 ADRs for fever; 3 ADRs each for chills, headaches, delirium; 2 ADRs each for weakness, pelvic pain; 1 ADR each for cardiac failure, nausea, hyperpyrexia, weakness generalized, hepatic function abnormal, hypersensitivity reaction, GGT increased, hypertriglyceridemia, weakness of limbs, ischemia cerebrovascular, anxiety, confusion, dyspnea, and hypertension not specified). Three serious ADRs in 2 patients were identified from the literature (1 ADR each for haemorrhage, haemolytic anaemia, and off label use).

The most notable and relevant off-label use adverse reaction report was a 9 month-old infant with intestinal failure and no prior history of bleeding, coagulopathy, or portal hypertension who developed a life-threatening hemorrhage following a standard central venous catheter change. The patient was completely PN dependent and while on Omegaven as the sole lipid therapy, after 26 days of treatment, experienced significant hemorrhage following a femoral catheter removal and subclavian catheter insertion. Bleeding occurred from both sites, required multiple transfusions of red blood cells (30 mL/kg) and platelets (10 mL/kg), transexamic acid (10 mL/kg IV q8hrs), desmopressin acetate tablets, and eventually resolved after 3 days.

US Expanded Access Experience

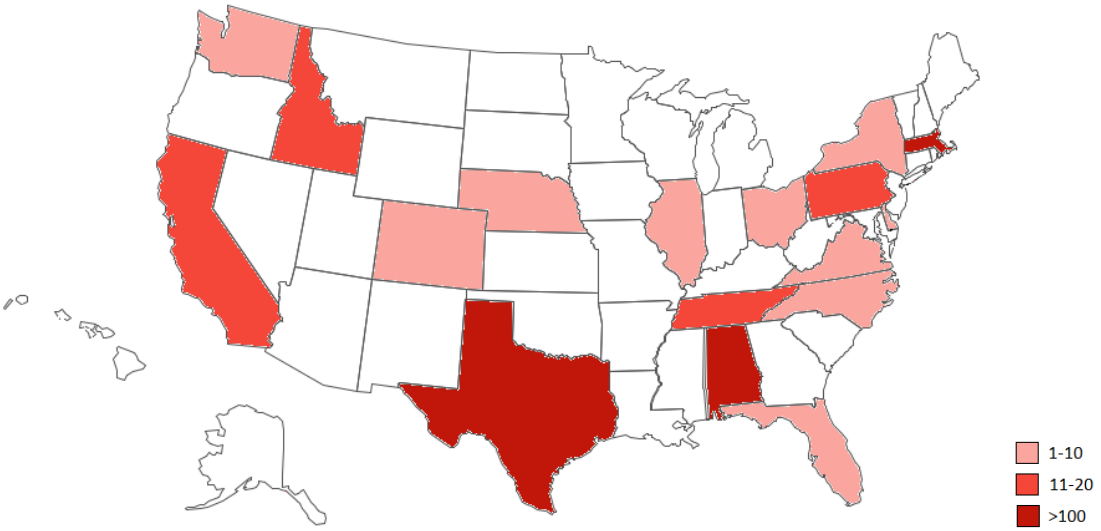
Since 2005, there have been approximately 500+ single patient INDS and intermediate size INDs, with an estimated 1000+ patients exposed to Omegaven. Of note, the safety information relies on voluntary safety reporting and annual report data by the investigators, of which approximately 10% of the IND files were reviewed (External Appendix: (b) (4)). The intermediate size INDs were regulated by the Division to ensure safety of the patients by maintaining consistency across the INDs for dose (0.5-1 gram/kg/day), enrollment criteria, and safety monitoring during administration of Omegaven. Under both the single patient and intermediate size INDs, the patient age ranged widely from premature newborns to <18 year old pediatric patients with PNAC (DBil ≥ 2 mg/dL).

Figure 20. Single Patient IND US Distribution from 2005 - 2013



Source: S.Seo

Figure 21. Intermediate Size IND US Distribution from 2013 – 2018



Source: S. Seo

Review of expanded access use information available to FDA at the time of NDA review revealed 1. similar safety profiles consistent with the integrated safety database, 2. no significant new safety signals across a more heterogeneous pediatric population, and 3. most clearly, a widespread lack of equipoise regarding the safety and efficacy of Omegaven for pediatric PNAC patients in the clinical community.

Expectations on Safety in the Postmarket Setting

The neonatal community is prone to off-label use as there is a paucity of approved medications for the neonatal population. Although the safety and effectiveness of SMOFlipid® have not been established in pediatric patients, results from the drug utilization consult review for novel lipid emulsion products revealed use of SMOFlipid in the pediatric population.[89] The national estimates obtained from hospital billing data suggest that NICU patients contributed approximately 25% of the overall use of SMOFlipid.[90] Based on this data, off-label use of Omegaven (i.e., in pediatric patients without PNAC) can be expected in the postmarket setting.

Given that the available efficacy and safety evaluation is limited to Omegaven use as a source of calories for patients with PNAC, there is no evidence of effectiveness or safety of Omegaven in the setting of treatment or prevention of PNAC. There is concern for off-label use for "prevention" of PNAC for those infants with mild transient cholestasis who would not progress to develop PNALD, or those infants who would be "at risk" for PNAC. Currently available information is inadequate to address the benefit and/or risk of Omegaven in these infants without PNAC/PNALD: Omegaven use as an alternative to soybean oil-based lipids could expose these infants, who would not otherwise be at risk of PNALD, to suboptimal nutrition with fewer calories or potential LCPUFA deficiencies. Due to the unknown potential neurodevelopmental risks of Omegaven usein the broader population of premature infants, the labelled indication is written for the more specific population of pediatric patients with PNAC, a seriously ill group of patients, in whom the benefit-risk ratio is acceptable.

Another potential off-label use of Omegaven as treatment of EFAD can be expected, following publications and from current expanded access requests. The studies conducted to support this marketing application did not address this indication or analyze this specific population. There are case reports of treatment of EFAD secondary to soybean allergy with Omegaven[91] published by the investigators. On the other hand, potential EFAD from Omegaven use has not been fully addressed (see Section 8.2.5.2). While the fatty acid profiles should be monitored, whether or not the T:T ratio is an adequate measure of EFAD, and whether there could be a risk of ARA deficiency or relative DHA:ARA imbalance remains an open question.

Finally, the current dosing regimen has evaluated a single dose of 1 gm/kg/day or maximum infusion rate of 0.15 g/kg/hr, based on nonclinical information and clinical judgement of the investigators. There was no dose ranging study done, and higher doses have not been assessed. Because typical lipid requirements can be as high as 3 to 4 gm/kg/day, there is concern for off-label use of higher Omegaven doses that have not been evaluated.

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89 (b) (4).

90 However, this estimate is likely conservative given standalone pediatric specialty hospitals are not represented in the data and lipid emulsions billed with "unspecified" billing descriptions were not included in the calculation.

91 Gura KM, Parsons SK, Bechard LJ, Henderson T, Dorsey M, Phipatanakul W, Duggan C, Puder M, Lenders C. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. Clinical nutrition. 2005 Oct 1;24(5):839-47.

The above concerns may be mitigated with labeling, to accurately describe the indication and specifically highlight the limitations of use. Furthermore, required postmarketing studies will address those off-label risks that cannot be mitigated by labeling alone.

8.2.11. Integrated Assessment of Safety

The evaluation of the safety of Omegaven as a source of calories in patients with PNAC was primarily based on the two open-label, non-randomized, single-center, unmatched historical-controlled studies. The safety database included n=189 patients treated with Omegaven at the to-be-marketed dose of 1 gm/kg/day and n=73 HC patients who received soybean oil-based lipid. Significant differences were noted between the treatment and the HC cohorts, in baseline characteristics and duration of exposure. However, the imbalances favored the safety profiles for the HC patients, who were less premature and bigger at birth, had less cholestasis than the Omegaven-treated patients at baseline, and had a shorter overall duration of exposure. Subgroups of concurrent enteral nutrition did not affect the safety analysis results.

Death and adverse events (both serious and common) were frequent and highly prevalent in the program, as expected for the neonatal population with PNAC burdened by both prematurity and intestinal failure. There were 35 deaths within the safety database, (24 patients (13%) in the Omegaven arm and 11 patients (15%) in the HC arm) with higher mortality in the HC group. Serious adverse events were more common, overall, in the HC group. Especially notable are the hepatic failure rates which were higher in the HC group than the Omegaven group; however, exceptions that were more common in the Omegaven group, especially in the exclusive parenteral lipid source group, included multiorgan failure, which includes hepatic dysfunction. Common adverse events were generally more frequent in the HC cohort. They included bacterial infections, vomiting, and infection NOS, consistent with the underlying disease. In general, although the AE incidences were lower in the Omegaven-treated patients, the evidence was insufficient to remove or except Omegaven from the lipid emulsion class safety labeling.

The specific hepatic composite safety endpoints and liver transplantation rate also favored Omegaven. This favorable hepatic safety profile generates a provocative hypothesis of PNAC prevention or PNALD treatment potential of Omegaven; however, the current trial designs prohibit statistical inference for such an indication, and the safety advantage is limited to the scope of Omegaven used as a nutritional source of calories in pediatric patients with PNAC.

With regards to EFAD, unknown risks remain. Reassurance of safety rests on the lack of evidence of clinical EFAD, a small proportion of patients meeting criteria for biochemical EFAD (T:T ratio >0.05) during the study, and the generally stable fatty acid profiles for Omegaven-treated patients treated at BCH. However, multiple open questions remain: lack of fatty acid profiles in the HC patients is a significant limitation, the clinical diagnosis requires a high index of suspicion and could be masked by the underlying comorbidities in the population, the questionable applicability of the Holman Index when receiving an omega-6 deficient lipid source, the unknown clinical significance of short duration peaks of T:T ratios in the neonatal period, undetermined optimal ratios of ARA:DHA and the potential risk for relative ARA deficiency. The requirement for long-term studies to evaluate EFAD and address the

neurodevelopmental impact of Omegaven use will be recommended.

Overall, safety signals were overwhelmed by the significant confounders of underlying conditions of prematurity and IFALD. Given the limitations of the available information, it is not possible to definitively exclude a causal association of Omegaven with the adverse events observed within the submitted safety database. Nonetheless, there were no specific safety signals identified for Omegaven. The additional safety information from the two parent expanded access INDs from 2012-2017, as well as the expanded access safety and annual reports available to the FDA at the time of the NDA review, were consistent with the findings in the submitted safety database without any new safety signals.

8.3. SUMMARY AND CONCLUSIONS

8.3.1. Statistical and Clinical Issues

Study 34 and Study 35 were not adequately designed and powered to demonstrate noninferiority or superiority of Omegaven to the soybean oil comparator.

There are limitations to the conclusions that can be drawn from the study results due to the design of Study 34 and Study 35. The anthropometric efficacy endpoints and treatment periods for evaluation of those endpoints were identified post-hoc, and the Applicant did not conduct rigorous statistical testing for those endpoints. The studies were not prospectively powered with a sufficient sample size to detect a difference in treatment effect between the two treatment groups for the anthropometric endpoints. Additionally, it is possible that the HC groups had unknown biases[92] which cannot be determined. The statistical literature has noted a bias inherent with historical controls, which is one reason why historical controls are not considered as reliable as randomized concurrent controls.

Additional evidence was reviewed to support the proposed indication due to the above limitations. We determined Omegaven's effect by comparing Omegaven study data to gender- and age-standardized growth charts (Fenton for preterm, WHO for 0-2 yrs, and CDC for 2-17 yrs) to assess age appropriate growth in PNAC patients. In addition, the well-established scientific fact that fatty acids in the form of triglycerides are major sources of dietary energy and the long chain fatty acids provide 9 kcal/g of energy[93,94], and the 100% bioavailability of Omegaven as an intravenously administered lipid product was collectively considered.
And finally, we considered the safety profile of 189 Omegaven-treated patients with PNAC who were dependent on parenteral nutrition. The median duration of Omegaven treatment in the safety population was 13.5 weeks (min 3 days, max 7.8 years).

[92] Pocock SJ. The combination of randomized and historical controls in clinical trials. Journal of Chronic Diseases. 1976; 29:175–188. [PubMed: 770493]
[93] Berg J.M., Tymoczko J.L., Stryer L., Biochemistry, 5th edition, New York: W H Freeman; 2002 (See Chapter17 Citric Acid Cycle).
[94] Berg, Chapter 22.

8.3.2. Conclusions and Recommendations

Study 34 and Study 35 support, in part, the approval of Omegaven as a source of calories and fatty acids in pediatric patients with PNAC. Nutritional efficacy was assessed by biomarkers of lipid metabolism, mean changes in fatty acid parameters, and anthropometric indices (body weight, length/height and head circumference).

These studies and generally accepted scientific knowledge regarding the provision of energy and a source of essential fatty acid support a finding of substantial evidence of effectiveness for the proposed indication.

Recommend approval in the population of pediatric patients with PNAC.

9 Advisory Committee Meeting and Other External Consultations

This application was not referred to an FDA Advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10 Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This section is not applicable to this NDA as the studied population was exclusively pediatrics, and the product obtained Orphan Drug Designation on 2/27/2008 for treatment of PNALD indication, then reverified on 1/25/2017 for the nutritional indication for patients with PNAC (designation #07-2515). Thus, this NDA is exempt from PREA requirements.

The DPMH consult review by Dr. Ethan Hausman, primarily focusing on labeling recommendations, has been filed separately.[95]

[95] CONSULT REV-DPMH-02 (Pediatric Review) 5/7/2018

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Highlights of final labeling negotiations with the Applicant include the following:

Boxed Warning:
The boxed warning for death in preterm infants related to decreased clearance of lipids and intravascular fat accumulation in the lungs reported with soybean-oil based lipid products, which is included in all the currently marketed intravenous lipid emulsion products, was not included for Omegaven. The Applicant provided plausible biochemical and mechanistic justification for why the risk would be different for Omegaven as compared to soybean oil-based lipid emulsions. In addition, no life-threatening pleural or pericardial effusions have been reported in the safety database (see Section 8.2.5.5). However, the information that is currently found in the Warnings and Precautions section of all lipid products which describes the "Risk of Death" from the boxed warning in more detail was also included for Omegaven. Enhanced pharmacovigilance as well as a PMR will further assess this risk.

Indications and Usage:
The indication is written to indicate Omegaven is a source of calories (i.e., nutrition) in pediatric patients. While the efficacy population in the trials was comprised of preterm neonates up to 2 and 5 years of age, the safety database included older children up to 17 years of age; therefore, the full pediatric age range was included in the approved indication.

Limitations of Use:
Two Limitations of Use (LOU) were included:

- Omegaven is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition (PN)-dependent patients.
- It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6: omega-3 fatty acid ratio of the product.

The intent of the first LOU statement is to communicate that the design of the trials prohibits any claims regarding prevention potential. While there was evidence for Omegaven as a source of nutrition for pediatric patients with PNAC, the trials conducted did not test the prevention potential of Omegaven for pediatric PNAC.

The second LOU statement is similar to the LOUs in Clinolipid® (Olive oil: Soybean oil) and Smoflipid® (soybean oil, MCT oil, olive oil, and fish oil) label, which state that the omega-6: omega-3 fatty acid ratio in the products "have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions." Due to the limitations of the clinical trial design for Omegaven, it is impossible to distinguish whether the safety benefits are due to the

product (i.e., decreased omega-6), due to the absence of a hepatotoxic ingredient (i.e., phytosterol), due to transition to enteral feeds, or a combination of these factors.

Section 6 Adverse Reactions:
Except for the prespecified safety endpoints, which were included in Section 14, all other endpoints (i.e., the secondary endpoints of time and number to liver transplant, time to resolution of PNAC, hypertriglyceridemia, hyperglycemia, bleeding, etc.) were considered as descriptive safety information[96], and included in Section 6.

The table of common adverse reactions lists only data from Omegaven-treated patients. Data for the historical control group were not included as it could be biased due to unknown factors not accounted for in randomization.

Section 12 Clinical Pharmacology:
Because the fatty acid profile is informative to prescribers to understand the typical course of fatty acid changes during Omegaven use, figures showing the plasma concentrations of the fatty acid components for Omegaven (i.e., EPA, DHA, ALA, ARA, and LA) were included for patients exclusively on Omegaven and for patients receiving Omegaven along with enteral nutrition.

Section 14 Clinical Studies:
Results of the anthropometic endpoints support the efficacy of Omegaven. The primary efficacy endpoint (i.e., change in weight from baseline) in Omegaven-treated patients was included (b) (4) and the other anthropometric parameters were summarized in the text. The efficacy analyses were based on the PM population. Given that the trials by design were non-randomized studies with post-hoc analyses, and due to several limitations of the HC data (i.e., differences in baseline growth parameters as compared to the treatment group, and a small number of HC patients having available data for analysis), a direct comparison of Omegaven to HC is inappropriate. Therefore, only descriptive data for the HC comparator data were included.

Please see the approved label for Omegaven for final agreed upon labeling.

[96] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf

12 Risk Evaluation and Mitigation Strategies (REMS)

The benefit-risk profile for Omegaven is favorable, and the risks can be mitigated through professional labeling (see Section 11), enhanced pharmacovigilance, and the postmarketing studies (see Section 13). There are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted. See Division of Risk Management (DRISK) review by Dr. Charlotte Jones filed on 6/12/2018.

13 Postmarketing Requirements and Commitment

PMR/PMC Description

3445-1 Conduct a prospective, longitudinal cohort study with an external control to assess the long-term safety (defined as patient monitoring for ≥ 1 year of continuous treatment) of Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use in pediatric patients with PNAC, evaluating the potential for essential fatty acid deficiency (EFAD) by measuring:
1. long-chain polyunsaturated fatty acid (LCPUFA) profiles with prespecified thresholds to assess EFAD during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and
2. the occurrence of serious bleeding events during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and
3. neurodevelopmental delays assessed later in life to include at least the baseline Bayley assessments at 6 months, 12 months and (b) (4) 2 years; and age appropriate assessment at 5 years of age.

In addition, life-threatening pleural and pericardial effusions will also be reported during Omegaven infusion and 4 weeks after discontinuation of Omegaven. Clinical narratives will be assessed to determine whether the pleural/pericardial effusions are clinically related to the infusions.

PMR/PMC Schedule Milestones

Draft Protocol Submission: 05/2019
Final Protocol Submission: 11/2019
Interim Report #1: 12/2021
Interim Report #2: 12/2022
Interim Report #3: 12/2024
Study Completion: 07/2026
Final Report: 06/2027

PMR/PMC Description

3445-2 Conduct a study to show that the levels of the elemental impurities, (b) (4) , are controlled in Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use.

This study should include a risk assessment and screening of the finished product for the elemental impurities as stated above including analysis of at least three batches of the product. Develop and validate a detailed rationale for the calculation of control thresholds and acceptance criteria for all elements stated above, with

consideration of the amount of each element that may be intentionally added to TPN.

PMR/PMC Schedule Milestones

Interim Report (which will include available screening data, rationale for control thresholds and acceptance criteria and an initial risk evaluation): 12/2018
Final Report Submission: 06/2019

14 Division Director (Clinical)

I concur with the reviewers that Omegaven (fish oil triglycerides) lipid emulsion for intravenous use provides intrinsic nutritional value that outweighs the potential risks, and recommend approval of NDA 210589 as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC).

This application was granted orphan drug status. The patient population is one that is dependent on parenteral nutrition where enteral nutrition is not possible, insufficient, or contraindicated.

The data used to support the approval of this product include:

1. Nutritional efficacy was assessed by biomarkers of lipid metabolism, mean changes in fatty acid parameters, and anthropometric indices (body weight, length/height and head circumference). (Study 34/35)
2. A comparison of the study data to gender- and age-standardized Fenton and WHO growth charts, especially where Omegaven was the exclusive lipid source (Study 34/35);
3. The well known biochemical and metabolic properties of lipids as a source of energy and essential fatty acids.

Taken together these data support a finding of substantial evidence of effectiveness for the following indication: “Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)”.

The proposed maximum daily dose of Omegaven for pediatric patients is 10 mL/kg/day (1 g lipid/kg/day). The recommended duration for infusion of Omegaven is between 8 and 24 hours, depending on the clinical situation. The proposed dosing scheme is consistent with total parenteral nutrient (TPN) dosing rationale, which is based upon the caloric needs of each patient.

ASPEN Guidelines (2002) for infants and preterm neonates recommend 0.5 to 1.0 g lipids/kg/day upon initiation of parenteral nutrition, increasing by 0.5 g/d to a maximum of 3.0 g lipids/kg/day. The studied dose of 1 g lipid/kg/day is lower than that recommended by these guidelines. However, patients in the clinical trial and in the compassionate-use program received a higher dose of glucose and amino acids to meet their caloric needs. The safety profile from these patients is acceptable. In addition, there was no evidence indicating that patients were at a higher risk of developing essential fatty acid deficiency (EFAD) during the studied treatment duration. See relevant review section on clinical safety.

We considered the safety profile of 189 Omegaven-treated patients with PNAC who were dependent on parenteral nutrition. The median duration of Omegaven treatment in the safety population was 13.5 weeks (min 3 days, max 7.8 years). No new safety issues were seen with Omegaven when comparing to the generally known safety profile of other parenteral lipid preparations. While there is a potential for the development of EFAD, no acute signs or symptoms were detected in the clinical trials. Further evaluation of this issue can be obtained post marketing in a required study (PMR). The potential risk of pleural and pericardial effusion will also be captured in this PMR. Typically in preparation of parenteral nutrition additional elements may be added to the admixture. Because of this, it is important to determine the level of certain elemental impurities in Omegaven to ensure that there is no danger of additive toxicity when products are combined. The sponsor submitted adequate information for the elements of concern, except for (b) (4). This will be studied in a separate PMR.

In addition to the PMRs we requested that for a period of 2 years from the U.S. approval date, the Applicant submit all cases of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported with Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use, as 15-day Alert reports, and that they provide detailed analyses of events of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported from clinical study and post-marketing reports in their periodic safety report.

The final labeling indication included limitations of use which address the potential risk of EFAD as well as any implied claim for the prevention of PNAC:

- Omegaven is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition (PN)-dependent patients.
- It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6:omega-3 fatty acid ratio of the product.

In conclusion, Study 34 and Study 35 support, in part, the approval of Omegaven as a source of calories and fatty acids in pediatric patients with PNAC. Nutritional efficacy was assessed by biomarkers of lipid metabolism, mean changes in fatty acid parameters, and anthropometric indices (body weight, length/height and head circumference). The data from these studies also

supported a finding of safety in this patient population. These studies and generally accepted scientific knowledge regarding the provision of energy and a source of essential fatty acid support a finding of substantial evidence of effectiveness for the proposed indication.

I recommend approval of Omegaven for use in the population of pediatric patients with PNAC.

15 Office Director (Office of Drug Evaluation III)

I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve NDA 210589 for Omegaven (fish oil triglycerides) injectable emulsion as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC). This product will address the unmet need for an alternative parenteral source of nutrition for pediatric patients with PNAC that is not soybean oil-based; soybean oil-based lipid emulsions are believed to contribute to progression of the manifestations of PNAC.

Omegaven treatment provided sufficient calories to adequately support growth in pediatric patients with PNAC, both as an exclusive lipid source and in conjunction with enteral nutrition. In investigator-initiated studies, growth assessed as change from baseline in body weight, height/length, and head circumference appeared similar in pediatric patients with PNAC treated with Omegaven for a median of 2.7 months (range 5 days to 8 years) and a historical control group treated with Intralipid, a soybean oil-based lipid emulsion, for a median of 3.6 months (range 16 days to 2 years). Further, patients treated with Omegaven as their exclusive lipid source achieved age-appropriate growth when compared to gender- and age-standardized Fenton, World Health Organization, and Center for Disease Control growth charts. The safety profile of Omegaven was similar to that of Intralipid and not unexpected for an intravenous lipid emulsion.

Product labeling will describe the potential for the following serious risks with use of Omegaven: 1) life-threatening pulmonary lipid accumulation which could lead to pleural or pericardial effusions, 2) hypersensitivity to fish oil or egg phospholipids, 3) risk of infection related to catheter placement and maintenance and preparation of the lipid emulsion, 4) fat overload syndrome, 5) refeeding syndrome, 6) hypertriglyceridemia, 7) aluminum toxicity, and 8) essential fatty acid deficiency. Use of Omegaven will be contraindicated in patients with 1) known hypersensitivity to fish or egg protein, 2) severe hemorrhagic disorders due to a potential effect on platelet aggregation, and 3) severe hyperlipidemia or severe disorders of lipid metabolism.

A REMS will not be required. A post-approval longitudinal cohort study will assess the potential risk of essential fatty acid deficiency and life-threatening pulmonary lipid accumulation with use of Omegaven compared to an external control. In addition, a study will be required to show that the levels of (b) (4) are controlled in the drug product.

16 Appendices

16.1. References

References are included in footnotes in the appropriate sections.

16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): OMEG-034-IP3, OMEG-035-IP3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 2 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

(b) (6)

The investigators will receive royalties, as estimated below in Table 41, from the Applicant for the sale of this product upon approval. Potential bias in the studies were mitigated by the third-party data retrieval.

Table 41. Financial Disclosure Information

(b) (6)

Source: Information Request Response dated January 30, 2018

16.3. Nonclinical Pharmacology/Toxicology

Safety Assessment of Leachables in Omegaven

Omegaven emulsion is packaged in glass vials with a (b) (4) rubber stopper. The Applicant applied a classification system for the safety assessment of leachables and extractables, which included qualification thresholds of (b) (4) µg/day for Class I (general toxicity), Class II (sensitizers), and Class III (genotoxicants), respectively. While the Agency does not specificially endorse this classification schema or the specific thresholds proposed, this approach was judged suitable for this drug development program, as described below.

The Applicant provided a toxicology evaluation of leachables detected in the drug product after storage for up to 24 months at 25°C ± 2°C/60% RH ± 5%. The maximum duration of Omegaven treatment was assumed to be 10 years. For safety assessments of potential leachables in Omegaven, the Applicant compared the maximum potential daily dose of each leachable (worst case) to the Permitted Daily Exposure (PDE) for a 50-kg bodyweight individual, as defined in ICH guidance Q3C(R4) (2009). The lowest calculated PDE values were used for this comparison. For some of the detected leachables, no toxicology data were available to support the PDE calculations. In these instances, the Applicant assigned these chemicals to one of the three

classes (I, II, or III) according to the Cramer classification system. The assigned Cramer class was used to generate a PDE. Most of the leachables evaluated in this manner did not raise safety concerns, because of the very low exposures (< (b) (4) µg/day) that may occur in the target patient population (i.e., infants), based on an assumed bodyweight of 5 kg. For the other leachables, the PDEs were appropriately derived from a no observed effect level (NOEL) in the most sensitive animal species.

Toxicity studies with chemicals identified as leachables are usually limited to the oral or inhalation routes. Because the route of exposure to leachables in Omegaven will be intravenous, an additional safety factor of 10 (i.e., F6 = 10) was used for the PDE calculations, to support the conversion of oral NOEL values to intravenous PDEs. This method is consistent with the safety assessment procedure previously used by DGIEP for leachables in large volume parenteral drug products.

The proposed dose for Omegaven, which is to be marketed in 50 mL and 100 mL bottles, is 1 g/kg/day (10 mL Omegaven/kg/day). The Applicant stated that the 50 mL bottle was used to calculate the worst-case exposure to leachables, because of the higher surface area to drug product volume ratio. Therefore, the worst-case exposure for a 50-kg individual would involve the administration of 10 bottles containing 50-mL of Omegaven in 24 hours (i.e., 500 mL/day). The Applicant conducted leachables studies with the complete container closure system filled with Omegaven under both long-term (0, 3, 6, 12, 18, and 24 months at 25°C ± 2°C/60% RH ± 5%) and accelerated (0, 3, and 6 months at 40°C ± 2°C/75 % RH± 5%) conditions. In addition, simulation studies were conducted using 13% ethanol as a model solvent for Omegaven, to evaluate leaching of specific stopper components that are difficult to measure in lipid emulsions. The Applicant stated that the model solvent (b) (4) The following extractables were measured only in the simulation studies using 13% ethanol:

(b) (4)

HPLC with pre-column concentration was used for evaluating non-volatile and low-volatile compounds. Head-space gas chromatography (HS-GC) with a flame ionization detector (FID) was used for analyzing highly volatile compounds. Gas chromatography with a FID was utilized for detection of vaporizable plastic additives, and HPLC was used to detect non-volatile and low-volatile plastic additives.

In the tables below, the Applicant provided a list of leachables from the two rubber stoppers, as detected in the leachables studies. The Applicant calculated the maximum daily exposure levels based on the maximum daily dose of Omegaven (500 mL/day in a 50-kg patient), along with the

corresponding PDE values or equivalent toxicological threshold levels [threshold of toxicological concern (TTC)]. The assumed bodyweight of 50 kg in the Applicant's safety assessment is not appropriate for the expected patient population (i.e., infants) in which Omegaven will be used. However, the Applicant's use of 50 kg as the assumed bodyweight provides an additional assurance of safety for the leachables which were shown to be compliant with the PDE at the maximum daily exposure.

Table 42. Leachables and Simulation Studies with Stopper (b) (4)

Leachable	CAS-No.	Maximum Detected Amount [µg/L]	Maximum Daily Exposure [µg/d] 1)	PDE [µg/d] 2)
(b) (4)				

n.d. – not detected
1) Worst Case dosage of Omegaven for a 50-kg patient in 24 hr (500 mL/day)
2) Permitted Daily Exposure for a 50-kg person
3) Class 2 solvent according to ICH Guidance Q3C(R6)
4) Class 3 solvent according to ICH Guidance Q3C(R6)
5) TTC (Threshold of Toxicological Concern), Cramer classification (not accepted by FDA)
6) Limit of Detection was (b) (4) could not be detected, possibly due to oxidation of the blank matrix solution used for the spiking experiment. Therefore spiking experiments with 2 x LOD will be performed with the next set of samples.
7) TTC (Threshold of Toxicological Concern), ICH Guidance M7, (less than lifetime approach for > 1 – 10 years of use)
8) Study performed by external laboratory (b) (4)

Table 43. Leachables and Simulation Studies with Stopper (b) (4)

Leachable	CAS-No.	Maximum Detected Amount [µg/L]	Maximum Daily Exposure [µg/d] 1)	PDE [µg/d] 2)
(b) (4)				

n.d. – not detected
1) Worst Case dosage of Omegaven for a 50-kg patient in 24 hr (500 mL/day)
2) Permitted Daily Exposure for a 50-kg person
3) TTC (Threshold of Toxicological Concern), current PQRI proposal (currently not accepted by FDA)
4) TTC (Threshold of Toxicological Concern), Cramer classification (not accepted by FDA)
5) TTC (Threshold of Toxicological Concern), ICH Guidance M7, (less than lifetime approach for > 1 – 10 years of use)
6) The intended Limit of Detection of (b) (4) could not be established, possibly due to oxidation of the blank matrix solution used for the spiking experiment. Therefore, spiking experiments with 2 x LOD will be performed with the next set of samples
7) Class 2 solvent according to ICH Guidance Q3C(R6)
8) Class 3 solvent according to ICH Guidance Q3C(R6)

9) (b) (4)

10) Study performed by external laboratory ((b) (4)

Both the (b) (4) stoppers will be used for packaging Omegaven in glass vials (50- and 100-mL). From the leachables listed for the (b) (4) stoppers, the calculated maximum daily exposure levels of four leachables exceeded the PDE or TTC levels with administration of 500 mL Omegaven. The safety assessment of these leachables is described below.

1. (b) (4)

The calculated maximum daily exposure level for (b) (4) based on data from the leachables study conducted with Omegaven. There were no experimental data to evaluate the genotoxicity of (b) (4). Therefore, the Applicant utilized two (Q)SAR methodologies, Derek Nexus (rule based for functional groups) and CASE Ultra™ (statistically based), to predict genotoxicity/ mutagenicity. Both Derek™ and CASE Ultra™ predicted that (b) (4) was negative for bacterial mutagenicity.

Although (b) (4) is considered non-mutagenic based on the (Q)SAR analysis, the Applicant did not provide an acceptable rationale to assure the safety of the maximum daily exposure ((b) (4) µg) based on the assumed bodyweight of 50 kg. However, for the expected population (infants) in which Omegaven will be used, it is reasonable to use an assumed bodyweight of 5 kg for safety assessment of leachables. Thus, maximum daily exposure to (b) (4) in the target patient population is estimated to be (b) (4) µg. Although this dose is quite low for a leachable considered non-mutagenic, there are no animal toxicology studies available to support a safety assessment related to general toxicity.

In the amendment dated June 7, 2018 (response to Information Request), the Applicant provided the following information regarding the prior use of the (b) (4) stopper in the Omegaven container closure system.

Fresenius Kabi confirms that the drug product, Omegaven, has been packaged and supplied for use in the intended patient population in the same container proposed for the commercial product, i.e. glass bottle, USP, (b) (4) colourless 50 mL or 100 mL, but with only the (b) (4) rubber stopper, (b) (4). The human safety data is based on product use in this container closure system administered in the 2 clinical studies submitted in the NDA (conducted under IND 73,488 and IND 102,843) as well as for Omegaven that has been administered in the United States under about 30 other compassionate-use INDs. The Omegaven usage using the stopper (b) (4) for the 2 clinical studies submitted in the NDA is shown in Table 3.

Table 3 Pediatric patients exposed under IND 73,488 and IND 102,843

IND Number	Time period[a]	Number of pediatric patients	Average duration of administration (days)[b]	Patient Years[c]
IND 73,488 (Boston Children's Hospital)	Sept 2004 to Dec 2017 (last reporting period)	279	368	281
IND 102,843 (Texas Children's Hospital)	Sept 2007 to October 2017 (last reporting period)	262	106	76

a. Patients continue to be enrolled and treated under the respective INDs
b. Average duration of Omegaven administration is based on the data submitted in the NDA (Table 14.3.1.1.1.4 in **OMEG-034-IP3** and **OMEG-035-IP3**)
c. Patient years calculated based on the number of pediatric patients and average duration of Omegaven administration

In addition, the overall usage of Omegaven in the US is shown in Table 4 below. The overall usage is based on the Omegaven units distributed in the US between 2005 to 2018. The patient exposure numbers have been estimated from the total units distributed in the US using the average dose, average body weight, and the average duration of Omegaven administration determined from the two studies conducted under IND 73,488 and IND 102,843.

Table 4 Estimate of overall patients exposed to Omegaven in the US

Year	2005-2008[a]	2009-2013	2014-2018
Omegaven 50 mL [units]	2,050	3,310	2,500
No. of Patients exposed	7	11	8
Omegaven 100 mL [units]	16,220	68,830	144,450
No. of Patients exposed	104	441	926
Omegaven Total [units]	18,270	72,140	146,950
Total no. of Patients exposed	**111**	**452**	**934**
Total Patient Years[b]	**86**	**351**	**610**

a. In 2004, one patient was treated at Boston Children's Hospital with Omegaven. However, the amount and unit size of Omegaven this patient received is not known.
b. Patient Years calculate based on the total number of exposed patients and the mean overall duration of Omegaven administration (**TABLE 10.2.1.4i** in the Integrated Summary of Safety)

The human experience with Omegaven packaged with the [redacted](b) (4) stopper and the resulting clinical safety data provide a reasonable assurance of safety for the estimated maximum daily exposure to [redacted](b) (4).

2. [redacted]

[redacted] was detected as a leachable in Omegaven. Although [redacted] is a listed leachable in the tables for both stoppers, the Applicant clarified that it should not have been listed for the [redacted] stopper, because [redacted] is not contained in this stopper. Since [redacted] was not detected in the product packaged with the [redacted] stopper, the limit of detection (LOD) of [redacted] µg/L was assumed to be the concentration. Therefore, the maximum daily exposure was calculated as [redacted] µg/day. The Applicant proposed that the intended LOD of [redacted] µg/L for [redacted] could not be established due to [redacted] used for the spiking experiment. The Applicant will be conducting additional experiments to reduce the LOD.

There were no experimental data to evaluate the genotoxicity of [redacted]. The Applicant utilized two (Q)SAR prediction methodologies, Derek Nexus (rule based for functional groups) and CASE Ultra™ (statistically based), to predict genotoxicity/mutagenicity. In the CASE Ultra Expert review, [redacted] was found to be positive for bacterial mutagenicity and in the mammalian in vitro assay (not specified). The results for the in vivo micronucleus were predominantly out of domain, and partly inconclusive. In the in vitro chromosomal aberrations assay, the (Q)SAR predictions were variable (positive, out of domain and inconclusive).

Based on the positive prediction for bacterial mutagenicity from Case Ultra, [redacted] is considered as genotoxic, and the recommendations from ICH M7 can be applied to support the safety assessment. The acceptable intake for genotoxic leachables in Omegaven is considered to be 10 µg/day, as recommended for the less than lifetime approach with > 1 – 10 years of use (ICH M7). The calculated (theoretical) maximum daily dose of [redacted] µg based on a 50-kg-body weight exceeds this level. However, for an assumed bodyweight of 5 kg in the target patient population (infants), the maximum daily dose is calculated to be [redacted] µg, which is compliant with the acceptable intake.

3. [redacted]

[redacted] was detected as a leachable in Omegaven packaged with the [redacted] stopper, and the calculated maximum daily exposure was [redacted] µg/day. In the CASE Ultra Expert review, [redacted] was found to be negative for bacterial mutagenicity assays, and positive in the in vitro mammalian assay. Based on the negative prediction for bacterial mutagenicity, [redacted] can be evaluated as a non-genotoxic leachable. In the absence of toxicology data to support a calculation of the PDE, the Applicant used the qualification threshold (50 µg/day) currently proposed by PQRI for non-genotoxic/non-sensitizing and non-irritating leachables in large volume parenterals. The FDA has not endorsed the qualification threshold proposed by PQRI.

For an assumed bodyweight of 5 kg in the target patient population (infants), the maximum daily dose of (b) (4) is calculated to be (b) (4) µg. Although this dose is quite low for a leachable considered as non-mutagenic, there are no animal toxicology studies available to support a safety assessment related to general toxicity. However, the (b) (4) stopper has been accepted for use in several FDA-approved parenteral nutrition products, including a lipid emulsion approved for pediatric patients. Therefore, based on prior human experience, there is a reasonable assurance of safety for the potential exposure to (b) (4) in Omegaven.

4. (b) (4)

(b) (4) were detected as a leachable in the simulation study conducted with 13% ethanol packaged with the (b) (4) stopper. The calculated maximum daily exposure is (b) (4) µg/day from treatment with Omegaven.

Genotoxicity potential of (b) (4) was evaluated using two (Q)SAR prediction methodologies, Derek Nexus and CASE Ultra™. (b) (4) were predicted to be inactive for bacterial mutagenicity by Derek Nexus. In the CASE Ultra Expert review, (b) (4) was predicted to be negative for bacterial mutagenicity. The prediction was inconclusive for the in vitro mammalian chromosomal aberration assay. The results were predominantly negative, but were also partly inconclusive or out of domain for the in vivo micronucleus assay and in vitro chromosome aberrations assay. Based on the negative predictions for bacterial mutagenicity, (b) (4) can be evaluated as a non-genotoxic leachable. In the absence of toxicology data to support a calculation of the PDE, the Applicant again used the qualification threshold (50 µg/day) currently proposed by PQRI for non-genotoxic/non-sensitizing and non-irritating leachables in large volume parenterals. As stated above, this qualification threshold is not currently accepted by the FDA.

For an assumed bodyweight of 5 kg in the target patient population (infants), the maximum daily dose of (b) (4) is calculated to be (b) (4) µg. This dose is quite low for a leachable considered as non-mutagenic, such that the concern for general toxicity is minimal. However, it should be noted that no animal toxicology studies are available to support a safety assessment related to general toxicity. As stated above, the (b) (4) stopper has been accepted for use in several FDA-approved parenteral nutrition products, including a lipid emulsion approved for pediatric patients. Therefore, based on prior human experience, there is a reasonable assurance of safety for the potential exposure to (b) (4) in Omegaven.

16.4. Investigator-Initiated Trial Designs

16.4.1. Study 34

Trial Design

Study 34 was conducted in a single center, BCH, as a non-randomized, compassionate-use, open-label, prospective, single-arm study. The efficacy and safety of Omegaven, as a source of calories and fatty acids in patients with PNAC, were evaluated by comparing Omegaven-treated patients from BCH to HC patients who were administered a soybean oil-based lipid emulsion as a part of their PN regimen from BCH, TCH, and UCLA.

Inclusion criteria for the Omegaven-treated patients were as follows:

- Patient was PN-dependent (unable to meet nutritional needs solely by EN) and expected to require PN for at least 30 more days.
- Patient had PNAC, defined as a DBil value ≥ 2.0 mg/dL or by histology, and/or was already receiving Omegaven through another protocol. Other causes of liver disease were to be excluded. A liver biopsy was not necessary for treatment.
- Patient had a DBil level > 2.0 mg/dL, had PNAC or PNALD by histology, or was already receiving Omegaven through another protocol.
- Signed patient informed consent.
- Patient failed standard therapies to prevent the progression of liver disease, including surgical treatment, cyclic PN, avoiding overfeeding, reduction/removal of copper and manganese from PN, advancement of enteral feeding, and the use of ursodiol.

Pertinent exclusion criteria were as follows:

- Pregnancy
- Other causes of liver disease (hepatitis C, cystic fibrosis, biliary atresia, and alpha 1 anti-trypsin deficiency)
- Signs of advanced liver disease including cirrhosis on biopsy, varices, ascites.

Investigational product:

- Omegaven manufactured by FK, provided as an emulsion from fish oils, as 50 mL and 100 mL of 10% Omegaven
- Starting dose of 0.5 g/kg/day infused over 12-24 hours, then after 2 days increased to the goal dose of 1 g/kg/day
- Additional fat calories to be provided via the enteral route if needed
- Parenteral fat emulsion (Intralipid) was to be administered only if necessary to

administer adequate calories during Omegaven therapy, as determined by the clinical team and the patient's primary physician

- Duration exceeding 6 months evaluated on a case-by-case basis by the Data Safety Monitoring Board (DSMB).

Note that the concurrent nutritional management performed without a pre-specified standardized protocol by clinical judgement for both EN and PN in the single-arm open-label trial, including the possibility of Intralipid co-administration during the Omegaven treatment, impacts the interpretability of this trial's nutritional outcomes.

Study Endpoints

Primary efficacy endpoints in the original Study 34 protocol were as follows:

- Normalization of hepatic enzymes and bilirubin
- Prevention of EFAD.

These initial "efficacy" endpoints were poorly defined and eventually evolved to become more specified as "safety" endpoints after multiple interactions with the Division.

Schedule of Assessments

Table 44 contains a schedule of nutritional monitoring assessments for Study 34.

Table 44. Study 34 Schedule of Procedures and Assessments

	Screening	Baseline	Daily	Weekly until DB <2mg/dL	Biweekly until DB <0.4 mg/dL	Monthly once DB <0.4mg/dL	Periodically
Day or Week No.		(pre-omegaven)					
Complete H&P	✓	✓					
Diagnosis of PNAC	✓	✓					
Weight	✓	✓	✓				
Fluid balance		✓	✓				
Vital Signs	✓	✓	✓				
Catheter site / function		✓	✓				
Laboratory Tests:				✓	✓	✓	
Sodium		✓		✓	✓	✓	
Potassium		✓		✓	✓	✓	
Chloride		✓		✓	✓	✓	
Glucose		✓		✓	✓	✓	
BUN		✓		✓	✓	✓	
Creatinine		✓		✓	✓	✓	
Triglycerides		✓		✓	✓	✓	
Calcium		✓		✓	✓	✓	
Magnesium		✓		✓	✓	✓	
Phosphorus		✓		✓	✓	✓	
Prealbumin		✓		✓	✓	✓	
C reactive protein		✓		✓	✓	✓	
Albumin		✓		✓	✓	✓	
Total protein		✓		✓	✓	✓	
SGPT		✓		✓	✓	✓	
Alkaline phosphatase		✓		✓	✓	✓	
Bilirubin (total and direct)	✓	✓		✓	✓	✓	
GGT		✓		✓	✓	✓	
AST		✓		✓	✓	✓	
Essential Fatty Acid Profile		✓		✓	✓	✓	
Free cholesterol		✓		✓	✓	✓	
Free fatty acids		✓		✓	✓	✓	
Lipid Panel		✓		✓	✓	✓	
Hemoglobin		✓		✓	✓	✓	
Hematocrit		✓		✓	✓	✓	
RBC		✓		✓	✓	✓	
WBC		✓		✓	✓	✓	
Platelets		✓		✓	✓	✓	
PT		✓		✓	✓	✓	
PTT		✓		✓	✓	✓	
INR		✓		✓	✓	✓	
Fibrinogen		✓		✓	✓	✓	
Selenium							✓
Zinc							✓
Aluminum							✓
Copper							✓
Iron							✓
Carnitine							✓
Vitamins A, D, E							✓
Retinol binding protein							✓

Source: Reviewer's table based on Study 34 Protocol Table 3: Suggested Monitoring Schedule for Omegaven Therapy, Protocol Amendment September 30, 2008

16.4.2. Study 35

Trial Design

Study 35 was conducted in a single center, TCH, as an open-label single-arm study.

Pertinent inclusion criteria for the Omegaven-treated patients were as follows:

- Greater than 14 and less than 180 days of age
- Infants / toddlers (0 – 36 months), premature infants (< 37 weeks)
- Have cholestasis defined as a DBil > 2 mg/dL
- Be receiving at least 20% of their calories by intravenous infusion
- Be expected to require intravenous nutrition for at least an additional 14 days.

Pertinent exclusion criteria were as follows:

- Have a congenitally lethal condition (e.g., trisomy 13)
- Have clinically severe bleeding not able to be managed with routine measures
- Have evidence of a viral hepatitis or primary liver disease as the primary etiology of their cholestasis
- Have other health problems such that survival is extremely unlikely even if the infant's cholestasis improves.

Investigational product:

- Omegaven manufactured by FK, provided as an emulsion from fish oils, at a dose of 1 g/kg/day.
- Parenteral fat emulsion (Intralipid) will be administered only if necessary to administer adequate calories during Omegaven therapy.
- Duration not to exceed 5 months.

Note that this single-arm open-label study protocol initially allowed Intralipid co-administration during Omegaven treatment, which is a significant confounder. Nutritional management was supervised by the study investigators (Dr. Abrams and Dr. Carter); however, no protocols were submitted, and subsequent amendments note that there were variabilities in nutritional management.

Study Endpoints

Primary efficacy endpoints in the original Study 35 protocol were as follows:

- Survival without liver transplant
- Total bilirubin 60 days after enrollment
- Bloodstream infections (# of episodes of sepsis)

- EFAD (3 and 6 weeks starting therapy).

Secondary efficacy endpoints in the original Study 35 protocol were as follows:

- Time to full feeds
- Evidence of rickets and resolution (maximum alkaline phosphatase activity)
- Growth in weight, length and head circumference.

The initial primary efficacy endpoint for Protocol H-21344 was survival without liver transplant. The Applicant at the time declared plans to explore the HC database to determine the appropriate sample size for another efficacy endpoint of decreasing total bilirubin after 60 days of therapy.

16.5. Protocol Amendments

16.5.1. Study 34

Protocol Amendment #1 9/30/2008

- Elaborated on the specific aims with corresponding hypothesis statements.
- Updated the patient exposure – additional 55 patients treated with Omegaven, and as of August 9, 2007, no patient receiving Omegaven has died of PN associated liver disease.
- Updated FDA IND 73488 status information, granted Safe-to-Proceed on December 13, 2006.
- Patient inclusion criteria modified to specify that PN dependent patients should be expected to require PN for at least another 30 days.
- Changed the dosing regimen to initiate at the goal dose of 1 g/kg/day and infused over 12 - 24 hours.
- Removed the co-administration of intralipids during treatment.
- Routine nutritional monitoring added (Table 3 in the protocol).
- Incorporated a conventional PN comparison group, “Soybean based Fat Emulsion (Intralipid and/or Liposyn)” as historical controls, a subset selected from patients previously studied by Andorsky et al. from 1985 – 1996.
- Outlined the plan for a second analysis using more contemporary historical controls 50 patients retrospectively enrolled and previously treated with soybean-based emulsions from 1999 -2004.
- Included arrangements for monitoring for home-use of Omegaven per discretion of principal investigator.
- Secondary fatty acid analysis on red blood cell (RBC) membranes added to examine the fatty acid composition of the RBC membranes which is significantly influenced by the ratio of dietary 3 to 6 fatty acids.
- Schedule of Assessments added.

Protocol Amendment #2 5/14/2009

- Changed the dosing regimen to infuse over 8 - 24 hours, as long as the infusion does not exceed a maximum infusion rate of 0.15 g/kg/hour.
- Replaced the Committee of Study Investigators meeting occurring every 3 months with the weekly Center for Advanced Intestinal Rehabilitation (CAIR) team weekly rounds.
- Further description of Andorsky et al. procedure[97].

Protocol Amendment #3 11/30/2009

- Changes made to the Reversal Lab Schedules to reduce the lab monitoring for patients who have reached DBil level to < 2 mg/dL.
    - Less frequent[98] monitoring for the patients after reaching the resolution of cholestasis cut-off (< 2 mg/dL)
    - Less stringent requirement of 1 vs. 2 consecutive DBil measurements of < 2 mg/dL to space out the lab monitoring interval to monthly for outpatients
- All instances of trademark symbol for Omegaven™ replaced with registered trademark symbol Omegaven®.
- List of DSMB members updated.

Protocol Amendment #4 1/31/2010

- Inclusion criteria updated to include that PNAC could have been identified through histology or patients may have already been receiving Omegaven under another protocol.
- The database management system was changed from Statistical Package for the Social Sciences (SPSS) to Research Electronic Data Capture (REDCap) to reflect changes in the institution's equipment.
- Details regarding sending de-identified discarded blood samples to a collaborator at the (b) (4), for lipidomic analysis were outlined.

16.5.2. Study 35

Initial protocol submitted on 6/5/2007

Initial approval by IRB for Baylor College of Medicine and Affiliated Hospitals on 7/24/2007

Amendment 1 (H-21344) approved on 12/3/2007

[97] For either brand, IFE was typically initiated at a low rate and advanced as tolerated. In the Andorsky et al cohort, a typical starting dose for VLBW infant was 0.5 - 1 g/kg/day that was advanced in increments of 0.5 g/kg/day until a goal of 3 g/kg/day is reached, provided that it did not exceed 60% of total calories.

The family (or legal guardian) will be billed for the Omegaven as part of their hospital bill from TCH

Amendment 2 (H-21344) approved on 6/4/2008

Broaden the inclusion criteria to patients greater than 14 days to less than 6 months corrected age (66 weeks PMA).

Generalized the Omegaven administration to "per TCH policies and procedures."
Increase the amount of blood drawn from 0.3 mL to 0.5 mL per sample, and specified a total blood volume drawn to 1 mL (routine) to 3 mL (if needed) during the trial.

Original Protocol (H-23365) submitted on 6/10/2008 and approved on 7/16/2008

- Submitted after completion of 14 of 15 patient enrollment on H-21344.
  Main changes from H-21344 to H-23365 were the eligibility criteria based on the data from the initial cohort of 14 babies:
  - Severe, life-threatening cholestasis defined as a DBil greater than or equal to 6 mg/dL (increased from 2 mg/dL)
  - Be receiving at least 60% of calories by intravenous infusion (increased from 20%)
  - Be expected to require intravenous nutrition for at least an additional 28 days (increased from 14 days)
- Primary efficacy measures and variables to be analyzed modified to:
  1. Total days of TPN
  2. Maximum conjugated bilirubin
  3. Time to resolution of bilirubin or death/transplant
  4. Positive blood cultures.
- Expanded the potential side effect section to include hyperglycemia, overdose and metabolic acidosis in patients who receive excessive doses without simultaneous administration of dextrose.
- Established an independent study specific DSMB to oversee the conduct of and assess the benefit/risk of the ongoing trial with a review of recruitment, safety and efficacy data every 6 months.
- Added Children's Nutrition Research Center to the list of institutions where the study will be conducted.
- Increased the hypertriglyceridemia limit from > 250 mg/dL to > 300 mg/dL.
- Schedule of assessments modified – After every 4 weeks that the patient remains without any enteral nutrition intake, 0.5 mL of blood will be taken for triene:tetraene ratios to determine EFAD. Specified the potential upper limit of total blood volume drawn for study as 2.5 mL.

Amendment 1 (H-23365) approved on 5/11/2009

- Addition of additional DSMB members.
- Updated with the IND number (from BCH IND 73488 to Texas-specific IND 102843).

Amendment 2 (H-23365) approved on 6/4/2009

- Changed the eligibility criteria to lower the definition of life-threatening cholestasis to DBil greater than or equal to 5 mg/dL from 6 mg/dL.
- Expanded section H2 and H3 to include specific items for Data and Safety Monitoring Plan.

Amendment 3 (H-23365) approved on 7/10/2009

- Updated the inclusion criteria to stratify DBil cut-off for short gut (> 50% of bowel removed) syndrome or known severe dysmotility (clinical evidence of non-functional gut) patients (≥ 2 mg/dL) and those without anatomic or dysfunctional short gut (≥ 4 mg/dL).

Amendment 4 (H-23365) approved on 10/12/2009

- Removed non-Baylor co-investigators, Dr. Mark Puder and Dr. Kathleen Gura, from BCH.
- Updated DSMB members and procedures:
    - Include Dr. Mark Puder, Kathleen Gura, and Stephanie Abrams.
    - Retained the same chair, Dr. Robert Shulman (BCM).
    - Removed all other previous members.
    - Changed the frequency of the DSMB meetings from every 6 months to once a year.

Amendment 5 (H-23365) approved on 2/10/2010

- Added allowance for home-use of Omegaven.
    - Extended the duration of therapy to "no minimum or maximum length of time for the patient to receive Omegaven. Referenced BCH experience of patients who have received Omegaven for over 2 – 5 years.
    - Broadened the inclusion criteria to ages 14 days to 5 years of age.
    - Outpatient Home-use population will include infants up to 5 years of age.
    - Ensure at least 72 hours of inpatient monitoring at initiation of outpatient therapy.
    - Outpatient monitoring every 2 weeks for the first 2 months, then monthly thereafter.
    - Only clinical assessment of EFAD for outpatient monitoring.

- Increased the sample size from 15/year to 25/year.

Amendment 6 (H-23365) approved on 7/20/2010

- Changed the title from "Compassionate use of an intravenous Fat Emulsion Comprised of Fish oil in the Treatment of Parenteral Nutrition Induced Liver Injury in Infants" to "Children".
- Increased the referenced Boston exposure from 200 to 300 patients with no changes in the known safety profile at the time.
- Specified monitoring plans and consent procedure for Home-use patients after readmission to the hospital.

Amendment 7 (H-23365) approved on 3/11/2011

- Dr. Muralidhar Premkumar added as a co-investigator.
- Increased the projected sample size from 25 to 50 patients/year.

16.6. Statistical Analysis Plan

After the change to the proposed nutritional indication, significant changes were implemented in the SAP finalized on September 30, 2016. For both studies, the primary and secondary efficacy endpoints were as follows:

Primary Endpoint

- Changes over time in body weight adjusted for age

Secondary Endpoints

- Changes over time in body length/height adjusted for age
- Changes over time in head circumference adjusted for age
- Time to and number of patients who achieve full enteral feeding, defined as ≥ 100 kcal EN/kg/day or evidence of patient weaned from PN
- Time to and number of patients with resolution of PNAC (ROPNAC), defined as the time (weeks) from baseline to when DBil levels decrease to < 2.0 mg/dL
- Changes over time in liver function parameters: DBil, AST, and ALT
- Time to and number of patients with liver transplantation.

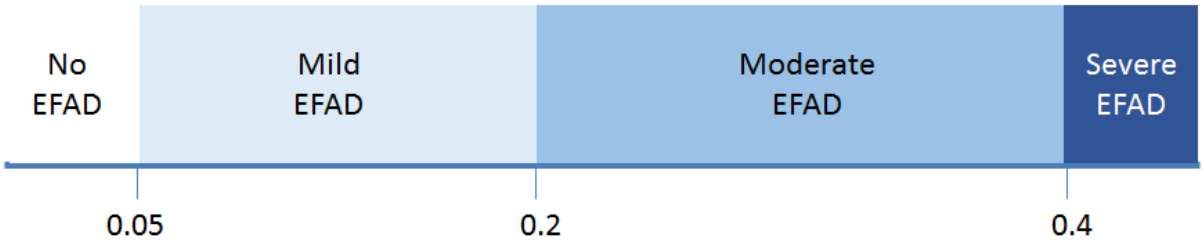
Safety Endpoints

In response to the Division's request, the Applicant submitted their originally planned efficacy endpoint (i.e., a composite endpoint of DBil < 2 mg/dL and AST or ALT < 3 x ULN) redefined as a safety endpoint. The time to and number of patients with ROPNAC (i.e., DBil < 2 mg/dL) and ALT

and AST < 3 x ULN were analyzed in the same manner as time to death and number of patients who died.

The number and percentage of patients with EFAD were measured by the triene/tetraene ratio (Holman Index). Respective data are only available for Omegaven-treated patients at BCH. The frequency of development of EFAD was broken down by severity categories defined by the calculated triene/tetraene ratio as shown in Figure 22.

Figure 22. EFAD Categorization

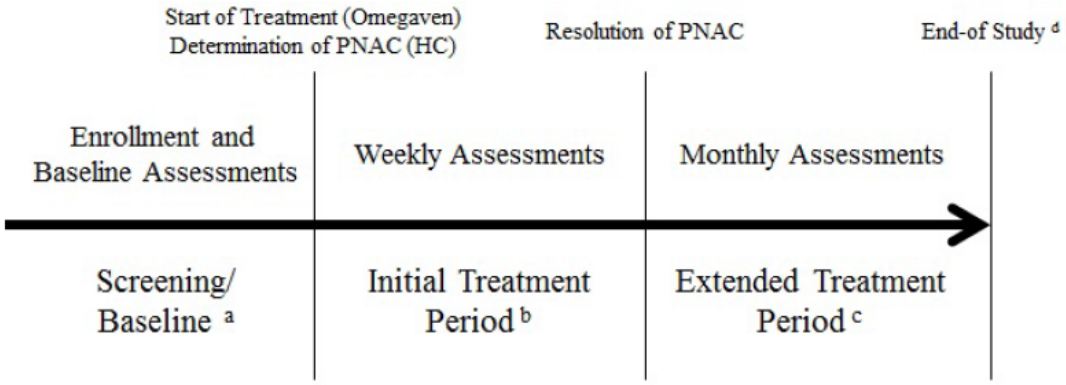


Source: Reviewer's figure based on Applicant's SAP

Study Analysis Periods

A general overview of the study design for both studies is shown in Figure 23.

Figure 23. General Study Design – Pivotal Studies



Source: Figure 1 from Applicant's SAP (p. 17)

Baseline was defined as the time point immediately prior (up to 3 days) to initiation of Omegaven administration (Omegaven-treated patients) or determination of PNAC (HC patients).

The initial treatment period was considered to start with the first administration of study drug (Omegaven-treated patients) or determination of PNAC by DBil ≥ 2 mg/dL on two consecutive samples (HC patients) and continued until resolution of PNAC, weaning from PN, patient

discontinuation, or June 30, 2012, whichever occurred first. The resulting date is the end of the initial treatment period (EOITP) date.

The extended treatment period started after resolution of PNAC and continued until one of the following events occurred (whichever occurred first):

- Weaning from PN
- June 30, 2012
- 12 months post ROPNAC (HC patients only)
- Patient's discontinuation from the study.

The extended treatment period for HC patients was limited to a maximum of 12 months. The resulting date is the end of extended treatment period (EOETP) date.

Patients were considered to have completed the study if they were weaned from PN (at least 30 days without PN), were still participating in the study as of June 30, 2012, or had been followed for 12 months after ROPNAC (HC patients only), whichever occurred first. The resulting date is the end of study (EOS) date. The EOS date was equivalent to the EOITP date for patients who did not experience resolution of PNAC or were not followed after resolution of PNAC, or the EOETP date for patients who were followed after resolution of PNAC.

Study Schedule

Table 45 shows the schedule of events for Study 34 and Study 35.

Table 45. Schedule of Events for the Pivotal Studies

	Baseline	Initial Treatment Period (weekly assessment)	Extended Treatment Period (monthly assessment)
Inclusion / Exclusion Criteria	✓		
Demographics	✓		
Medical History	✓		
Nutritional History	✓		
Laboratory Parameters	✓	✓	✓
Anthropomorphic Parameters	✓	✓	✓
Study Drug Administration		✓	✓
Nutritional Information (PN, EN)		✓	✓
Adverse Events		✓(daily)	✓(daily)
Concomittant Medications	✓	✓(daily)	✓(daily)

Source: Reviewer's table based on Applicant's SAP Table 1

Study Populations

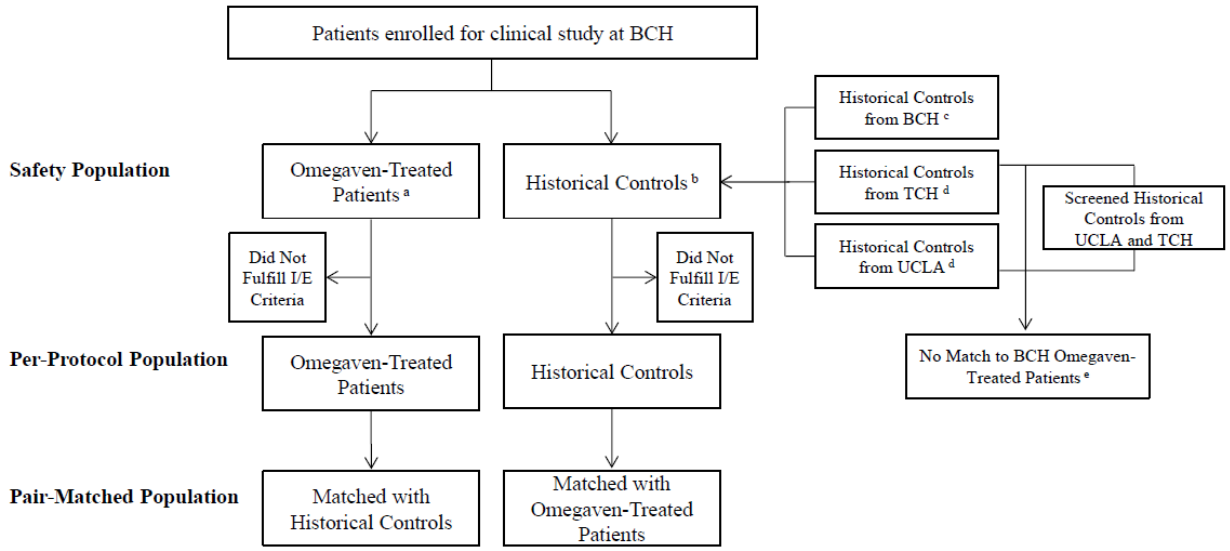
Patient populations for both studies are described below and shown in Figure 24 and Figure 25.

- Safety population –
  - Study 34: All enrolled patients who received any dose of Omegaven, all HC patients from BCH, and additional HC patients from the other sites (i.e., TCH and/or UCLA) who could be matched to Omegaven-treated patients from the PP population at BCH. All patients who received any amount of Omegaven were to be included in the Omegaven treatment group of the safety population regardless of whether they fulfilled all enrollment criteria.
    - Compassionate-use group – This subpopulation of the safety population comprises patients from BCH who did not fulfill all enrollment criteria outlined in the study protocol, but were deliberately included in the study to collect safety data.
  - Study 35: All enrolled patients who received Omegaven, all HC patients from TCH, and additional HC patients from the other sites (i.e., BCH and/or UCLA) who could be matched to Omegaven-treated patients from the PP population at TCH. All patients who received any amount of Omegaven were to be included in the Omegaven treatment group of the safety population regardless of whether they fulfilled all enrollment criteria.

- PP population – All patients from the safety population who met the inclusion/exclusion criteria, and had no major protocol deviations.

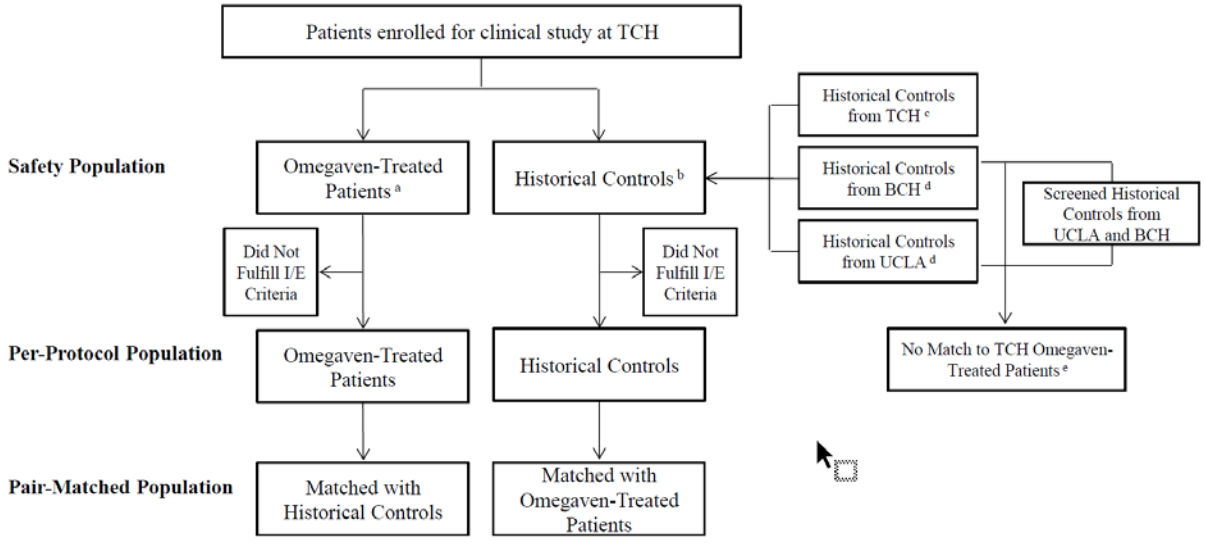
- PM population – All pair-matched Omegaven-treated patients (from the PP population) and their respective matches (HC patients), regardless of the study site for the HC patient.

Figure 24. Patient Populations for Study 34



Source: Figure 2 from Applicant's SAP (p. 25)

Figure 25. Patient Populations for Study 35



Source: Figure 3 from Applicant's SAP (p. 26)

The PM population was the primary population for the analysis of all efficacy endpoints. The PM population was used as the primary analysis population for the evaluation of efficacy because Omegaven-treated and HC patients were matched according to several baseline characteristics to provide a more homogenous population and balanced comparisons between

groups. The Applicant conducted an analysis for the primary and secondary efficacy endpoints using the PP population to provide supportive data, but results from the PP population are not shown in this review. The safety population was the primary population for the analysis of safety (see Section 8.2).

HC Matching

The Applicant used a "greedy" matching algorithm to find an optimal matching solution for a fixed set of matching options and criteria. Matching was performed using the entire pool of Omegaven-treated patients in the PP populations from BCH and TCH. The HC patients included in the matching procedure comprised patients from BCH, TCH and UCLA who received Intralipid according to the standard of care at the respective study sites, fulfilled all enrollment criteria, and for whom complete CRFs were retrieved.

DBil and PMA were the two main variables that the Applicant used for matching. Five additional secondary matching factors were ALT, AST, birthweight, underlying surgical condition, and sepsis present at baseline.

Matching Algorithm

The Applicant's HC matching algorithm contained the following steps:

1) For each HC patient, determine the number of possible matches from the Omegaven treatment group.
2) Only for 2:1 matching: Delete all HC patients who have either
    a. only one possible match to an Omegaven-treated patient from either BCH or TCH, or
    b. two possible matches, but only one possible match to an Omegaven-treated patient from BCH and one possible match to an Omegaven-treated patient from TCH.
3) Determine all HC patients with the minimum number of possible matches and choose one of them at random using a uniform distribution.
4) From all possible matches for this HC patient, choose one (or two from the same study for 2:1 matching ratio) Omegaven-treated patient(s) at random using a uniform distribution.
5) Delete all possible matches pertaining to the chosen patients (i.e., HC and Omegaven-treated patient[s]) in the previous step from the dataset with all possible matches.
6) If the dataset with all possible matches is not empty, start again with the first step. Otherwise, stop the algorithm, as there are no possible matches left.

The SAP indicated that this approach was to lead to one possible allocation of HC patients to Omegaven-treated patients. The algorithm was to be performed 100 times for an allocation

ratio of 1:1 and 2:1 to create a total of 200 solutions. A random seed was to be determined and listed for each run to ensure reproducibility of results.

Matching Selection

The evaluation of the goodness of matching was based on the following three criteria:

1) number of matched patients
2) balance between groups
3) loss function value (LFV).

The criteria were to be used sequentially to increase the number of matched patients and achieve a balanced match.

The methodology that DB VII used for deriving the full matched (FM) population is described in Appendix Section 16.9.

Sample Size

The number of patients included in the Omegaven treatment group was not derived prospectively and was not based on statistical power, but on the need for treatment with Omegaven. The number of patients included in the HC group was based on the number of selected HC patients available at BCH, TCH, and UCLA. Thus, the two studies were not prospectively powered with a sufficient sample size to detect a difference in treatment effect between the two treatment groups for any of the efficacy endpoints. The two studies were also not designed to demonstrate NI of Omegaven compared to Intralipid.

Derived Parameters

Gestational age (in weeks), chronological age at enrollment (in weeks), and PMA at enrollment (in weeks) as well as duration of drug exposure (in days), average dose (in g/day) and cumulative dose (in g) were derived parameters. Growth and development of infants were evaluated based on the parameters of body weight, body length/height, and head circumference and were gender- and age-standardized using the Fenton and the World Health Organization (WHO) growth charts. Standardization according to the WHO recommendations was derived for all growth parameters using the SAS macros provided by WHO. Age-standardized z-scores and corresponding quantiles of the standard normal distribution were derived using a publicly available Microsoft Excel calculation tool.

For patients in the Omegaven treatment group only, data on soybean oil-based lipid emulsion dosing prior to baseline were available for the week immediately preceding baseline. Records of study drug dosage in g/kg were converted to calories based on the following calculation rule of 10% lipid as 1.1 kcal/mL and 20% as 2 kcal/mL.

The intake of the essential fatty acids α-linolenic acid and linoleic acid was estimated based on the administered dose of study drug and the concentration of these essential fatty acids per drug. For Intralipid, the concentrations of α-linolenic acid and linoleic acid were 8% and 53%, respectively; for Omegaven, the concentrations of α-linolenic acid and linoleic acid were 1.3 g/L and 3.2 g/L, respectively. These intake values were calculated by averaging the concentrations of α-linolenic acid and linoleic acid reported in the certificates of analysis of Omegaven batches used at each study site.

The total kcal/kg/day and the percentage of total calories provided as PN or EN were derived. For PN components, the intake of protein and carbohydrates attributed to PN was calculated by multiplying the given dosage (g/kg) by 4.0 kcal/g protein and 3.4 kcal/g for dextrose. For EN components, the intake of protein, lipids, and carbohydrates attributed to EN was calculated based on the product information.

Missing Data

Missing values were to be imputed only for the computation of exposure to study drug and nutritional intake. The process consisted of two steps. In the first step, logical derivation of missing data was performed. For example, if it was known that the total PN was 50 kcal/kg/day, the calories from study drug were 10 kcal/kg/day, and the amount of dextrose was 20 kcal/kg/day, then a missing amount of amino acids could be deduced as being 20 kcal/kg/day. In a second step, missing data gaps of one visit were to be closed by imputation. The Applicant provided additional details regarding imputation strategies in a submitted memo titled "Derivation of Analysis Datasets ADNURAW and ADNUSUM for Omegaven US Study".

Subgroup Analysis

Subgroup analyses for the two separate studies were planned only for the Omegaven groups and only for the PP and safety populations. Results from those analyses are not shown in this review.

Interim Analysis

No interim analysis was planned.

Data Analysis Plan

All inferential statistical methods were performed with a 2-sided level of significance of 5%. However, no adjustment for multiple comparisons was implemented for any efficacy endpoints, and no formal statistical testing was performed for any efficacy endpoints.

For the primary efficacy endpoint of change over time in body weight adjusted for age, change from baseline to the EOITP, EOETP, and EOS time points were compared by an analysis of covariance (ANCOVA) with baseline value and treatment as fixed effects.

The null hypothesis of equal effects of Omegaven and Intralipid is written as $H_O: \mu_{Omegaven} = \mu_{Intralipid}$, and the alternative hypothesis of unequal effects of the treatments is written as $H_1: \mu_{Omegaven} \neq \mu_{Intralipid}$, where $\mu_{Omegaven}$ and $\mu_{Intralipid}$ denote the mean change in weight from baseline for Omegaven and Intralipid, respectively.

The secondary efficacy anthropometric endpoints of changes over time in body height/length adjusted for age, and changes over time in head circumference adjusted for age, were analyzed in the same manner as the primary efficacy endpoint.

The reviewer conducted additional efficacy analyses for the three anthropometric endpoints. These analyses evaluated the endpoints using the FM population derived by DB VII as described in Appendix Section 16.9 and/or time points that were not included in the Applicant's primary analysis.

Additionally, the secondary efficacy endpoints of time to full enteral feeding, time to ROPNAC, and time to liver transplantation were analyzed using the Kaplan-Meier method and log-rank tests. Differences between treatments in the proportions of patients who met the secondary efficacy endpoints were analyzed with the Chi-squared test or Fisher's exact test as appropriate.

Supportive univariate (including interaction between treatment group and covariate) and stepwise multivariate Cox regression analyses providing hazard ratios (HRs) with 95% CIs and corresponding p-values were performed using the following covariates observed at baseline: treatment group, PMA, DBil, study site, underlying surgical condition, birth weight, ALT, AST, and sepsis. Liver function parameters (AST, ALT, and DBil) were evaluated in safety analyses.

16.7. Additional Efficacy Analysis

Results in this section are exploratory.

16.7.1. Study 34

16.7.1.1 FM Population and Primary Analysis Methods

An analysis for the three anthropometric endpoints was conducted using the FM population and the same methods used in the primary analysis. The FM population for this study consisted of 140 patients (89 patients in the Omegaven group and 51 patients in the HC group). The Applicant's pair matching for this study resulted in an acceptable match according to the Division's full matching method, since the standard mean difference (SMD) for 5 of the 9 covariates used in the Division's full matching was < 0.1. This occurred for the GA, DBil, ALT,

AST, and sepsis covariates.

As in the primary efficacy analysis, the treatment group effect in this analysis was not statistically significant for the three anthropometric endpoints. In this population, the EOITP and EOS time points occurred at week 12 or earlier for most patients with evaluable endpoint data.

In general, results from this analysis were consistent with those of the primary analysis and suggested that for the three endpoints, when adjusting for the baseline value, there was no significant difference in mean change from baseline between the Omegaven and HC groups during the three time periods.

ANCOVA model results for the three anthropometric endpoints are shown in Table 46 through Table 48. Table 49 contains the Applicant's and Division's SMD values for the 9 covariates used in the full matching method. Mean changes from baseline in age-adjusted endpoint values over time are shown in Figure 26 through Figure 28.

Table 46. Primary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Weight (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=134)**	**EOETP (N=56)**	**EOS (N=122)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0009	<.0001	<.0001
Treatment group	0.0877	0.5210	0.8286
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.36 [-0.64, -0.09]	0.46 [0.00, 0.91]	0.17 [-0.20, 0.54]
Historical control	0.05 [-0.33, 0.43]	0.01 [-1.29, 1.32]	0.10 [-0.36, 0.57]
Difference	-0.41 [-0.88, 0.06]	0.44 [-0.94, 1.83]	0.07 [-0.53, 0.66]

Source: Reviewer's table
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 26. Mean Change from Baseline in Age-adjusted Body Weight Over Time in Study 34 (FM Population)

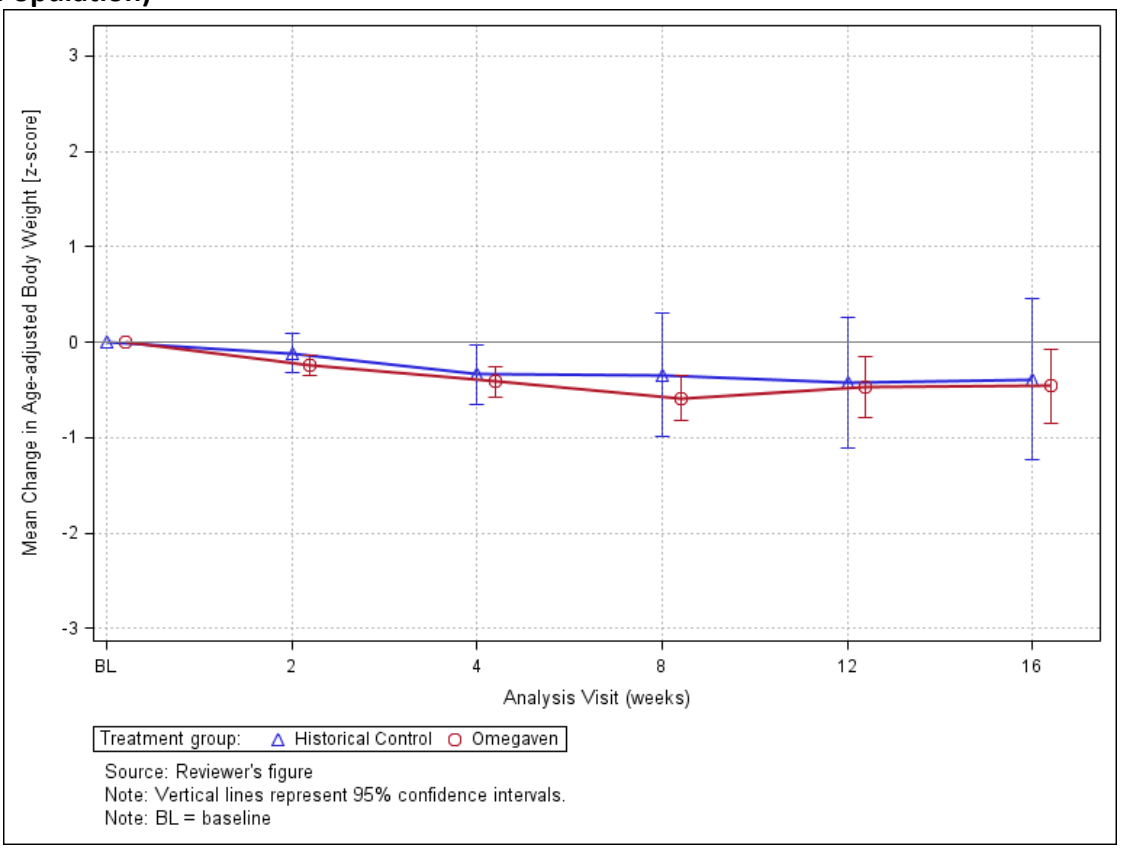


Table 47. Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Height/Length (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=97)**	**EOETP (N=46)**	**EOS (N=90)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.1406	0.0012	0.0073
Treatment group	0.0670	0.3441	0.0935
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.07 [-0.35, 0.20]	0.18 [-0.35, 0.71]	0.02 [-0.35, 0.40]
Historical control	-0.57 [-1.02, -0.12]	-0.80 [-2.80, 1.20]	-0.56 [-1.14, 0.01]
Difference	0.49 [-0.04, 1.02]	0.98 [-1.09, 3.05]	0.59 [-0.10, 1.27]

Source: Reviewer's table
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 27. Mean Change from Baseline in Age-adjusted Body Height/Length Over Time in Study 34 (FM Population)

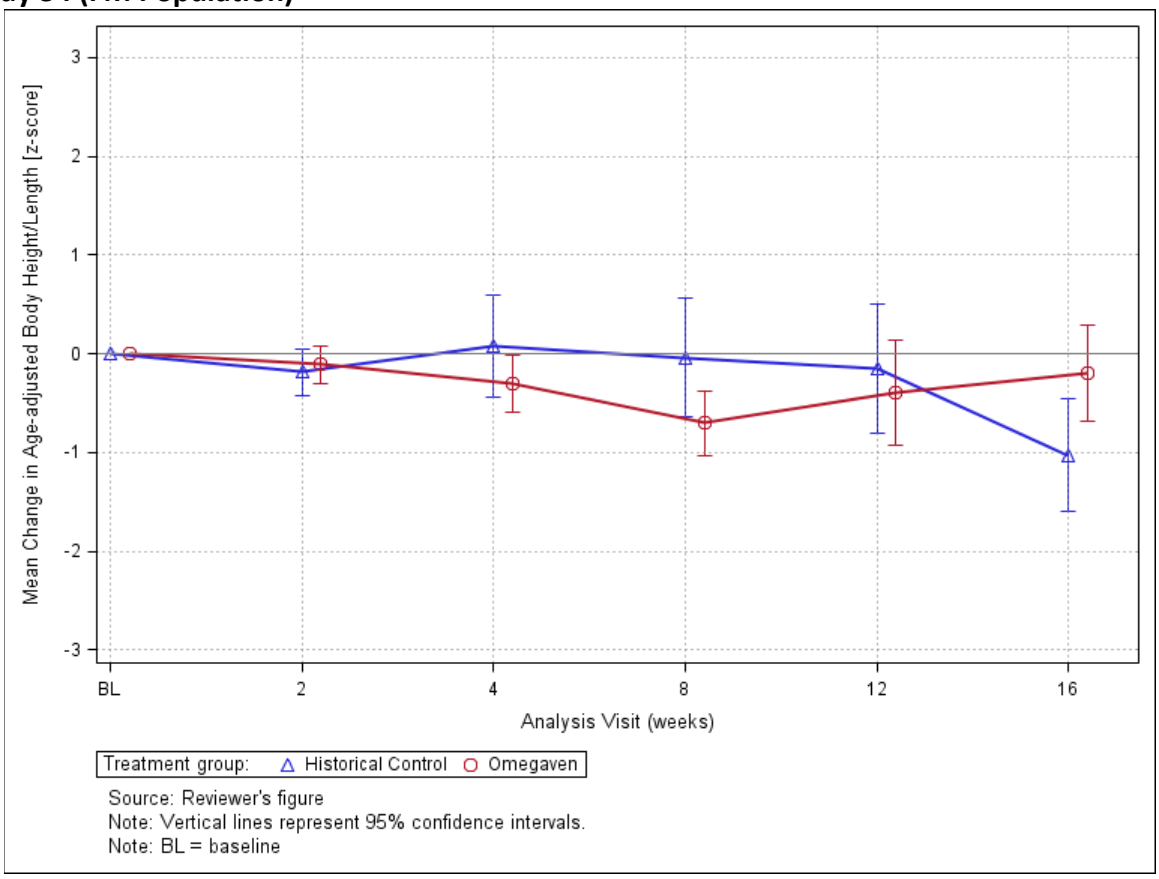


Table 48. Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Head Circumference (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=90)**	**EOETP (N=37)**	**EOS (N=77)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0063	0.2431	0.1365
Treatment group	0.1176	0.0904	0.0925
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	0.12 [-0.13, 0.38]	0.50 [0.00, 0.99]	0.24 [-0.13, 0.61]
Historical control	-0.29 [-0.73, 0.16]	-0.99 [-2.66, 0.67]	-0.35 [-0.93, 0.22]
Difference	0.41 [-0.11, 0.93]	1.49 [-0.25, 3.23]	0.59 [-0.10, 1.28]

Source: Reviewer's table
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 28. Mean Change from Baseline in Age-adjusted Head Circumference Over Time in Study 34 (FM Population)

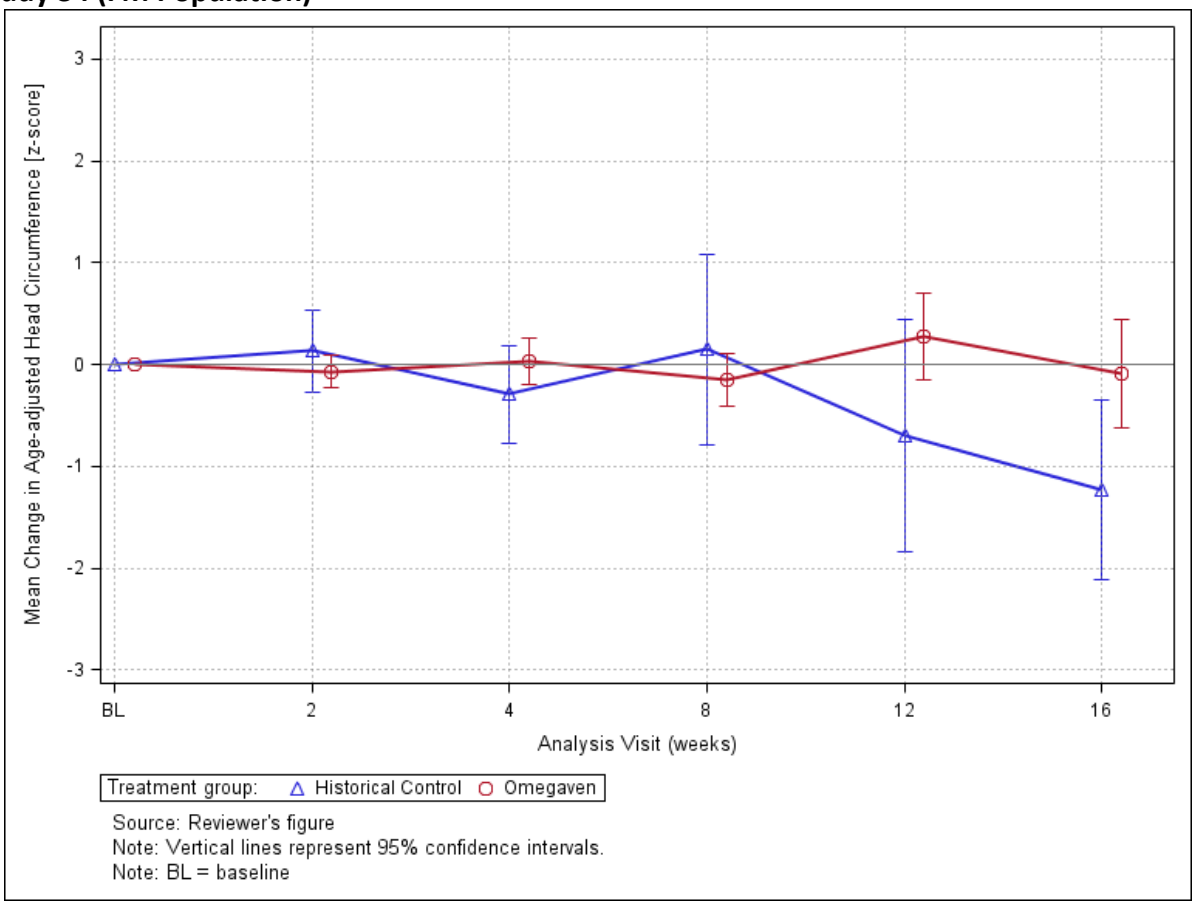


Table 49. SMD Values for Covariates Used in Full Matching Method for Study 34

	Covariate SMD Value								
Source population	**GA**	**PMA**	**DBil**	**ALT**	**AST**	**Sepsis**	**Birth Weight**	**Sex**	**Underlying Surgical Condition**
Applicant's PM population	0.035	0.131	0.064	0.107	0.003	0.094	0.322	0.234	0.469
Division's FM population	0.045	0.066	0.234	0.120	0.126	<0.10	0.019	0.094	0.252

Source: Reviewer's table

16.7.1.2 PM Population and Analysis Visits

An analysis for the three anthropometric endpoints was conducted using the PM population evaluated at the weekly analysis visits up to week 12. As described in Section 8.1.6, the Applicant's prespecified analysis time points were based on ROPNAC, the original efficacy

endpoint for the treatment of PNAC, which was somewhat arbitrary for growth assessment for a nutritional indication as source of calories. This analysis was conducted to ascertain patients' growth in the PM population independent of the liver endpoints in the Applicant's primary analysis.

In this additional efficacy analysis, the treatment group effect was not statistically significant for the three anthropometric endpoints. ANCOVA model results are shown in Table 50 through Table 52.

Table 50. Primary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Weight by Analysis Visit (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=68) [Omegaven (n=45)] [HC (n=23)]**	**Week 8 (N=57) [Omegaven (n=39)] [HC (n=18)]**	**Week 12 (N=39) [Omegaven (n=25)] [HC (n=14)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0987	0.0887	0.0820
Treatment group	0.6392	0.3906	0.3117
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.41 [-0.64, -0.18]	-0.69 [-1.10, -0.29]	-0.37 [-0.91, 0.17]
Historical control	-0.32 [-0.64, 0.00]	-0.38 [-0.98, 0.21]	-0.83 [-1.55, -0.10]
Difference	-0.09 [-0.49, 0.30]	-0.31 [-1.03, 0.41]	0.46 [-0.45, 1.37]

Source: Reviewer's table

Table 51. Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Height/Length by Analysis Visit (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=51) [Omegaven (n=37)] [HC (n=14)]**	**Week 8 (N=47) [Omegaven (n=32)] [HC (n=15)]**	**Week 12 (N=31) [Omegaven (n=20)] [HC (n=11)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.1398	0.4401	0.0223
Treatment group	0.0776	0.1291	0.9957
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.31 [-0.70, 0.09]	-0.60 [-1.03, -0.16]	-0.16 [-0.71, 0.39]
Historical control	0.38 [-0.27, 1.03]	-0.01 [-0.64, 0.63]	-0.16 [-0.90, 0.58]
Difference	-0.68 [-1.45, 0.08]	-0.59 [-1.36, 0.18]	0.00 [-0.92, 0.92]

Source: Reviewer's table

Table 52. Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Head Circumference by Analysis Visit (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=50) [Omegaven (n=37)] [HC (n=13)]**	**Week 8 (N=46) [Omegaven (n=33)] [HC (n=13)]**	**Week 12 (N=27) [Omegaven (n=19)] [HC (n=8)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0046	0.0010	0.0647
Treatment group	0.9340	0.2161	0.1439
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.13 [-0.41, 0.14]	-0.23 [-0.61, 0.14]	0.18 [-0.34, 0.71]
Historical control	-0.11 [-0.57, 0.35]	0.21 [-0.39, 0.80]	-0.54 [-1.36, 0.28]
Difference	-0.02 [-0.56, 0.52]	-0.44 [-1.14, 0.27]	0.72 [-0.27, 1.71]

Source: Reviewer's table

16.7.1.3 FM Population and Analysis Visits

The reviewer conducted an analysis for the three anthropometric endpoints using the FM population evaluated at the weekly analysis visits up to week 12. As described in the previous section, this analysis was conducted to ascertain patients' growth in the FM population independent of the liver endpoints in the Applicant's primary analysis. In this additional efficacy analysis, the treatment group effect was not statistically significant for the three anthropometric endpoints. ANCOVA model results are shown in Table 53 through Table 55.

Table 53. Primary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Weight by Analysis Visit (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=119) [Omegaven (n=79)] [HC (n=40)]**	**Week 8 (N=97) [Omegaven (n=67)] [HC (n=30)]**	**Week 12 (N=75) [Omegaven (n=50)] [HC (n=25)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0045	0.0129	0.0493
Treatment group	0.4261	0.2951	0.6974
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.43 [-0.60, -0.25]	-0.60 [-0.90, -0.30]	-0.50 [-0.86, -0.13]
Historical control	-0.31 [-0.55, -0.06]	-0.32 [-0.76, 0.12]	-0.37 [-0.89, 0.14]
Difference	-0.12 [-0.43, 0.18]	-0.28 [-0.81, 0.25]	-0.12 [-0.76, 0.51]

Source: Reviewer's table

Table 54. Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Body Height/Length by Analysis Visit (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=85) [Omegaven (n=64)] [HC (n=21)]**	**Week 8 (N=70) [Omegaven (n=54)] [HC (n=16)]**	**Week 12 (N=52) [Omegaven (n=39)] [HC (n=13)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0547	0.6147	0.0859
Treatment group	0.1887	0.0582	0.5699
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.30 [-0.58, -0.02]	-0.70 [-1.02, -0.38]	-0.41 [-0.89, 0.07]
Historical control	0.07 [-0.41, 0.56]	-0.05 [-0.64, 0.55]	-0.13 [-0.96, 0.70]
Difference	-0.37 [-0.93, 0.19]	-0.65 [-1.33, 0.02]	-0.27 [-1.24, 0.69]

Source: Reviewer's table

Table 55. Secondary Efficacy Endpoint Analysis in Study 34: Change from Baseline in Age-adjusted Head Circumference by Analysis Visit (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=81) [Omegaven (n=61)] [HC (n=20)]**	**Week 8 (N=65) [Omegaven (n=52)] [HC (n=13)]**	**Week 12 (N=45) [Omegaven (n=36)] [HC (n=9)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0007	0.0024	0.0628
Treatment group	0.3473	0.3251	0.1470
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	0.00 [-0.22, 0.22]	-0.15 [-0.43, 0.12]	0.22 [-0.20, 0.65]
Historical control	-0.21 [-0.60, 0.18]	0.16 [-0.40, 0.71]	-0.50 [-1.37, 0.38]
Difference	0.21 [-0.24, 0.66]	-0.31 [-0.93, 0.31]	0.72 [-0.26, 1.70]

Source: Reviewer's table

16.7.2. Study 35

16.7.2.1 FM Population and Primary Analysis Methods

An analysis for the three anthropometric endpoints was conducted using the FM population and the same methods used in the primary analysis. The FM population for this study consisted of 113 patients (54 patients in the Omegaven group and 59 patients in the HC group). The Applicant's pair matching for this study resulted in a poor match according to the Division's full matching method, since the SMD for 8 of the 9 covariates used in the full matching was ≥ 0.1. This occurred for the GA, PMA, DBil, ALT, AST, sepsis, birth weight, and underlying surgical condition covariates. However, the FM population had SMD values < 0.1 for five covariates (GA, PMA, DBil, sex, and sepsis).

In this additional efficacy analysis, the treatment group effect was not statistically significant for the three anthropometric endpoints. In this population, the EOITP time point occurred at week 8 or earlier for most patients with evaluable endpoint data, and the EOS time point occurred at week 12 or earlier for most patients with evaluable endpoint data.

The absolute difference in least squares mean values at the EOITP and EOS time points in this analysis were smaller than those seen in the primary analysis. For example, for change in age-adjusted body weight, the least squares mean difference estimate at the EOITP time point was -0.14, and in the primary analysis, the estimate was -0.92. The Omegaven group had slightly smaller mean changes from baseline in age-adjusted body weight, and larger mean changes from baseline in age-adjusted body height/length and age-adjusted head circumference than those seen in the primary analysis.

ANCOVA model results for the three anthropometric endpoints are shown in Table 56 through Table 58. Table 59 contains the Applicant's and Division's SMD values for the 9 covariates used in the full matching method. Mean changes from baseline in age-adjusted endpoint values over time are shown in Figure 29 through Figure 31.

Table 56. Primary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Body Weight (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=107)**	**EOETP (N=35)**	**EOS (N=108)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0025	0.0209	0.0014
Treatment group	0.5857	0.9257	0.5982
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.33 [-0.69, 0.03]	-0.38 [-1.04, 0.28]	-0.31 [-0.73, 0.10]
Historical control	-0.19 [-0.55, 0.17]	-0.31 [-1.63, 1.00]	-0.16 [-0.58, 0.26]
Difference	-0.14 [-0.65, 0.37]	-0.07 [-1.54, 1.41]	-0.16 [-0.75, 0.43]

Source: Reviewer's table
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 29. Mean Change from Baseline in Age-adjusted Body Weight Over Time in Study 35 (FM Population)

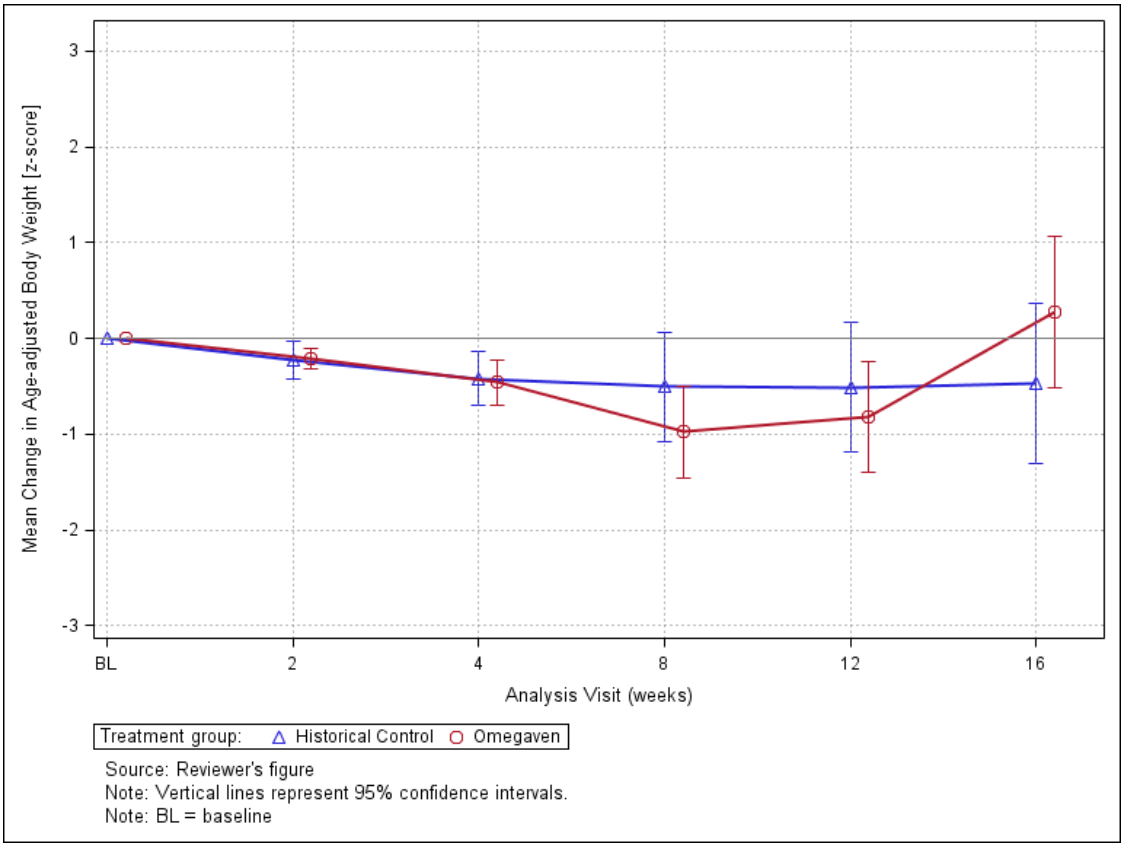


Table 57. Secondary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Body Height/Length (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=86)**	**EOETP (N=32)**	**EOS (N=87)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.7323	0.4571	0.6564
Treatment group	0.9403	0.5627	0.9138
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.66 [-0.97, -0.35]	-0.66 [-1.21, -0.11]	-0.65 [-1.00, -0.30]
Historical control	-0.68 [-1.06, -0.29]	-0.21 [-1.69, 1.27]	-0.68 [-1.12, -0.24]
Difference	0.02 [-0.48, 0.51]	-0.45 [-2.03, 1.13]	0.03 [-0.53, 0.59]

Source: Reviewer's table
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 30. Mean Change from Baseline in Age-adjusted Body Height/Length Over Time in Study 35 (FM Population)

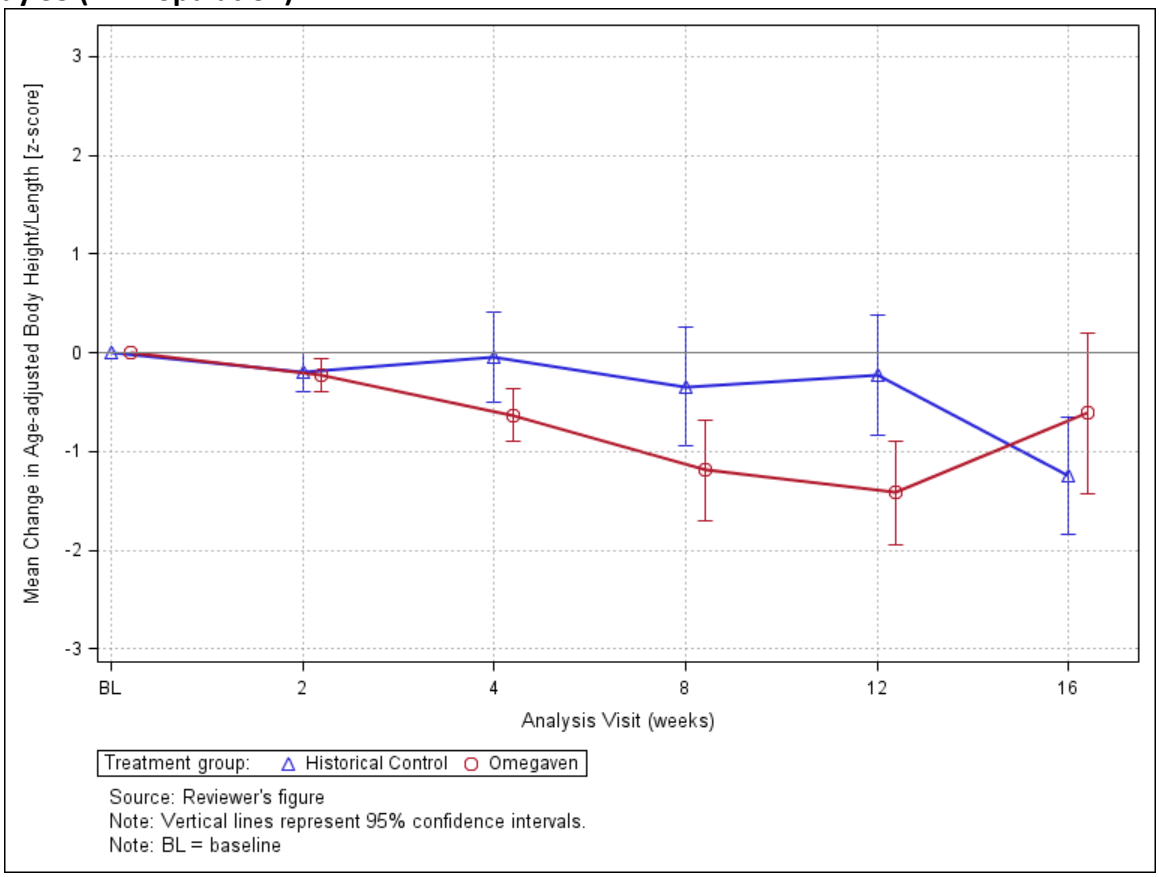
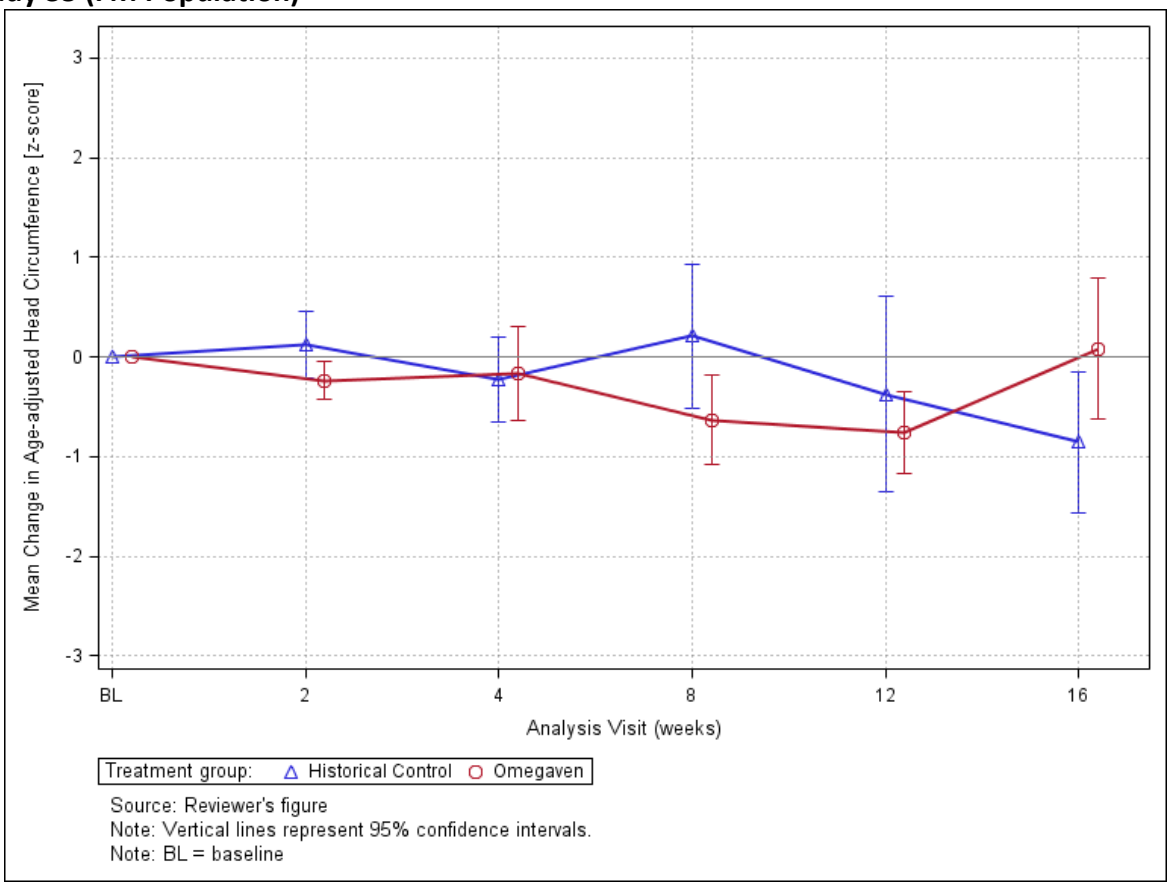


Table 58. Secondary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Head Circumference (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**EOITP (N=80)**	**EOETP (N=25)**	**EOS (N=76)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0088	0.0560	0.0314
Treatment group	0.9314	0.0611	0.7110
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.19 [-0.49, 0.11]	0.09 [-0.30, 0.48]	-0.14 [-0.49, 0.20]
Historical control	-0.21 [-0.61, 0.19]	-0.98 [-2.04, 0.08]	-0.25 [-0.69, 0.19]
Difference	0.02 [-0.48, 0.52]	1.08 [-0.05, 2.21]	0.11 [-0.46, 0.67]

Source: Reviewer's table
EOETP = end of extended treatment period; EOITP = end of initial treatment period; EOS = end of study

Figure 31. Mean Change from Baseline in Age-adjusted Head Circumference Over Time in Study 35 (FM Population)



Source: Reviewer's figure
Note: Vertical lines represent 95% confidence intervals.
Note: BL = baseline

Table 59. SMD Values for Covariates Used in Full Matching Method for Study 35

	Covariate SMD Value								
Source population	**GA**	**PMA**	**DBil**	**ALT**	**AST**	**Sepsis**	**Birth Weight**	**Sex**	**Underlying Surgical Condition**
Applicant's PM population	0.576	0.121	0.122	0.393	0.418	0.180	0.418	<0.001	0.567
Division's FM population	0.090	0.075	0.049	0.168	0.118	<0.10	0.168	0.061	0.281

Source: Reviewer's table

16.7.2.2 PM Population and Analysis Visits

The reviewer conducted an analysis for the three anthropometric endpoints using the PM population evaluated at the weekly analysis visits up to week 12. In this additional efficacy analysis, the treatment group effect was not statistically significant for the three anthropometric endpoints. The Omegaven group had increasing mean changes from baseline in all three endpoints over time. ANCOVA model results are shown in Table 60 through Table 62.

Table 60. Primary Efficacy Endpoint Analysis in Study 35: Change in Age-adjusted Body Weight by Analysis Visit (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=36)**	**Week 8 (N=25)**	**Week 12 (N=23)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.1321	0.0571	0.1613
Treatment group	0.5163	0.2902	0.1995
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.56 [-0.94, -0.19]	-1.21 [-1.94, -0.47]	-1.02 [-1.89, -0.14]
Historical control	-0.36 [-0.86, 0.13]	-0.53 [-1.60, 0.55]	-0.12 [-1.22, 0.97]
Difference	-0.20 [-0.82, 0.42]	-0.68 [-1.98, 0.62]	-0.89 [-2.29, 0.51]

Source: Reviewer's table

Table 61. Secondary Efficacy Endpoint Analysis in Study 35: Change in Age-adjusted Body Height/Length by Analysis Visit (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=29)**	**Week 8 (N=20)**	**Week 12 (N=18)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.9903	0.7952	0.8416
Treatment group	0.7137	0.5650	0.4895
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.60 [-0.99, -0.21]	-1.02 [-1.86, -0.19]	-1.42 [-2.18, -0.67]
Historical control	-0.75 [-1.52, 0.01]	-1.62 [-3.61, 0.36]	-0.89 [-2.30, 0.52]
Difference	0.16 [-0.71, 1.02]	0.60 [-1.56, 2.76]	-0.53 [-2.13, 1.07]

Source: Reviewer's table

Table 62. Secondary Efficacy Endpoint Analysis in Study 35: Change in Age-adjusted Head Circumference by Analysis Visit (PM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=28)**	**Week 8 (N=19)**	**Week 12 (N=16)**
p-Value for class effect/covariate (Type III)			
Baseline value	0.9868	0.0622	0.9199
Treatment group	0.4027	0.5713	0.8797
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	0.14 [-0.54, 0.83]	-0.24 [-0.71, 0.24]	-0.46 [-0.92, 0.00]
Historical control	-0.51 [-1.88, 0.87]	-0.64 [-2.04, 0.76]	-0.38 [-1.36, 0.60]
Difference	0.65 [-0.93, 2.23]	0.40 [-1.08, 1.88]	-0.08 [-1.17, 1.02]

Source: Reviewer's table

16.7.2.3 FM Population and Analysis Visits

As in Study 34, an analysis for the three anthropometric endpoints was conducted using the FM population evaluated at the weekly analysis visits up to week 12. In this additional efficacy analysis, the treatment group effect was statistically significant in favor of the HC patients for the change in age-adjusted body height/length endpoint at all 3 time points and for the change in age-adjusted head circumference endpoint at week 8. For the change in age-adjusted body height/length endpoint, the ANCOVA least squares mean difference estimate and 95% CI at week 4, week 8, and week 12 were -0.59 (-1.07, -0.11), -0.81 (-1.59, -0.03), and -1.14 (-1.93, -

0.36), respectively. For the change in age-adjusted head circumference endpoint, the ANCOVA least squares mean difference estimate and 95% CI at week 8 were -0.83 (-1.57, -0.08).

The treatment group effect was not statistically significant at the other time points. In general, the Omegaven group had increasing mean changes from baseline in all three endpoints over time, except for the change in age-adjusted body weight endpoint, which had a mean change from baseline of -0.46 at week 4, -0.98 at week 8, and -0.85 at week 12.

ANCOVA model results are shown in Table 63 through Table 65. Mean changes from baseline in age-adjusted body height/length and head circumference values over time are shown in Figure 32 and Figure 33.

Table 63. Primary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Body Weight by Analysis Visit (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=87) [Omegaven (n=41)] [HC (n=46)]**	**Week 8 (N=64) [Omegaven (n=30)] [HC (n=34)]**	**Week 12 (N=50) [Omegaven (n=24)] [HC (n=26)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0158	0.0083	0.0020
Treatment group	0.8251	0.1855	0.3744
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.46 [-0.72, -0.20]	-0.98 [-1.50, -0.46]	-0.85 [-1.42, -0.27]
Historical control	-0.42 [-0.66, -0.18]	-0.51 [-0.99, -0.02]	-0.49 [-1.05, 0.06]
Difference	-0.04 [-0.39, 0.32]	-0.48 [-1.19, 0.23]	-0.36 [-1.16, 0.44]

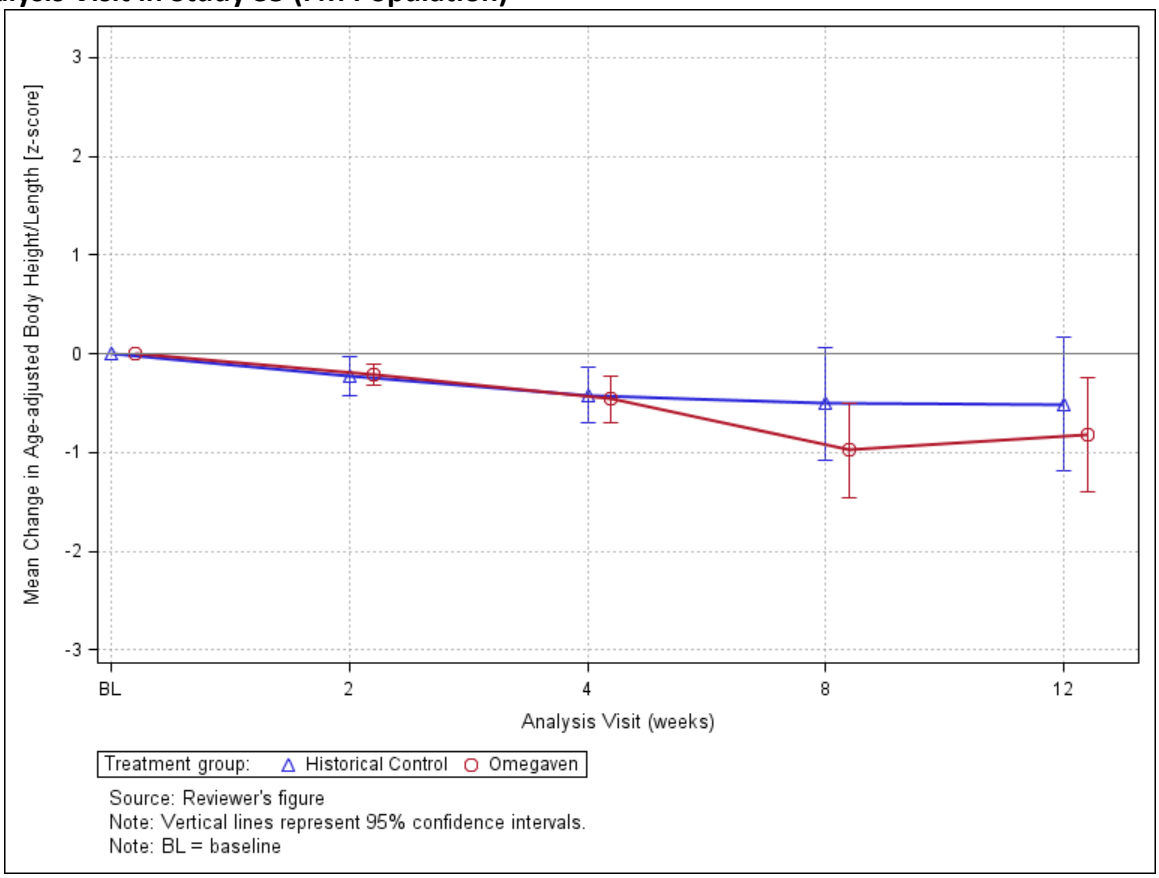
Source: Reviewer's table

Table 64. Secondary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Body Height/Length by Analysis Visit (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=66) [Omegaven (n=41)] [HC (n=25)]**	**Week 8 (N=49) [Omegaven (n=30)] [HC (n=19)]**	**Week 12 (N=40) [Omegaven (n=24)] [HC (n=16)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.5037	0.3332	0.2103
Treatment group	0.0174	0.0416	0.0056
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.63 [-0.93, -0.34]	-1.18 [-1.66, -0.69]	-1.40 [-1.90, -0.90]
Historical control	-0.04 [-0.42, 0.34]	-0.37 [-0.97, 0.24]	-0.26 [-0.87, 0.35]
Difference	-0.59 [-1.07, -0.11]	-0.81 [-1.59, -0.03]	-1.14 [-1.93, -0.36]

Source: Reviewer's table

Figure 32. Mean Change from Baseline in Age-adjusted Body Height/Length Over Time by Analysis Visit in Study 35 (FM Population)



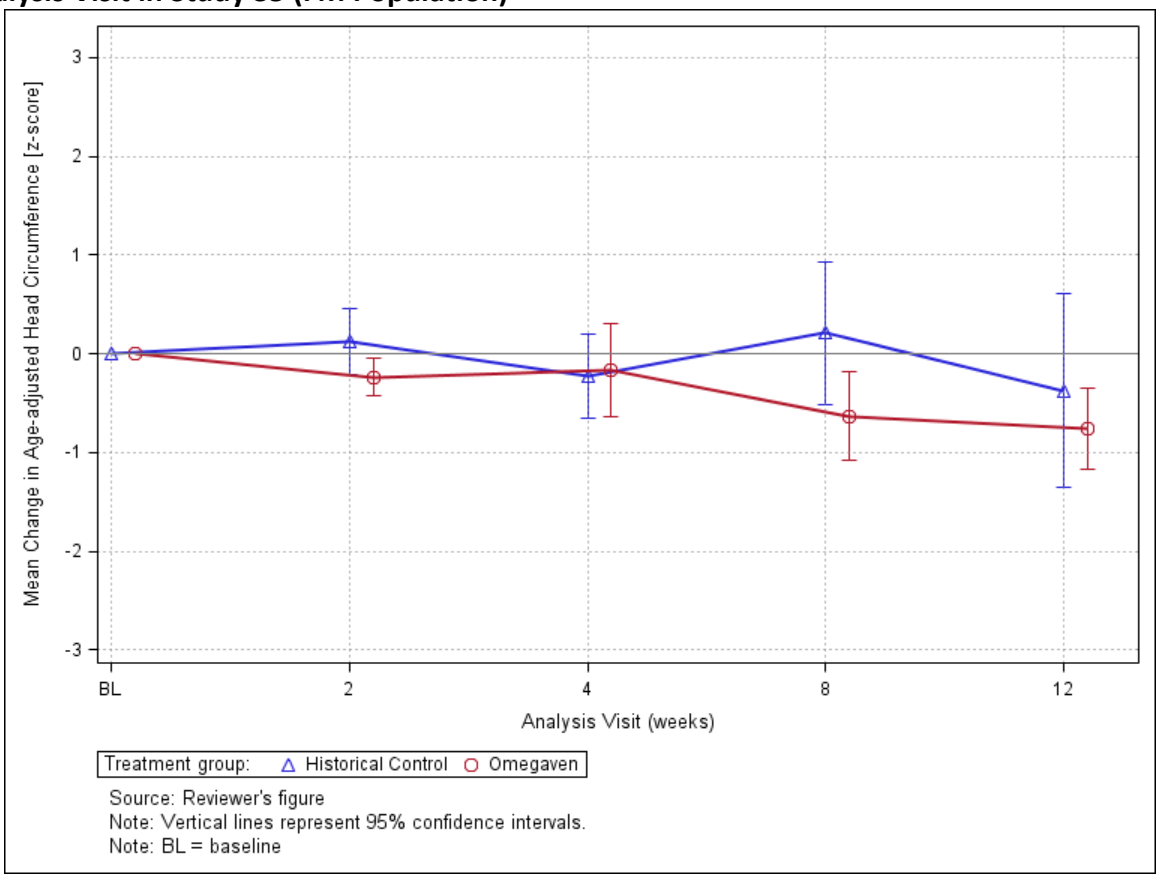
Source: Reviewer's figure
Note: Vertical lines represent 95% confidence intervals.
Note: BL = baseline

Table 65. Secondary Efficacy Endpoint Analysis in Study 35: Change from Baseline in Age-adjusted Head Circumference by Analysis Visit (FM Population)

	Time Point (Observations)		
Analysis parameter/group	**Week 4 (N=62) [Omegaven (n=38)] [HC (n=24)]**	**Week 8 (N=44) [Omegaven (n=27)] [HC (n=17)]**	**Week 12 (N=32) [Omegaven (n=20)] [HC (n=12)]**
p-Value for class effect/covariate (Type III)			
Baseline value	0.0220	0.0347	0.0112
Treatment group	0.8689	0.0307	0.1559
Least squares mean (Z-score) [95% confidence interval]			
Omegaven	-0.21 [-0.61, 0.19]	-0.63 [-1.09, -0.16]	-0.83 [-1.32, -0.34]
Historical control	-0.16 [-0.66, 0.35]	0.20 [-0.38, 0.78]	-0.26 [-0.89, 0.38]
Difference	-0.05 [-0.70, 0.60]	-0.83 [-1.57, -0.08]	-0.57 [-1.38, 0.23]

Source: Reviewer's table

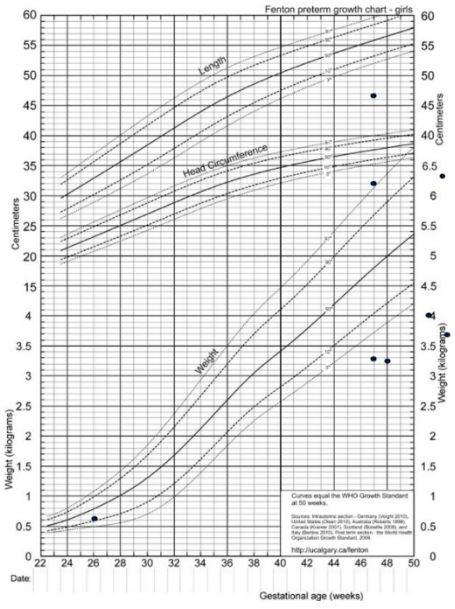
Figure 33. Mean Change from Baseline in Age-adjusted Head Circumference Over Time by Analysis Visit in Study 35 (FM Population)

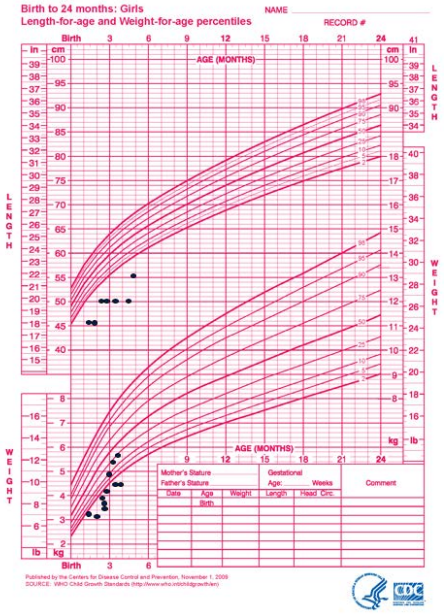


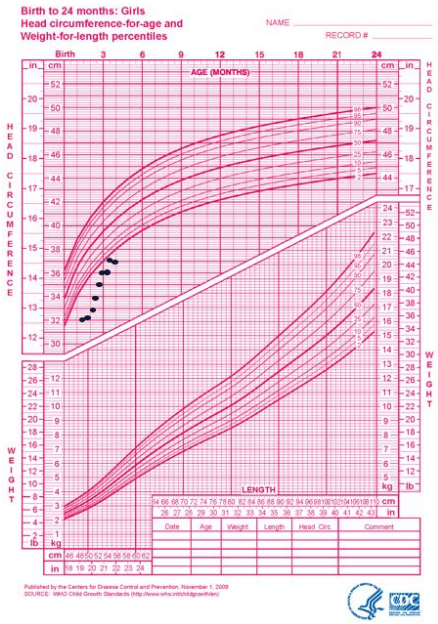
Source: Reviewer's figure
Note: Vertical lines represent 95% confidence intervals.
Note: BL = baseline

16.8. Growth Charts for Exclusive Omegaven Lipid Fed Patients

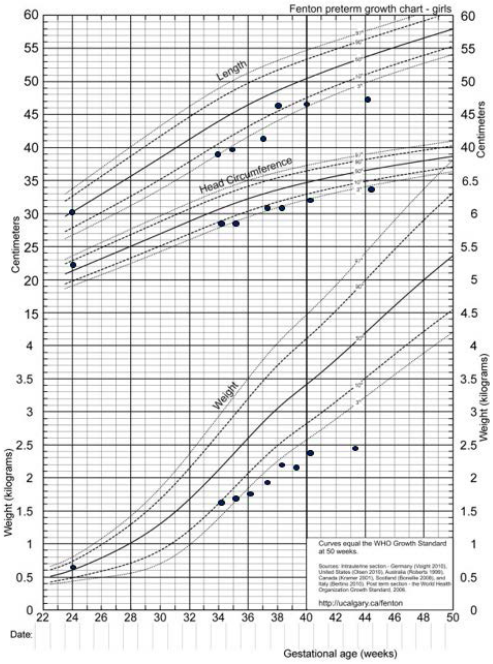
(b) (6) PM



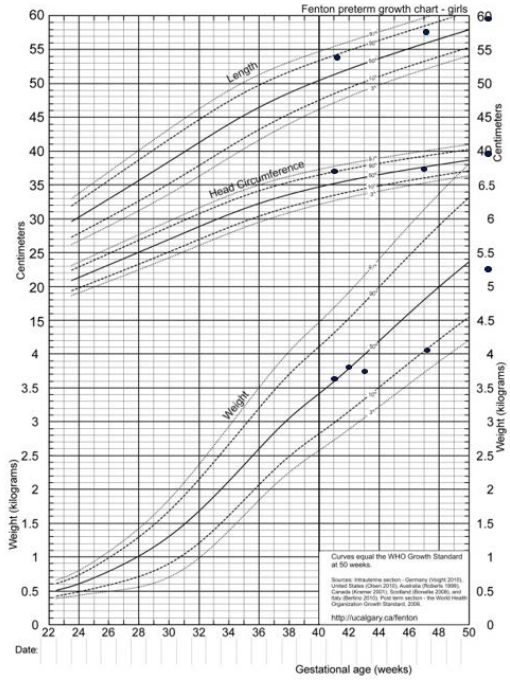




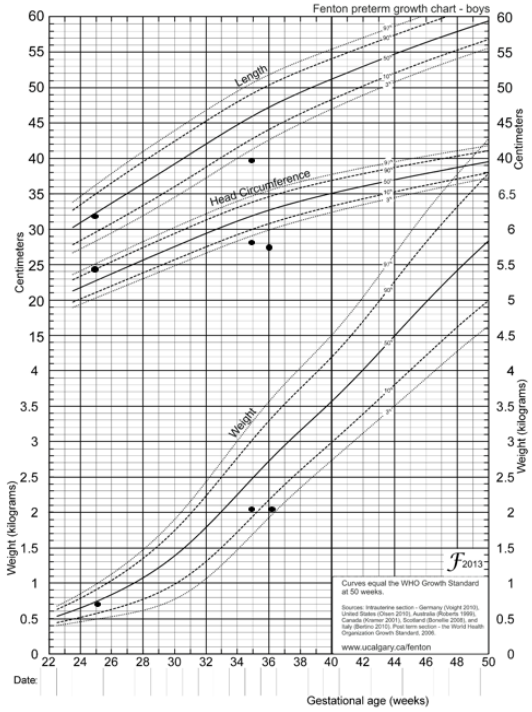
(b) (6) PM



(b) (6) PM


Fenton preterm growth chart - girls
Length
Head Circumference
Weight
Centimeters
Weight (kilograms)
Curves equal the WHO Growth Standard at 50 weeks.
http://ucalgary.ca/fenton
Date:
Gestational age (weeks)

(b) (6)


Fenton preterm growth chart - boys
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Centimeters
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Gestational age (weeks)

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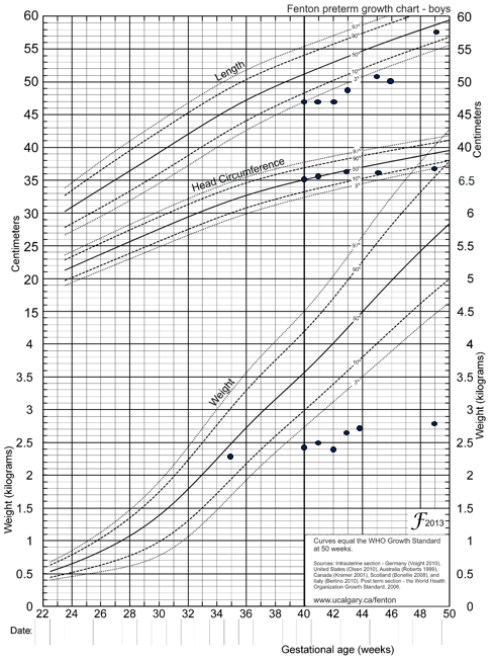
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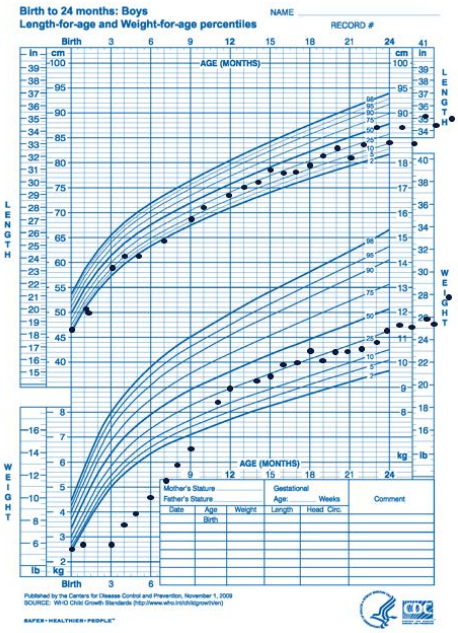
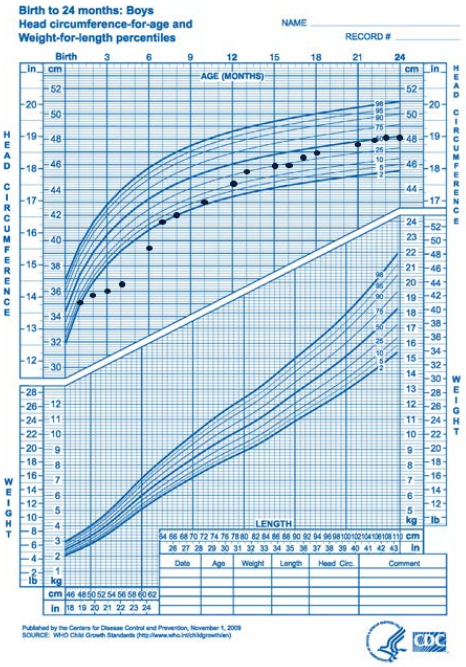

Birth to 24 months: Boys
Length-for-age and Weight-for-age percentiles
NAME
RECORD #
AGE (MONTHS)
LENGTH
WEIGHT
Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)


Birth to 24 months: Boys
Head circumference-for-age and
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RECORD #
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HEAD CIRCUMFERENCE
WEIGHT
LENGTH
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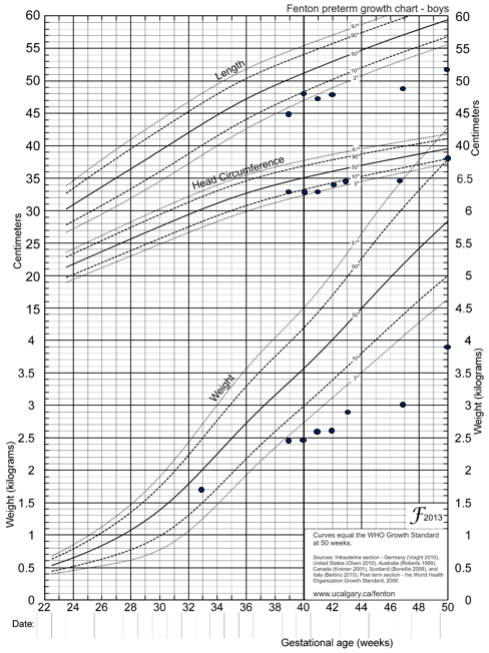
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Weight
Centimeters
Weight (kilograms)
Gestational age (weeks)
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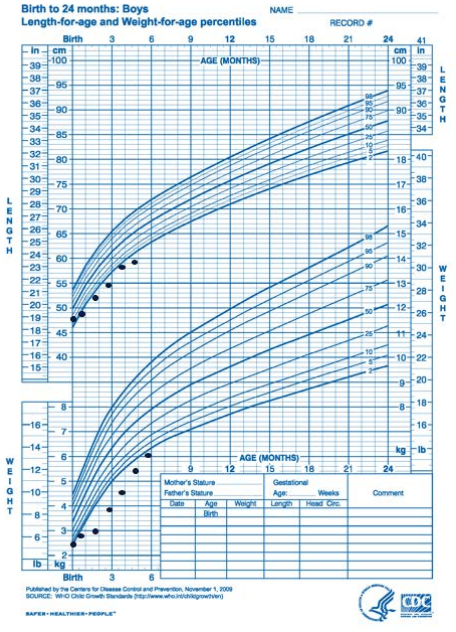
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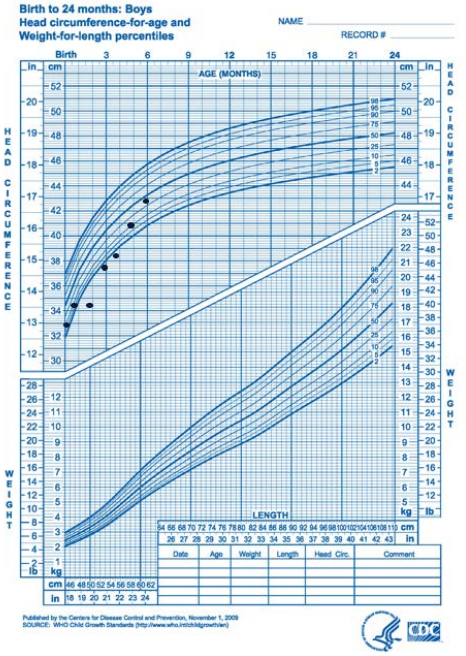
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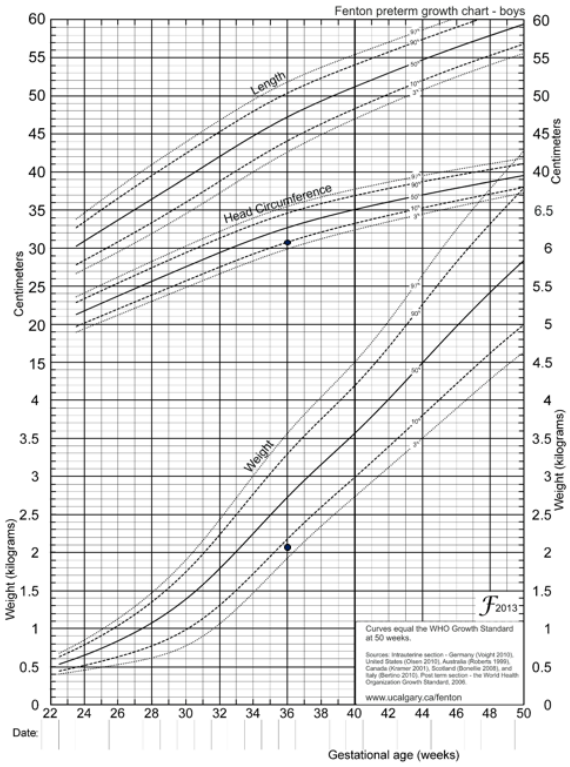
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Date:
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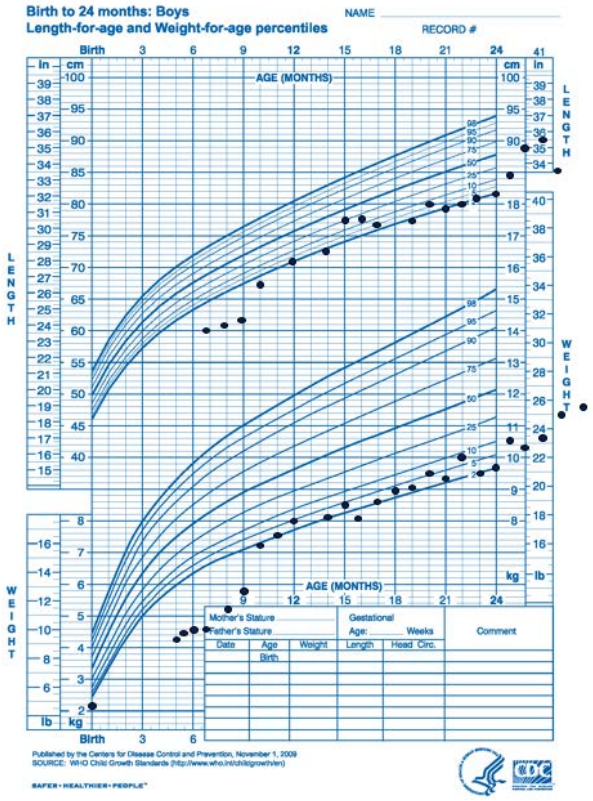
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RECORD #
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Mother's Stature
Father's Stature
Gestational
Age: Weeks
Comment
Date
Age
Weight
Length
Head Circ.
Birth
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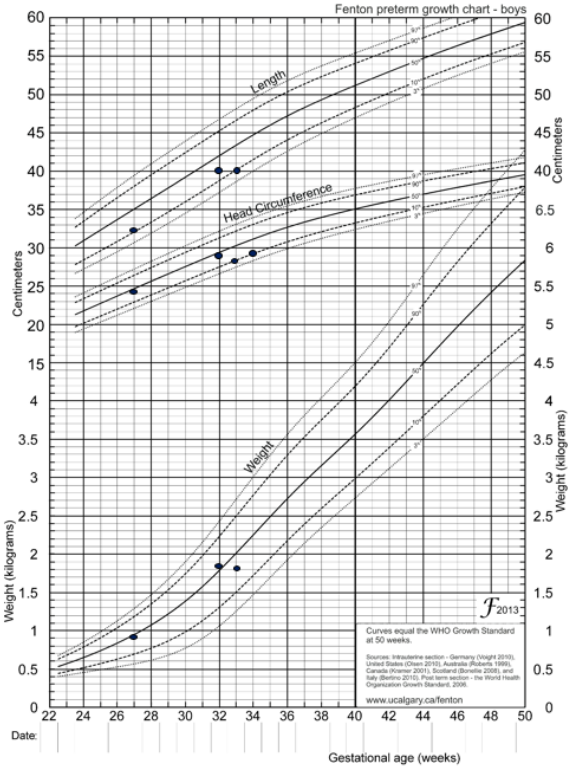
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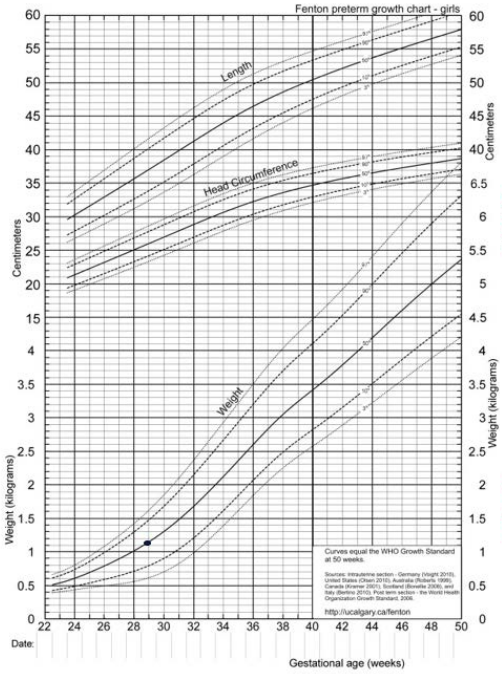
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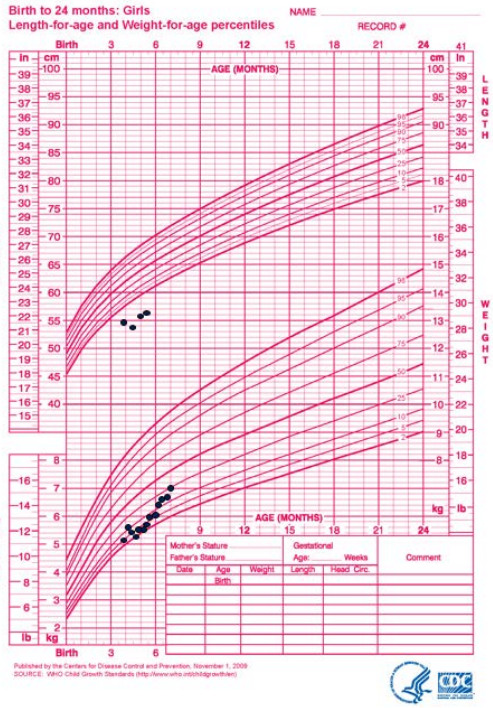
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WEIGHT
Mother's Stature
Father's Stature
Gestational Age: Weeks
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Age
Weight
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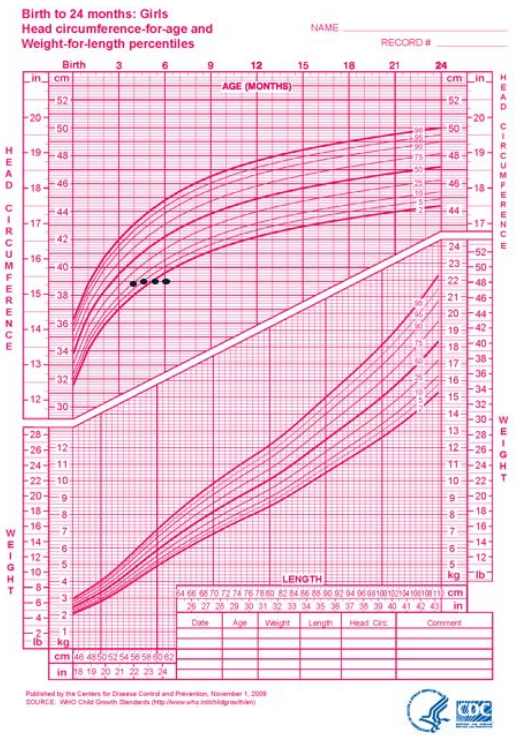
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Head circumference-for-age and
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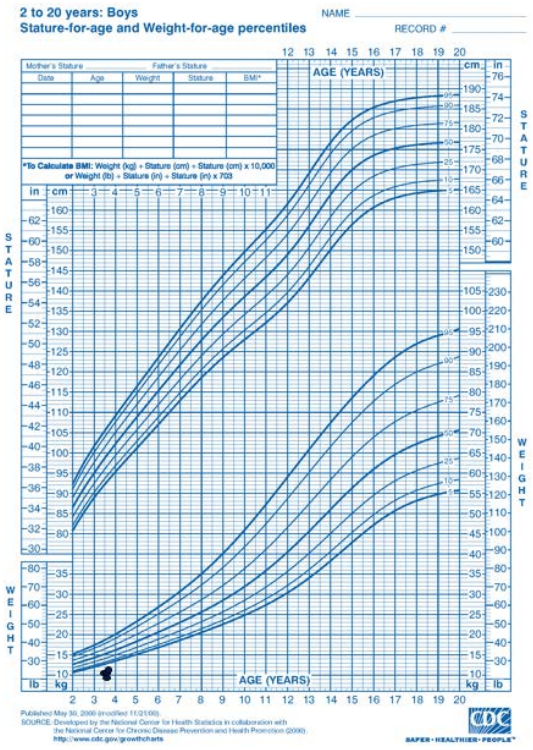
2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
AGE (YEARS)
STATURE
WEIGHT
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
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or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
Published May 30, 2000 (modified 11/21/00).
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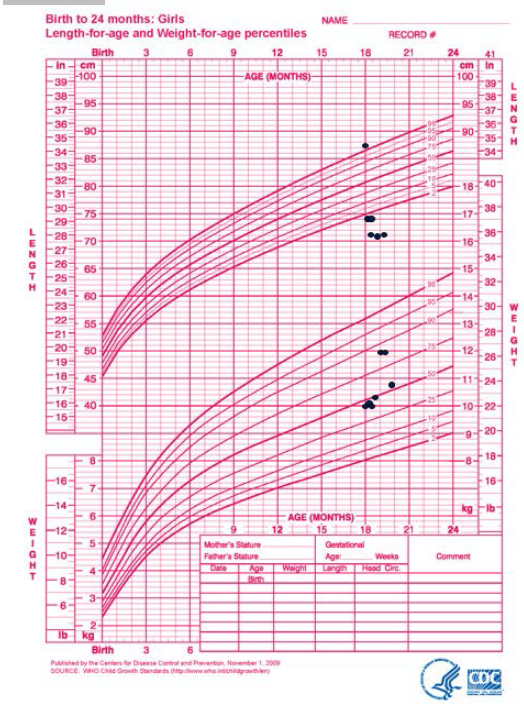
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Father's Stature
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Weeks
Date
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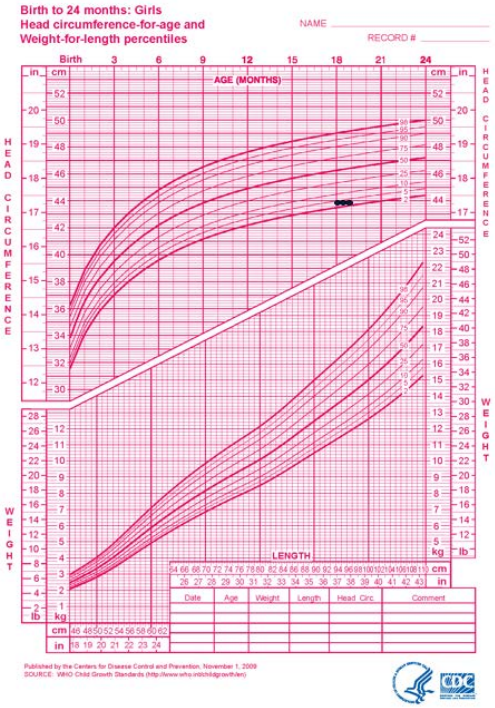
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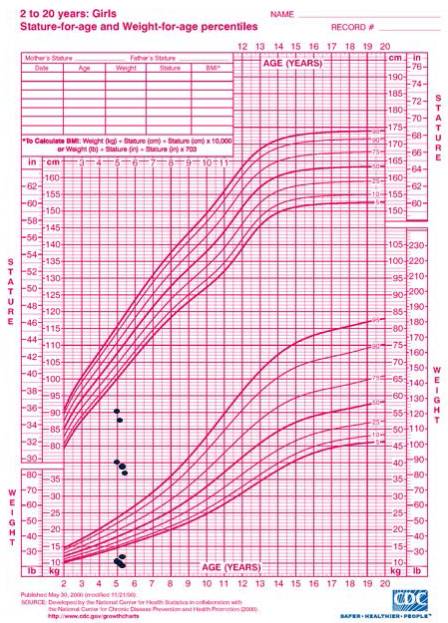
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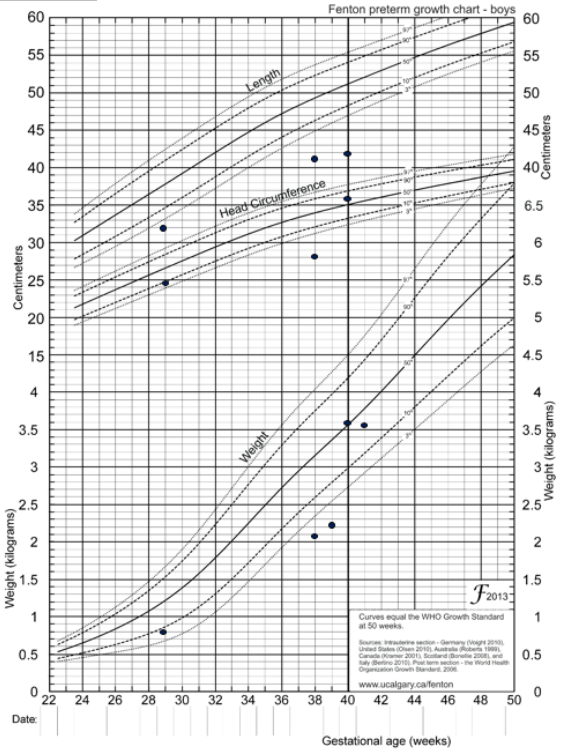
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Length
Head Circumference
Weight
Centimeters
Weight (kilograms)
Gestational age (weeks)
Date:
Curves equal the WHO Growth Standard at 50 weeks.
www.ucalgary.ca/fenton

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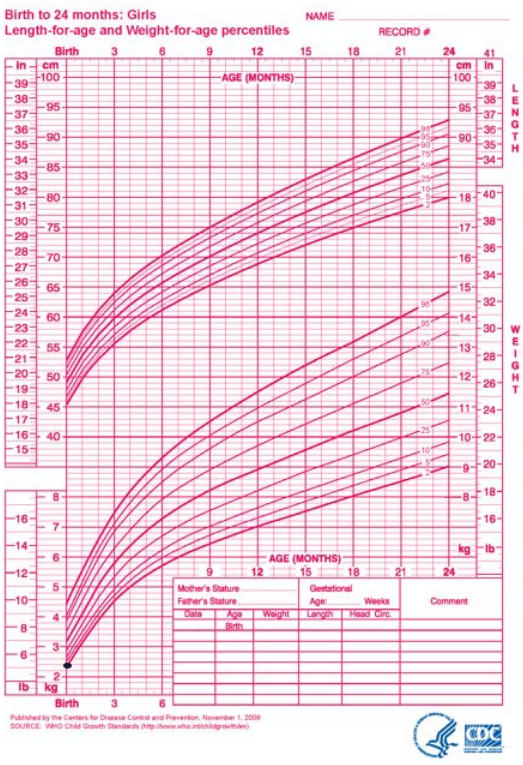
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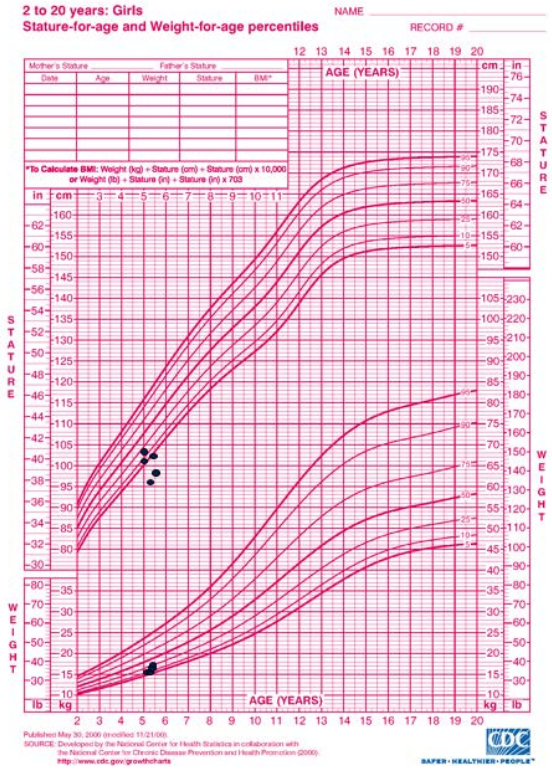
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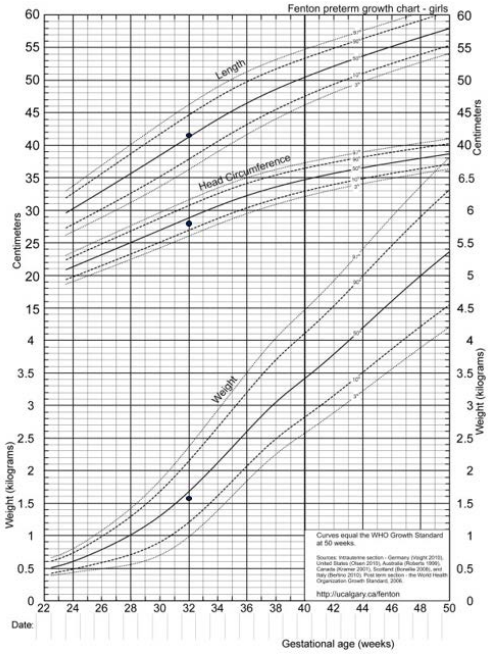

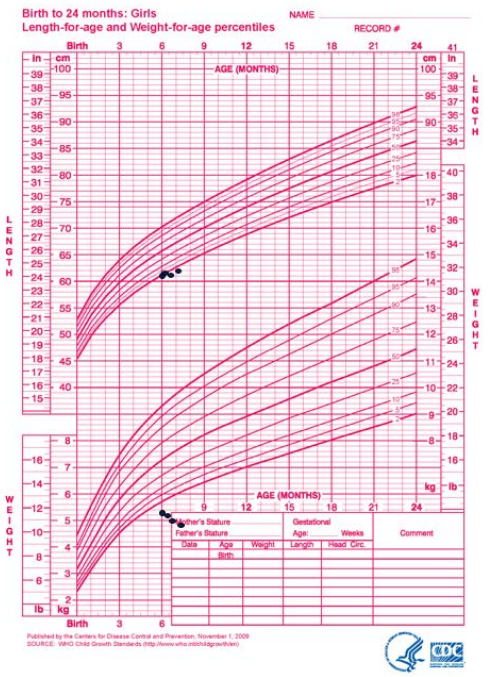

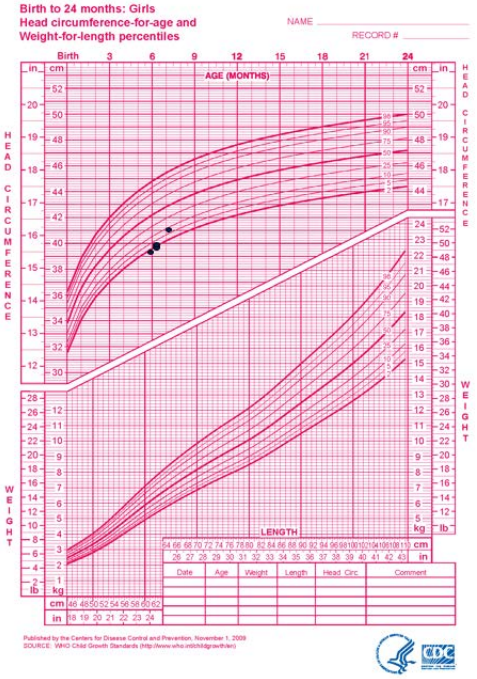

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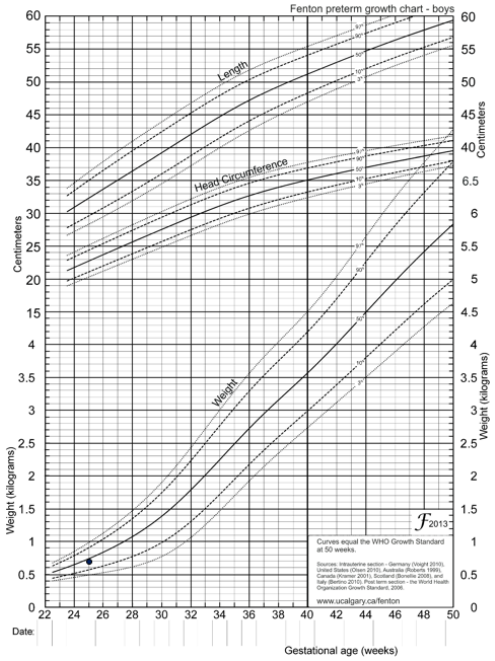
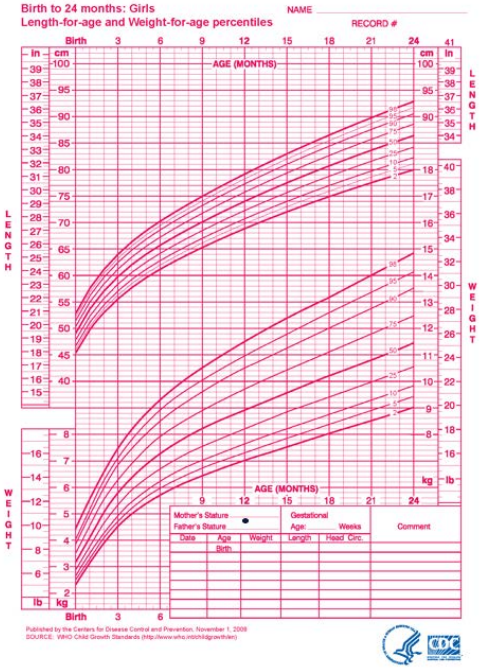
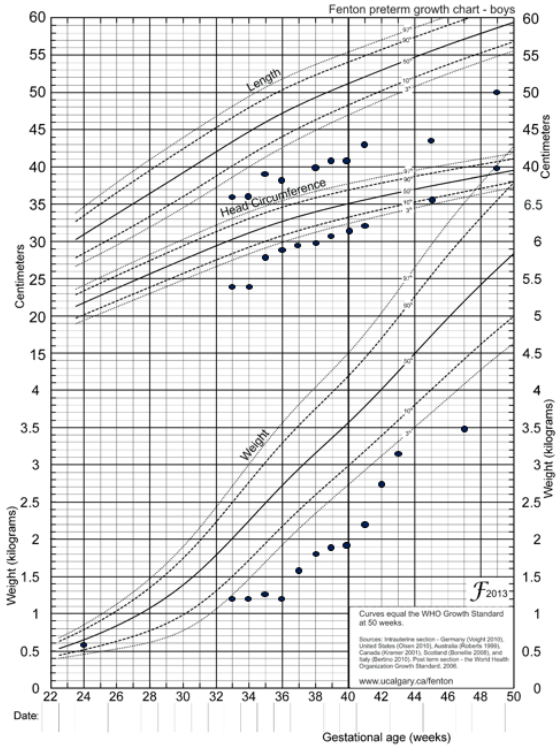




ELBW infant with no baseline anthropometric measurements, except weight at enrollment (12 months), who died within 3 days of treatment from multiorgan failure and NEC.

(b) (6)


Fenton preterm growth chart - boys
Length
Head Circumference
Weight
Centimeters
Weight (kilograms)
Gestational age (weeks)
Date:
Curves equal the WHO Growth Standard at 50 weeks.
www.ucalgary.ca/fenton

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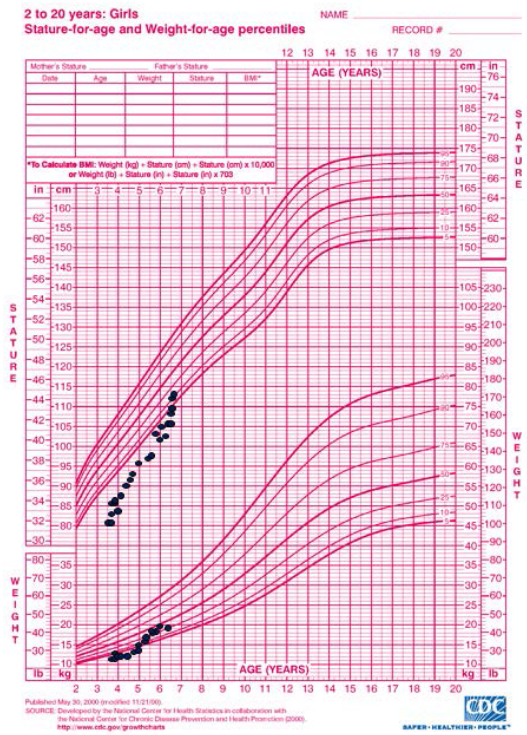
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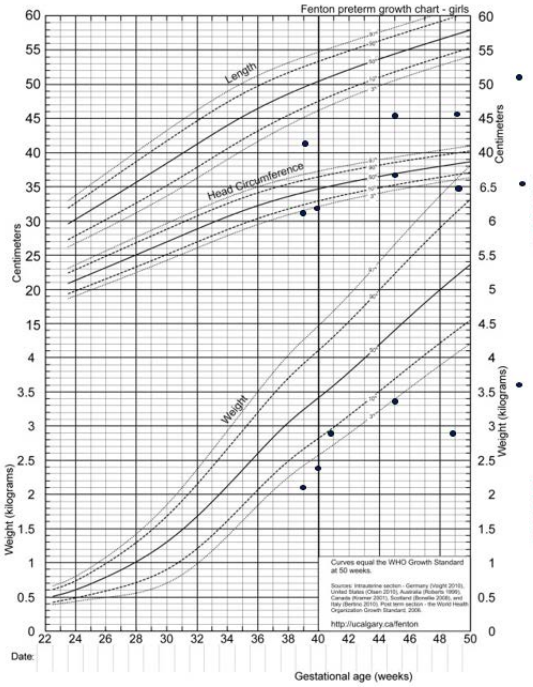
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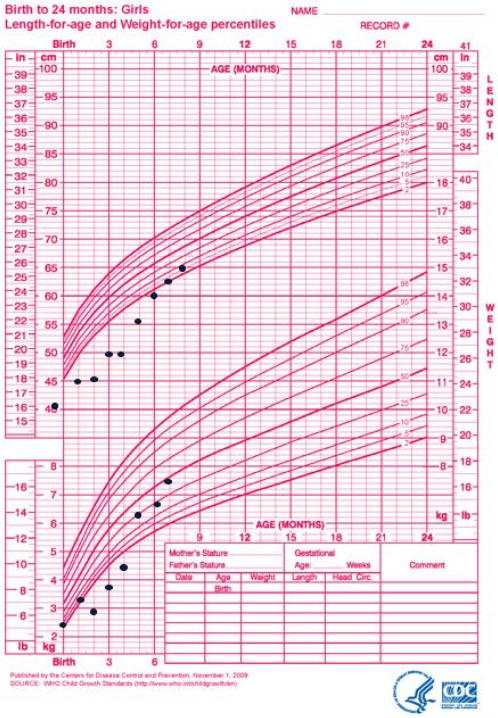
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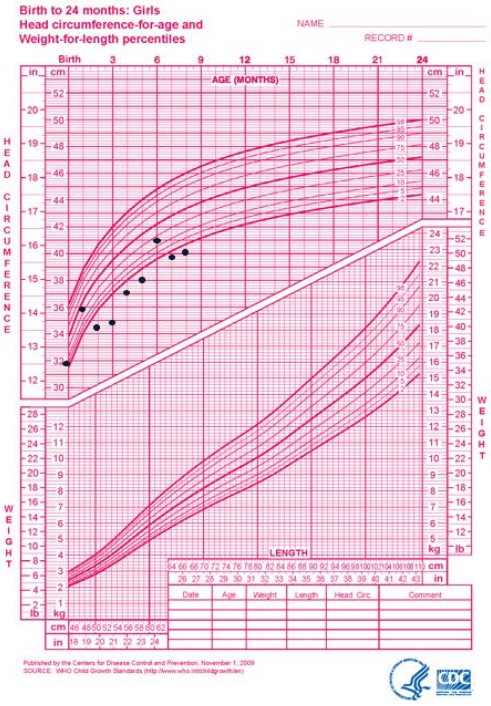
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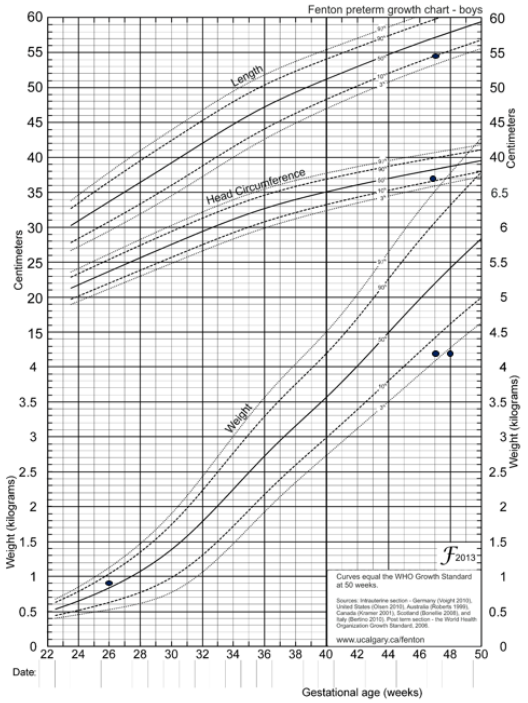
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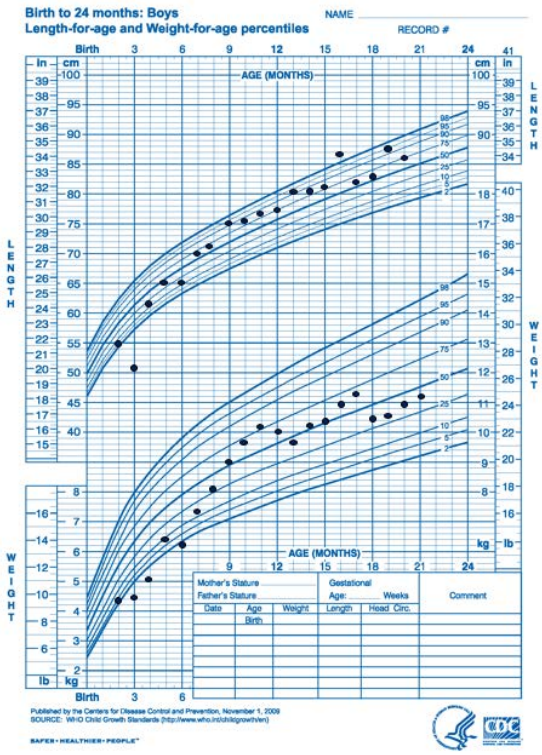
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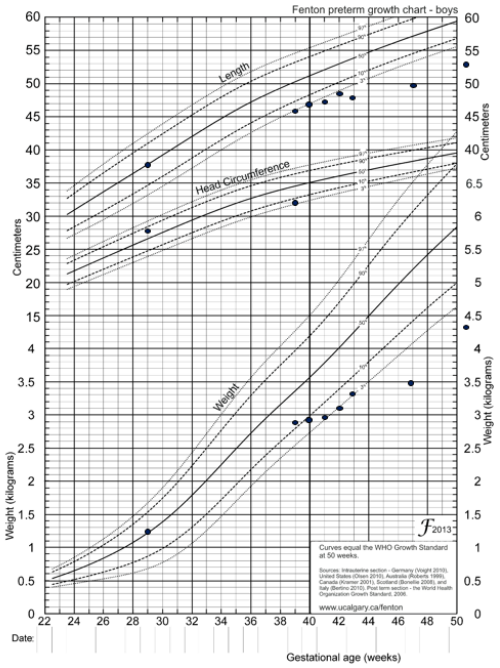
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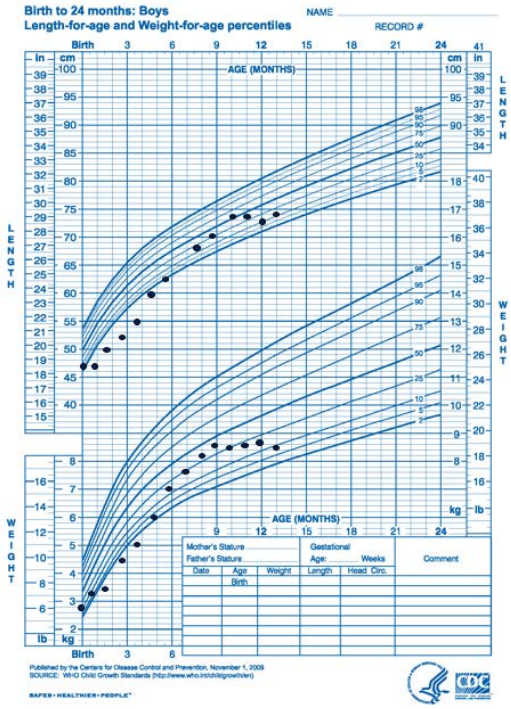
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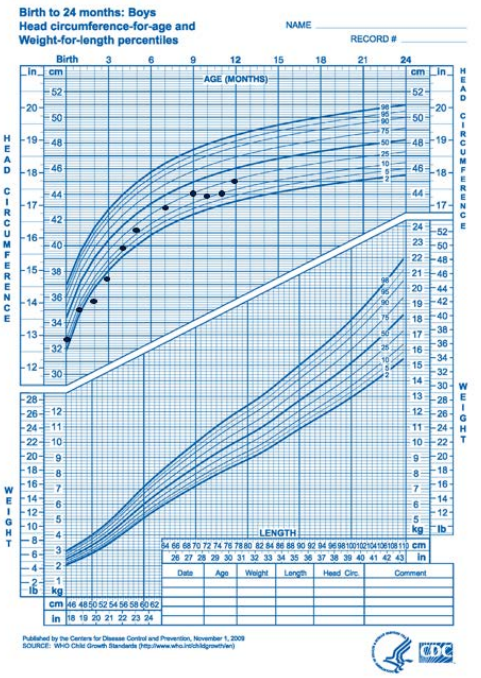
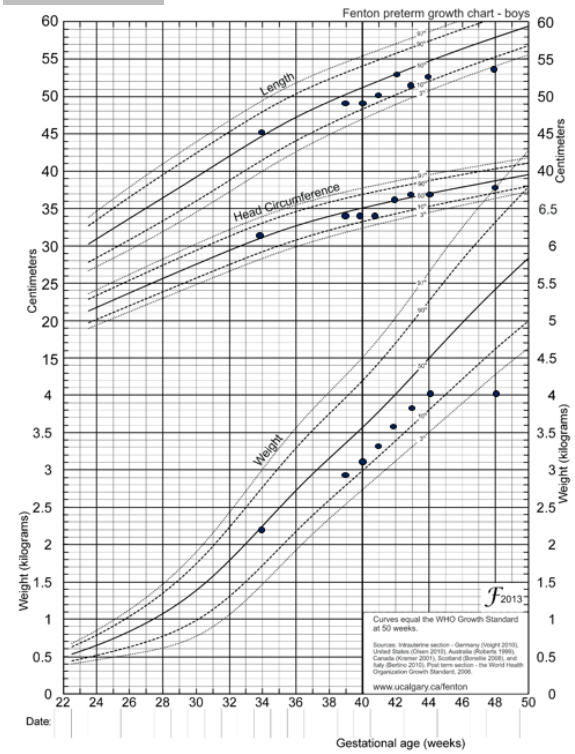
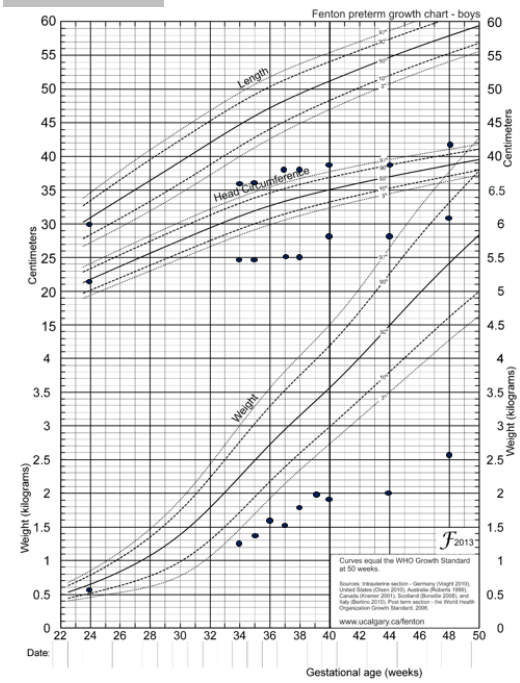
Head Circ.
Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)


Birth to 24 months: Boys
Head circumference-for-age and
Weight-for-length percentiles
NAME
RECORD #
AGE (MONTHS)
HEAD CIRCUMFERENCE
WEIGHT
LENGTH
Date
Age
Weight
Length
Head Circ.
Comment
Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

(b) (6) PM

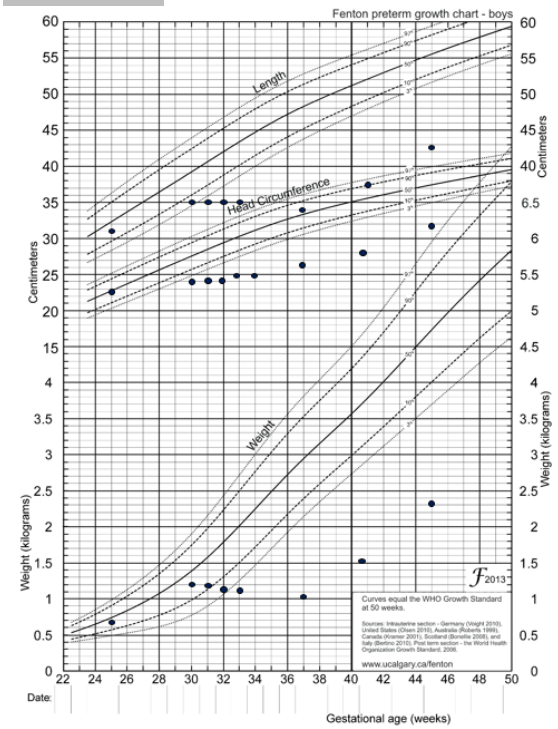

Fenton preterm growth chart - boys
Length
Head Circumference
Weight
Centimeters
Weight (kilograms)
Gestational age (weeks)
Date:
Curves equal the WHO Growth Standard at 50 weeks.
www.ucalgary.ca/fenton

(b) (6) PM



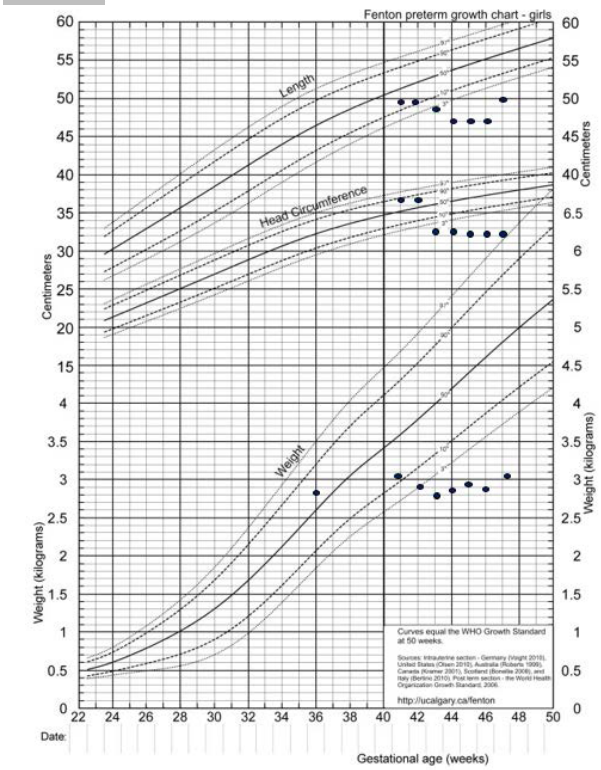
ELBW infant with initial DBil <5mg/dL who reached resolution of cholestasis (DBil <2mg/dL) within 12 weeks of Omegaven therapy. Patient resumed Intralipid® at the end of treatment.

(b) (6) PM



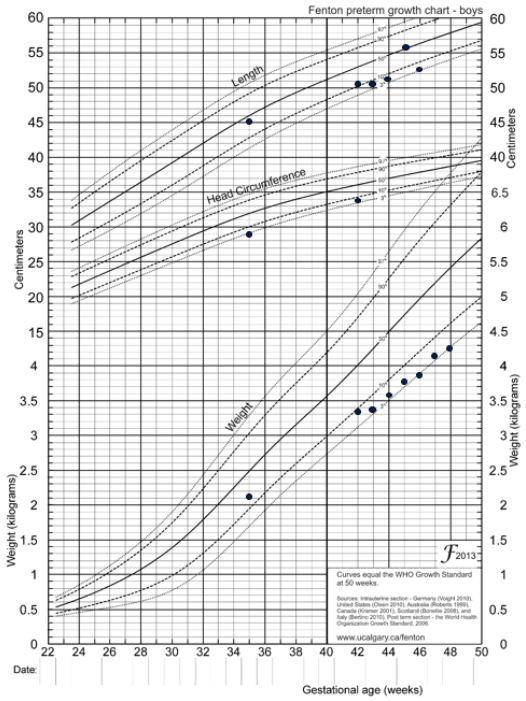
ELBW infant who experienced (second) intestinal perforation approximately 4 weeks into Omegaven treatment (~34 weeks PCA). Patient weaned off parenteral nutrition and transitioned to enteral nutritioini by end of therapy at 45 weeks PCA.

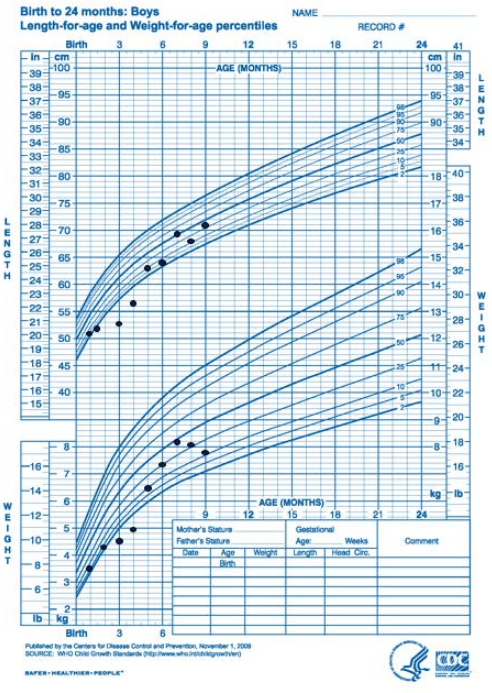
(b) (6)



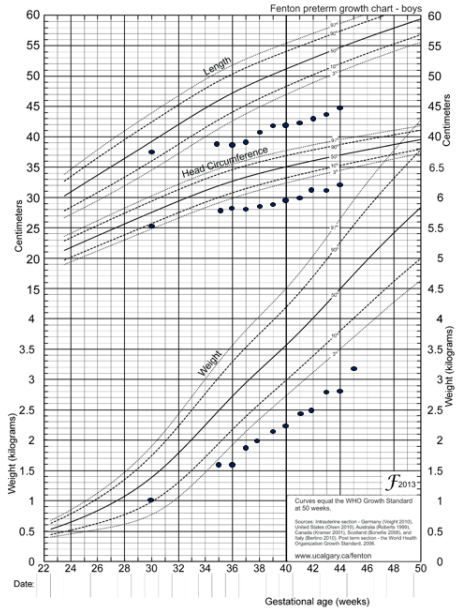
Preterm infant who began treatment at 41 weeks PCA, and had non-fatal SAE's including GI hemorrhage 2 days after starting Omegaven, and subsequent respiratory complications.

(b) (6)

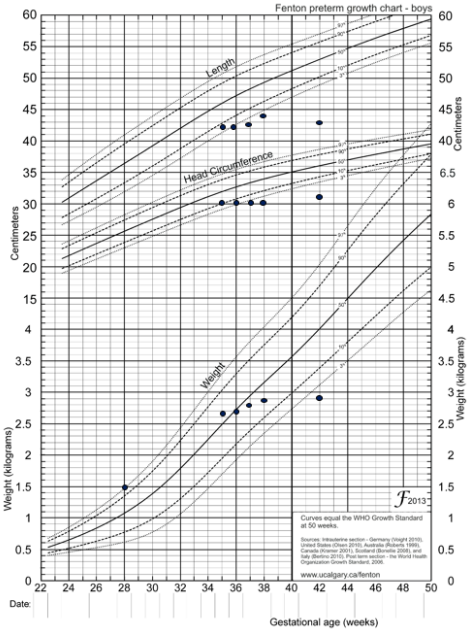




(b) (6) PM

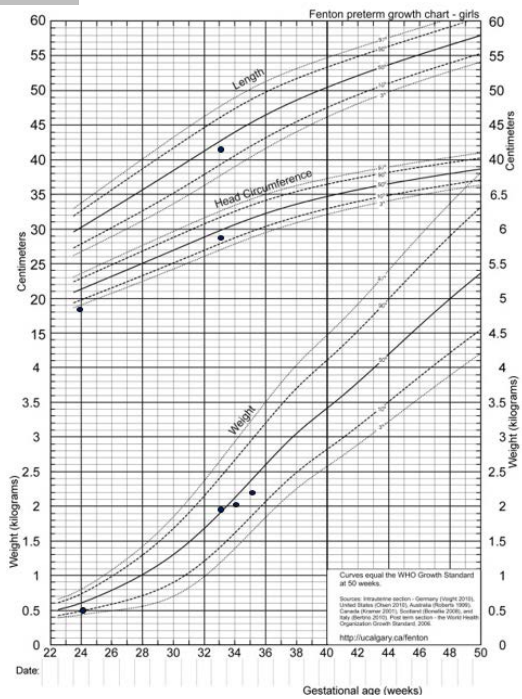


(b) (6)

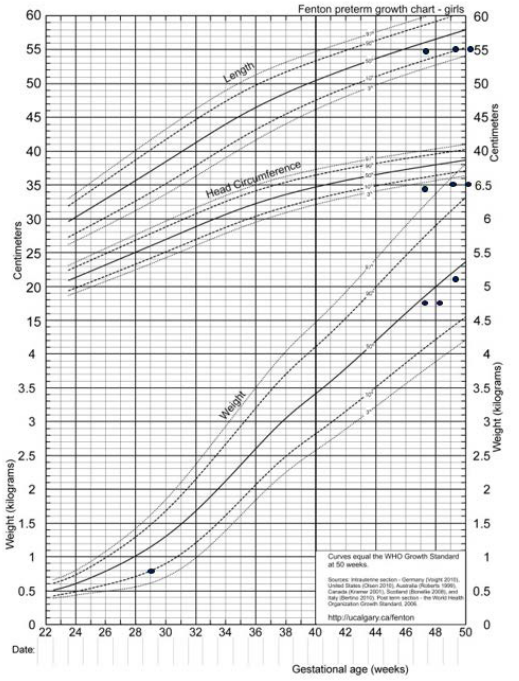


VLBW preterm infant who experienced multiple SAEs of significant apneas and bradycardia (A/B) within the first 2 weeks of treatment, and subsequently diagnosed with fungal opthalmitis and infections complications with candida wound and staphylococcal abscess during treatment. Patient resumed Intralipid® at the end of treatment with Omegaven.

(b) (6)



(b) (6)



†Shorter duration of growth assessments (i.e., <12 months), especially in older (>2year old) children were not as informative as the longer duration of follow-up in younger patients.

16.9. Safety Statistics Review

Introduction

Omegaven® (lipid injectable emulsion) is a fish oil emulsion administered intravenously in patients who require parenteral nutrition supplementation with long chain omega-3 fatty acids. The proposed indication of Omegaven is source of calories and fatty acids in pediatric patients with PNAC.

Two investigator-initiated clinical efficacy and safety studies of Omegaven monotherapy in pediatric patients with PNAC are being used to support the NDA: one study (n = 141) conducted at BCH/Harvard Medical School (Study 34) during 2004 - 2012 and the other study (n = 61) conducted at TCH/Baylor College of Medicine (Study 35) during 2007 - 2012. The Applicant used HC (n = 93) patients treated with Intralipid (a soybean oil-based lipid emulsion) from BCH (n = 47), TCH (n=28), and UCLA Mattel Children's Hospital (n=18) during 1999 - 2004. The per PP population included 151 Omegaven patients and 64 HC patients.

Based on the PP population, the Applicant used greedy matching based on DBil and PMA to match Omegaven patients to HC patients in a 2:1 ratio. Thus, the PM population comprised 82 Omegaven-treated patients and 41 HC patients. The safety endpoints were time to resolution of PNAC, time to composite safety endpoints, and time to liver transplant. The Applicant used univariate and multivariate Cox regression models for the analyses.

The Applicant's analysis has two major limitations. First, the Applicant adjusted for confounders by primarily matching Omegaven patients and HC patients on two main covariates. Therefore, the results might be confounded by other potential confounders. Second, by matching in a 2:1 ratio, the Applicant's analysis excluded 42.8% of the patients (45.7% of Omegaven patients). Therefore, to adjust for additional confounders and include most available patients in the analysis, DB VII conducted a propensity scores analysis using full matching.

This review includes the methods subsection, which illustrates the prespecified SAP for the DB VII analysis, followed by the results and conclusions. The data used in this review were located at \\CDSESUB1\evsprod\NDA210589\0006\m5\datasets\iss-ise\analysis\adam\datasets.

Methods

Baseline Characteristics

For baseline characteristics, we estimated the mean for continuous variables, and the prevalence for categorical variables by treatment arm. We then compared the Omegaven and HC patients from the PP population with respect to their baseline characteristics before conducting propensity score matching using the SMD, which compares the difference in means

in units of the pooled standard deviation. An SMD of less than 0.1 is considered a negligible difference in the mean or prevalence of a covariate between treatment groups.

Safety Endpoints

The safety endpoints were as follows:

- Time to ROPNAC: the time (week) from baseline to when DBil levels decrease to < 2 mg/dL
- Time to composite safety endpoints: DBil < 2 mg/dL and AST or ALT < 3 x ULN
- Time to liver transplant.

Propensity Score Estimation

We estimated propensity scores (PS) using a logistic regression model with treatment as the outcome variable, and potential confounders as the independent variables. The potential confounders that were collected for both Omegaven patients and HC patients, identified by the clinical team included DBil, ALT, AST, PMA, gestational age, sepsis, birth weight, sex and underlying surgical condition. If patients had missing data in at least one of the covariates, we imputed the missing values using regression prediction conditional on covariates that had no missing values. Each patient had an estimated PS, the probability of being treated with Omegaven. Because inference cannot be made for patients without a comparator with a similar PS, only patients within the range where the two PS distributions for Omegaven and HC overlapped were considered for matching.

Matching with Propensity Scores

To maximize the number of matched patients, we used optimal full matching that creates a series of matched sets that contains at least one Omegaven patient and at least one HC patient[99,100]. Full matching uses all available patients. Therefore, it avoids bias due to incomplete matching and generalizability issues.

Full matching finds optimal matches by minimizing the average of the distances between each treated patient and control patient within each matched set. We used constrained full matching by setting the maximum of Omegaven-treated patients in one matched set to five patients. We used the R 'MatchIt' package by setting method = "full."

[99] Hansen BB. Full matching in an observational study of coaching for the SAT. Journal of the American Statistical Association. 2004 Sep 1;99(467):609-18.
[100] Austin PC, Stuart EA. Optimal full matching for survival outcomes: a method that merits more widespread use. Statistics in medicine. 2015 Dec 30;34(30):3949-67.

Evaluating Balance between Omegaven and Historical Control Groups after Propensity Score Matching

To assess whether PS matching improved balance between the Omegaven and HC groups, we estimated the SMDs post-PS matching. Full matching requires different weights for each matched set. Omegaven patients weight is the marginal probability of receiving Omegaven in the overall sample multiplied by the number patients in the given matched set divided by the number of Omegaven patients in that matched set. Similarly, HC patients weight is the marginal probability of receiving HC in the overall sample multiplied by the number of patients in the given matched set divided by the number of HC patients in that matched set.

Outcome Model

For each PM and FM population, we plotted Kaplan-Meier curves and conducted Cox regression analyses using the three safety endpoints as the outcomes. Weights from the FM population were applied to analysis. Thus, weighted Kaplan-Meier curves and weighted Cox regression models were used where variance was estimated with resampling methods. The univariate Cox regression model included treatment group only, while the multivariate analysis included four additional confounders (i.e., DBil, sepsis, underlying surgical condition, and birth weight) selected by the Applicant's stepwise variable selection procedure.

Results

Baseline Characteristics

Table 66 describes the mean and prevalence for continuous and categorical baseline characteristics, respectively, by group; and the SMDs. Most of the variables except sepsis and sex showed imbalance in the PP population. Particularly, DBil was highly imbalanced between the two groups.

Table 66. Difference Between Omegaven-treated and HC Patients in PP Population

Variable (Mean)	Omegaven-treated (N=151)	Historical Control (N=64)	SMD
Gestational Age	30.68	32.16	0.309
Post-menstrual Age	43.84	41.20	0.206
Direct Bilirubin	6.63	3.88	0.831
Alanine Aminotransferase	2.16	1.30	0.473
Aspartate Aminotransferase	3.01	1.90	0.436
Sepsis (Yes)	21%	23%	0.070
Birth Weight	1.59	1.72	0.146

Sex (Male)	60%	58%	0.050
Underlying Surgical Condition			
Abdominal Wall Defects	17%	28%	0.263
Necrotizing Enterocolitis	31%	20%	0.235
Both	1%	3%	0.122
Other	42%	33%	0.199
Unknown	9%	16%	0.216

Source: Reviewer's table

Full Matched Population and Balance

The full matching excluded 10 patients (7 Omegaven-treated patients and 3 HC patients) from the PP population. We assessed the balance of covariates between the two groups after the full matching and compared that to the PM population (Table 67). The SMD of each variable in the PP population decreased in the PM and FM populations. DBil was imbalanced (SMD > 0.2) between the two groups after full matching; ALT and AST remained marginally imbalanced (SMD < 0.2). Imbalance with respect to UNDLSCO after pair matching improved in the FM population.

Table 67. Baseline Covariates Between Two Groups in PM and FM Populations

	PM Population			**FM Population**		
Variable (Mean)	**Omegaven-Treated (N= 82)**	**Historical Control (N = 41)**	**SMD**	**Omegaven-treated (N= 144)**	**Historical Control (N = 61)**	**SMD**
Gestational Age	30.98	31.85	0.195	31.63	32.00	0.018
Post-menstrual Age †	41.40	40.39	0.124	42.79	41.34	0.050
Direct Bilirubin †	4.60	4.41	0.085	4.68	3.96	0.277
Alanine Aminotransferase ‡	1.81	1.51	0.163	1.56	1.30	0.155
Aspartate Aminotransferase ‡	2.38	2.13	0.122	1.95	1.66	0.160
Sepsis (Yes) ‡	20%	20%	<0.01	22%	23%	0.018
Birth Weight ‡	1.68	1.66	0.032	1.84	1.73	0.063
Sex (Male)	51%	59%	0.147	61%	57%	0.055
Underlying Surgical Condition ‡						
Abdominal Wall Defects	18%	32%	0.314	25%	30%	0.079
Necrotizing Enterocolitis	26%	24%	0.028	22%	21%	<0.01
Both	1%	2%	0.091	2%	2%	0.020
Other	48%	29%	0.383	40%	34%	0.090

Unknown	7%	12%	0.165	12%	13%	0.018

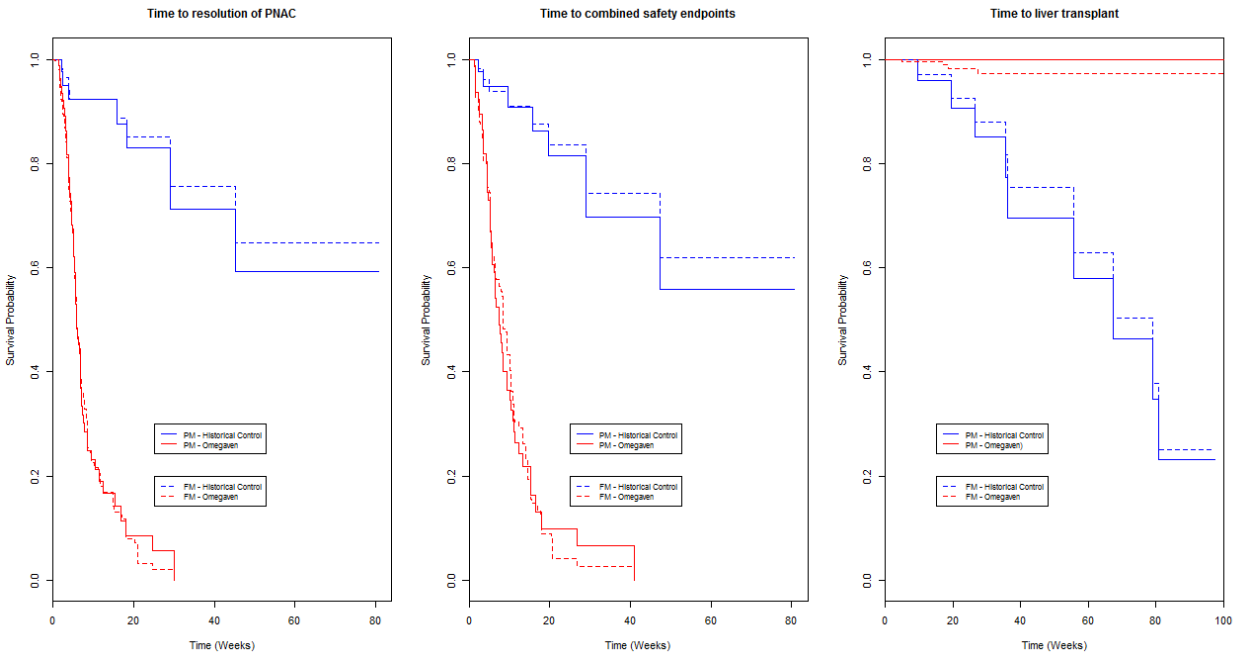
† Main variables used for Applicant's matching; ‡ Additional variables considered for Applicant's matching
Source: Reviewer's table

Outcome Analysis

The Applicant provided Kaplan-Meier survival curves and conducted Cox regression analysis with the time to resolution of PNAC endpoint in the PM population (ISE document page 35). Similarly, we used the FM population to plot the Kaplan-Meier survival curves and used Cox regression to estimate the HRs between the treatment groups with respect to the three safety endpoints.

Figure 34 describes the survival curves of Omegaven-treated (red) and HC patients (blue) for each endpoint. Solid lines indicate the PM population, and the dotted lines indicate the FM population. No patients in the PM population Omegaven-treated group had a liver transplant.

Figure 34. Kaplan-Meier Survival Curves of PM and FM Populations



Source: Reviewer's figure

Table 68 presents the results of univariate Cox regression analysis of each safety endpoint.

Table 68. HR of the Treatment Group in Univariate Cox Regression Analyses in PM and FM Populations

HR [95% CI]	PM Population	FM Population
Time to ROPNAC	11.868 [5.110, 27.566]	15.598 [7.018, 34.666]
Time to combined safety endpoints	10.777 [4.625, 25.113]	13.965 [6.194, 31.487]
Time to liver transplant	NA†	0.050 [0.013, 0.190]

†NA due to no event in the Omegaven-treated group; PP population showed 0.206 [0.072, 0.590] and 6 liver transplant events exist in the Omegaven-treated group.
Source: ISE document page 141 and reviewer's analyses.

The results of the multivariate Cox regression analysis are as follows: the PM population showed a larger HR of the treatment effect than the FM population (Table 69). This occurred because the Applicant's stepwise analysis excluded 31 patients out of 123 patients because of the missing data. The multivariate analysis using the Applicant's final variables only in the FM population showed a lower HR.

Table 69. HR of the Treatment Group in Multivariate Cox Regression Analyses in PM and FM Populations

HR [95% CI]	PM Population	FM Population
Time to ROPNAC	35.56 [9.96, 126.94]	23.18 [8.95, 60.02]

Source: ISE document page 143 (Table 39) and reviewer's analysis.

Summary and Conclusion

To make the HC and Omegaven-treated groups comparable, the Applicant used greedy matching to form a PM population. In contrast, we conducted a propensity score analysis using full matching to adjust for multiple confounders. The FM population excluded only 4.6% of the patients from the PP population, while the PM population excluded 42.8% of the patients. Because the proportion of events and censoring were similar (46% censoring in PM versus 48% censoring in FM), the Cox regression analysis results were similar. Although the propensity score method allows for adjusting for several confounders, our analysis was limited because some potential confounder information was not collected. However, our analysis included most of the Omegaven-treated patients and improved the balance of confounders, such as underlying surgical condition.

1. Fat-free parenteral alimentation of infants. Nutrition reviews. 1974;32(5):134-6.
2. Faulkner WJ, Flint LM, Jr. Essential fatty acid deficiency associated with total parenteral nutrition. Surgery, gynecology & obstetrics. 1977;144(5):665-7.

16.10. Recoding Scheme of MedDRA Level Preferred Terms During Review

Recoded	AEDECOD (Preferred Term)
Abscess	Abscess, Abdominal Abscess, Abscess Drainage, Abscess Limb, Abscess Neck, Abdominal Wall Abscess, Catheter Site Abscess, Peritoneal Abscess, Stitch Abscess, Stoma Site Abscess, Staphylococcal Abscess, Wound Abscess, Incision Site Abscess
Acidosis	Acidosis, Blood Bicarbonate Decreased, Blood Ph Decreased, Metabolic Acidosis, PCO2 Increased, Base Excess Increased, Respiratory Acidosis, Carbon Dioxide Decreased
Agitation	Agitation, Agitation Neonatal
Alkalosis	Base Excess Increased, Alkalosis Hypochloraemic, Blood Bicarbonate Increased, Metabolic Alkalosis
Anemia	Anaemia, Haematocrit Decreased, Haemoglobin Decreased, Normochromic Normocytic Anaemia
Apnea	Apnoea, Infantile Apnoea
Arrhythmia	Arrhythmia, Atrial Flutter, Extrasystoles, Ventricular Extrasystoles, Ventricular Tachycardia, Sinus Arrhythmia, Supraventricular Tachycardia, Ventricular Arrhythmia
Bacterial Infection	Alpha Haemolytic Streptococcal Infection, Acinetobacter Bacteraemia, Acinetobacter Test Positive, Acinotobacter Infection, Bacterial Test Positive, Bacterial Tracheitis, Bacterial Infection, Bacteraemia, Bacillus Infection, Bacillus Bacteraemia, Citrobacter Infection, Clostridium Difficile Infection, Clostridium Difficile Colitis, Clostridium Test Positive, Conjunctivitis Bacterial, Endocarditis Bacterial, Enterobacter Bacteraemia, Enterobacter Infection, Enterobacter Test Positive, Enterococcal Bacteraemia, Enterococcal Infection, Enterococcus Test Positive, Escherichia Bacteraemia, Escherichia Infection, Escherichia Test Positive, Escherichia Urinary Tract Infection, Eye Infection Staphylococcal, Gastroenteritis Pseudomonas, Haemophilus Test Positive, Klebsiella Bacteraemia, Klebsiella Infection, Klebsiella Test Positive, Meningitis Bacterial, Meningitis Staphylococcal, Morganella Infection, Lactobacillus Infection, Pantoea Agglomerans Infection, Pertussis, Pneumococcal Bacteraemia, Pneumococcal Infection, Pneumonia Haemophilus, Pneumonia Klebsiella, Pneumonia Pseudomonal, Pneumonia Staphylococcal, Propionibacterium Infection, Proteus Infection, Pseudomonas Aeruginosa Meningitis, Pseudomonas Infection, Pseudomonas Test Positive, Respiratory Tract Infection Bacterial, Rhodococcus Infection, Serratia Bacteraemia, Serratia Infection, Serratia Test Positive, Sinusitis Bacterial, Stenotrophomonas Infection, Stenotrophomonas Test Positive, Staphylococcus Test Positive, Staphylococcal Bacteraemia, Staphylococcal Infection, Streptococcal Bacteraemia, Streptococcal Infection, Streptococcal Urinary Tract Infection, Urinary Tract Infection Bacterial, Urinary Tract Infection Enterococcal, Urinary Tract Infection Pseudomonal, Wound Infection Bacterial, Wound Infection Pseudomonas, Wound Infection Staphylococcal
Bandemia	Bandaemia, Band Neutrophil Count Increased
Blood Gases Abnormal	Blood Ph Abnormal, Blood Gases Abnormal
Cardiac Arrest	Cardio-Respiratory Arrest, Cardiac Arrest
Cardiac Failure	Cardiac Failure, Cardiac Failure Acute

Catheter Site Complications	Pain, Phlebitis, Related Reaction, Catheter Site Hemorrhage, Catheter Site Erythema, Catheter Site Inflammation, Catheter Site Discharge, Catheter Site Cellulitis, Catheter Site Erosion, Catheter Site Extravasation, Catheter Site Granuloma, Catheter Site Swelling, Catheter Site Rash, Catheter Site Vesicles, Catheter Site Ulcer, Catheter Site Eczema, Catheter Site Induration, Infusion Site Extravasation, Vascular Access Malfunction
Cholangitis	Cholangitis, Cholangitis Acute
Chronic Lung Disease	Bronchopulmonary Disease, Bronchopulmonary Dysplasia, Chronic Respiratory Failure
Coagulopathy	Coagulopathy, Coagulation Factor Increased, Coagulation Test Abnormal, Coagulation Time Prolonged, Activated Partial Thromboplastin Time Prolonged, International Normalised Ratio Increased
Deafness	Conductive Deadness, Deadness Neurosensory, Deafness Unilateral
Developmental Delay	Gross Motor Delay, Growth Retardation, Developmental Delay, Motor Developmental Delay
Device Complications	Device Occlusion, Device Malfunction, Device Dislocation, Device Leakage, Device Breakage, Medical Device Site Discharge, Medical Device Site Erythema, Medical Device Site Haemorrhage, Medical Device Site Irritation, Medical Device Site Laceration, Medical Device Site Swelling, Unintentional Medical Device Removal, Thrombosis In Device
Fracture	Femur Fracture, Humerus Fracture, Rib Fracture, Ulna Fracture
Fungal Infection	Anal Candidiasis, Candiduria, Candida Infection, Candida Nappy Rash, Candida Test Positive, Encephalitis Fungal, Eye Infection Fungal, Fungaemia, Fungal Cystitis, Fungal Peritonitis, Fungal Skin Infection, Fungal Test Positive, Gastrointestinal Candidiasis, Oral Candidiasis, Skin Candida, Urinary Tract Infection Fungal, Wound Infection Fungal
Hematuria	Blood Urine Present, Hematuria
Hernia	Hiatus Hernia, Hernia, Incarcerated Inguinal Hernia, Inguinal Hernia, Umbilical Hernia
Hepatic Enzyme Increased	Transaminases Increased, Hepatic Enzyme Increased
Hyperammonemia	Ammonia Increased, Hyperammonaemia
Hyperbilirubinemia	Blood Bilirubin Increased, Hyperbilirubinemia
Hyperkalemia	Blood Potassium Increased, Hyperkalemia
Hypertension	Blood Pressure Systolic Increased, Blood Pressure Increased
Hypertriglyceridemia	Blood Triglycerides Increased, Hypertriglyceridaemia
Hypoalbuminemia	Blood Albumin Decreased, Hypoalbuminemia
Hypoglycemia	Blood Glucose Decreased, Hypoglycaemia
Hypotension	Blood Pressure Diastolic Decreased
Hypovolemia	Hypovolemia, Volume Blood Decreased
Infection NOS	Abdominal Infection, Abdominal Wall Infection, Catheter Site Infection, Culture Positive, Diarrhoea Infectious, Device Related Infection, Ear Infection, Enteritis Infectious, Eye Infection, Infection, Meningitis, Otitis Media, Otitis Media Acute, Pneumonia, Respiratory Tract Infection, Shunt Infection, Stoma Site Infection, Urinary Tract Infection, Upper Respiratory Tract Infection, Tracheostomy Infection, Vaginal Infection, Wound Infection
Intestinal Anastamosis Complication	Intestinal Anastomosis Complication, Gastrointestinal Anastomotic Leak
Jaundice	Jaundice, Jaundice Cholestatic
Multiorgan Failure	Neonatal Multi-Organ Failure, Multiple Organ Dysfunction Syndrome, Multi-Organ Disorder

Respiratory Distress	Use of Accessory Respiratory Muscles, Grunting, Nasal Flaring, Respiratory Distress, Wheezing
Seizure	Generalized Tonic-Clonic Seizure, Seizure, Hypoglycaemic Seizure, Partial Seizures
Sepsis	Abdominal Sepsis, Bacterial Sepsis, Candida Sepsis, Citrobacter Sepsis, Device Related Sepsis, Enterobacter Sepsis, Enterococcal Sepsis, Escherichia Sepsis, Fungal Sepsis, Klebsiella Sepsis, Pseudomonal Sepsis, Sepsis Neonatal, Septic Shock, Serratia Sepsis, Staphylococcal Sepsis, Streptococcal Sepsis, Thrombophlebitis Septic, Urosepsis
Tachycardia	Heart Rate Increased, Tachycardia
Tachypnea	Respiratory Rate Increased, Tachypnoea
Temperature Instability	Body Temperature Decreased, Body Temperature Increased, Hypothermia, Body Temperature Fluctuation, Body Temperature Increased, Chills, Hyperthermia, Pyrexia
Thrombocytopenia	Platelet Count Decreased, Thrombocytopenia
Thyroid Dysfunction	Thyroxine Decreased, Thyroid Function Test Abnormal, Thyroxine Increased
Stoma Complication	Stoma Site Cellulitis, Stoma Complication, Stoma Site Discharge, Stoma Site Erythema, Stoma Site Extravasation, Stoma Site Haemorrhage, Stoma Site Hypergranulation, Stoma Site Irritation, Stoma Site Ischaemia, Stoma Site Pain, Stoma Site Rash, Stoma Site Reaction, Stoma Site Ulcer, Stomal Hernia, Gastrointestinal Stoma Complication, Gastrointestinal Stoma Necrosis
Viral Infection	Adenovirus Test Positive, Adenovirus Infection, Viral Infection, Coxsackie Virus Test Positive, Echovirus Test Positive, Gastroenteritis Norovirus, Gastroenteritis Rotavirus, H1n1 Influenza, Human Rhinovirus Test Positive, Influenza, Oral Herpes, Parainfluenzae Virus Infection, Pneumonia Influenza, Pneumonia Respiratory Syncytial Viral, Pneumonia Viral, Respiratory Syncytial Virus Bronchiolitis, Respiratory Syncytial Virus Infection, Respirovirus Test Positive, Rhinovirus Infection, Rotavirus Infection, Rotavirus Test Positive, Simplex Virus Test Positive, Viral Test Positive, Viral Upper Respiratory Tract Infection
Vomiting	Vomiting, Vomiting Projectile
Withdrawal Syndrome	Drug Withdrawal Syndrome Neonatal, Withdrawal Syndrome

Source: S. Seo. ADAE.xpt.

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

/s/

MIMI T PHAN
07/27/2018

JULIE G BEITZ
07/27/2018