Protocol Title	Absorption and Safety with Sustained Use of Relizorb™ Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding
Protocol Number	0000498
Indication	Exocrine Pancreatic Insufficiency
Date of Protocol	07 March 2016
Revision Date	NA
Sponsor	Alcresta Pharmaceuticals, Inc. One Newton Executive Park, Suite 100 Newton, MA 02462 Email: Phone:

PROTOCOL AGREEMENT	
Protocol Title	Absorption and Safety with Sustained Use of Relizorb™ Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding
Protocol Number	0000498
Investigational Device	Relizorb™ immobilized lipase (iLipase™) cartridge
Indication	Exocrine Pancreatic Insufficiency
Protocol Date	07 March 2016
Revision Date	NA

I have read this protocol and agree to conduct this research study as outlined herein. I will ensure that all subinvestigators and other study staff members have been trained and understand all aspects of this protocol. I agree to cooperate fully with Alcresta Pharmaceuticals, Inc. or any third parties utilized during the study. I will adhere to all Food and Drug Administration and other applicable regulations and guidelines regarding research studies during and after study completion.

Principal Investigator	_____
Printed Name	_____
Signature	_____
Date *(ddmmmyyyy)*	_____

STUDY SYNOPSIS

Title	Absorption and Safety with Sustained Use of Relizorb™ Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding
Sponsor	Alcresta Pharmaceuticals, Inc., One Newton Executive Park, Suite 100, Newton, MA 02462

Sponsor Contacts	*Name*	*Title*	*Phone*
		Chief Medical Officer Director, Clinical Operations	

Investigational Device Background	The Relizorb™ digestive enzyme cartridge is a single-use, point-of-care device that connects in-line with existing enteral pump feed sets and pump extension sets. Relizorb is designed to hydrolyze fats contained in the enteral formulas, mimicking the function of the digestive enzyme lipase that is normally secreted by the pancreas. By hydrolyzing fats from enteral formula, Relizorb allows for the delivery of absorbable fatty acids and monoglycerides for patients who receive enteral nutrition and cannot hydrolyze fats normally. The active component in Relizorb is the digestive enzyme lipase, which is covalently attached to polymeric beads; the lipase-bead complex is called iLipase™. As the enteral formula passes through Relizorb during a tube feeding, it makes contact with the iLipase and the fat in the formula is hydrolyzed into its absorbable forms (fatty acids and monoglycerides) prior to ingestion. The iLipase remains in the cartridge and is not ingested.
Indication and Classification	The proposed indication is for use in children and adults to hydrolyze fats in enteral formula. The lipase used in Relizorb is designated by the US Food and Drug Administration (FDA) as generally recognized as safe (GRAS 000216). The FDA Center for Food Science and Applied Nutrition (CFSAN) cleared iLipase as a Food Contact Substance under the Food Contact Notification process on January 20, 2015 (FCN 1498). RELIZORB was cleared by the FDA Center for Devices and Radiological Health (CDRH) as a Class II low-risk device through a *de novo* application on November 20, 2015 (DEN150001) and is indicated for use in adults to hydrolyze fats in enteral formula.
Number of Patients	Approximately 35 male and female patients with cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI) will be enrolled in Protocol 0000498 with the intention of obtaining at least 30 evaluable subjects who complete the study. Subjects must be ≥4 years of age, with no upper age limit. Since the inclusion/exclusion criteria for this study is similar to Protocol 0000497, patients who participated in Protocol 0000497 will be eligible to participate in this study after they have completed participation

in Protocol 0000497.

Sites

Approximately 10 sites in the United States will participate in this study. Sites that are actively enrolling patients for Protocol 0000497 will preferentially participate in this study.

Objective

The overall objective of the study is to assess safety and tolerability and demonstrate improved fat absorption with sustained use of Relizorb in patients with CF who have EPI and are receiving enteral nutrition as part of their total nutritional therapy. In this study, subjects will be receiving a semi-elemental formula containing pre-hydrolyzed protein that has a high content of long chain triglycerides (Impact® Peptide 1.5) and will be using Relizorb during their enteral feeding in place of other therapies currently used to aid in fat digestion and absorption, such as pancreatic enzyme replacement therapy (PERT). Plasma concentration of long-chain polyunsaturated fatty acids (LCPUFAs) such as docosahexaenoic acid (DHA; C:22:6n-3) and eicosapentaenoic acid (EPA; C20:5n-3) will be measured as biomarkers of fat absorption. Tissue accretion of LCPUFAs assessed through measurement of erythrocyte membrane concentrations of LCPUFAs such as DHA and EPA, as well as determination of the profile of fatty acids in plasma will also be evaluated as additional biomarkers of fat absorption. Plasma fat-soluble vitamin and serum protein concentrations will also be measured as indicators of effectiveness. All fatty acid, fat-soluble vitamin, and protein concentrations will be assessed in relation to values obtained at the beginning of the run-in period (Day -7), at baseline (Day 0), and during Relizorb use (Days 30, 60, and 90). Safety and tolerability of sustained use of Relizorb will be assessed during use and compared with gastrointestinal symptoms recorded during the observation phase of the study (Day -14 through Day -7).

Efficacy

- Evaluate effect of sustained Relizorb use during enteral feedings on fat absorption through serial measurements of plasma and tissue (erythrocyte membrane) concentrations of physiologically relevant LCPUFAs such as DHA & EPA as well as serial determinations of the plasma fatty acid profile changes as biomarkers of fat absorption
- Evaluate effect of sustained Relizorb use during enteral feedings on plasma fat-soluble vitamin concentrations
- Evaluate effect of sustained Relizorb use on the ratio of omega-6 to omega-3 fatty acids as a potential indicator of immunomodulation
- Evaluate effect of sustained Relizorb use on urinary leukotriene levels
- Evaluate effect of sustained Relizorb use on serum protein levels
- Evaluate effect of sustained Relizorb use on growth

Safety

- Evaluate the safety and tolerability of sustained use of Relizorb as part

of an enteral feeding regimen.

Endpoints

Efficacy

- Change over time in plasma concentrations of omega-3 fatty acids such as DHA and EPA
- Change over time in tissue (erythrocyte membrane) fatty acid concentrations such as DHA and EPA
- Change over time in the plasma fatty acid profile
- Change over time in the ratio of omega-6 to omega-3 fatty acids
- Change over time in plasma concentrations of fat soluble vitamins A, D, and E
- Change over time in serum protein concentrations (total protein, prealbumin, albumin, transferrin)
- Change over time in markers of inflammation (urinary leukotrienes)
- Change over time in weight and body mass index (BMI) and weight and BMI z-scores

Safety

- Frequency and severity of adverse events and unanticipated adverse device effects (UADEs)
- Evaluation of clinical and laboratory findings
- Concomitant medication assessment
- Frequency and severity of gastrointestinal signs and symptoms (abdominal pain, vomiting, loss of appetite, bloating, flatulence and steatorrhea)

Study Duration

The duration of the study is approximately 7-8 months. Three and a half months will be allocated for patient enrollment. Patient time in study will be at least three and a half months (1 week observation period, 1 week run in, 3 months treatment), and UADEs that occur towards the end of the study may require another 30 days of follow up.

Study Design

Protocol 0000498 is a multicenter open label study to evaluate the effect of sustained Relizorb use during enteral feeding on fat absorption, as well as safety and tolerability of sustained Relizorb use, in patients with CF and EPI who are receiving enteral tube feeding.

At study entry (Day -14), blood and urine will be collected as part of the screening evaluation and to assess baseline plasma and erythrocyte membrane concentrations of LCPUFAs such as DHA and EPA, plasma concentrations of other long chain fatty acids, plasma concentrations of fat-soluble vitamins, serum protein concentrations, and urinary leukotriene concentrations. Body weight, height, and BMI will be recorded, as well as historical quantification of use of PERT with daytime meals and with enteral feeding. During an initial 7 day observation period subjects will receive their usual enteral nutrition regimen. If subjects use PERT with their enteral nutrition, this will continue through the observation period, and PERT use will be recorded. The subject will also record gastrointestinal symptoms during the observation week in a

gastrointestinal symptom diary. During a 7-day run in period Day -7 to Day -1), subjects will use a standard enteral formula that contains a prehydrolyzed protein (Peptamen® 1.5) at their normal volume of administration from 500 mL up to a maximum volume of 1000 mL per feeding. If subjects use PERT with their enteral nutrition, this will continue through the run in period, and PERT use will be recorded. Throughout the study, individualized patient standard use of PERT with daily meals and snacks will continue.

Following the run in period, subjects will receive an enteral formula similar to Peptamen 1.5 that has a higher long chain triglyceride to medium chain triglyceride ratio (Impact® Peptide 1.5) at their normal volume of administration from 500 mL up to a maximum volume of 1000 mL per feeding using Relizorb in line for the 90 day treatment period.

During the 90-day treatment period, individualized patient standard use of oral PERT is allowed with daily meals, but use of therapeutic agents currently used to aid in fat absorption, such as PERT, will not be used with Relizorb during enteral feedings.

Serial measurements (Days 0, 30, 60, and 90) of plasma concentrations and erythrocyte levels of LCPUFAs such as DHA and EPA, plasma concentrations of other long chain fatty acids, plasma concentrations of fat soluble vitamins, serum protein and concentrations, urinary leukotriene concentrations, and body weight and BMI will be obtained and compared with each other as well as with values obtained at study entry (Day -14).

Safety and tolerability will be assessed using a gastrointestinal symptom diary, as well as recording adverse events (AEs), and unanticipated adverse device effects (UADEs).

STUDY SCHEMATIC

Table 1: Schedule of Events

Evaluation	Visit 1 **Day -14** *Study Entry*	Visit 2 **Day 0** *Baseline*	Visit 3 **Day 30** *Treatment*	Visit 4 **Day 60** *Treatment*	Visit 5 * **Day 90** *End of Study*
Informed Consent	X				
Inclusion / Exclusion Criteria	X				
Demographics	X				
Medical History [a]	X				
Physical Examination	X				X
Height, Weight, Body Mass Index [b]	X	X	X	X	X
Vital Signs [c]	X	X	X	X	X
Hematology [d]	X				X
Clinical Chemistry [e]	X				X
Urinalysis [f]	X				X
Blood Lipids [g]	X	X	X	X	X
Serum Proteins [h]	X	X	X	X	X
Serum Pregnancy Test (β-hCG) [i]	X				
Urinary Leukotrienes	X	X	X	X	X
7-Day Gastrointestinal Symptom Diary	X	X	X	X	X
Plasma Fatty Acid Samples [j]	X	X	X	X	X
Vitamins A, D, and E [k]	X	X	X	X	X
Peptamen® 1.5 500 to 1000 mL [l]	X				
Impact® Peptide 500 to 1000 mL		X	X	X	X
Relizorb Administration		X			
Relizorb Accountability Log		X			
Unanticipated Adverse Device Effects		X			

Note: Tests and procedures should be performed according to the above schedule but changes in scheduled study visits (±4 days) are allowed with permission from the site for holidays, vacations, etc. The amount of blood taken from subjects will be limited to no more than 3 mL/kg in 24 hours and no more than 7 mL/kg over the course of the study.

* If any Unanticipated Adverse Device Event (UADE) is reported on Day 90, then a safety follow-up telephone call will occur on Day 91, and the subject will be followed until either resolution of the event or for 30 days, whichever is shorter.

a. A complete medical history will be obtained.
b. Height and weight will be measured and recorded, and BMI will be calculated and recorded at each study visit. Four weight and BMI measurements recorded at 3 month intervals over the previous 12 months before Day -14 will be obtained from the medical record.
c. Vital signs will include blood pressure, pulse rate, respiratory rate and oral/tympanic temperature and will be obtained on in-clinic days.
d. Hematology includes complete blood count and white blood cell differential.
e. Clinical chemistry includes albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen, calcium, chloride, cholesterol, creatine phosphokinase, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, prealbumin, sodium, total and direct bilirubin, total protein, uric acid and A1C levels.
f. Urinalysis to include bilirubin, blood, glucose, ketones, leukocyte esterase, pH, protein, specific gravity, urinary creatinine and uric acid.
g. Blood lipids will include total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL).
h. Serum proteins include total protein, prealbumin, albumin, and transferrin.
i. A serum Beta-Human Chorionic Gonadotropin (β-hCG) pregnancy test will be performed only for females of childbearing potential. Results must be available prior to Day 1.
j. Blood samples will be obtained for plasma and red blood cell fatty acid analysis.
k. Blood samples will be collected to measure levels of Vitamins A, D, and E.
l. Peptamen 1.5 will be administered as the enteral formula during the run in phase from Day -7 through Day -1.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AA	Arachidonic Acid
AE	Adverse Event
ALCT-460	Rhizopus Oryzae Lipase (synonymous with FCS/enzyme)
ALCT-463	Enteral Feeding In-line Cartridge
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
β-hCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
CF	Cystic Fibrosis
CFRD	Cystic Fibrosis Related Diabetes
DHA	Docosahexaenoic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFIC	Enteral Feeding In-line Cartridge
EPA	Eicosapentaenoic acid
EPI	Exocrine Pancreatic Insufficiency
FA	Fatty Acid
FCS/Enzyme Complex	Food Contact Substance/enzyme complex
FDA	Food and Drug Administration
fND	Fortified Nutritional Drink
GCMS	Gas Chromatography Mass Spectrometry
GI	Gastrointestinal
GRAS	Generally Recognized As Safe
G-tube	Gastrostomy Feeding Tube
HDL	High-Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
kcal	Kilocalorie
LA	Linoleic Acid
LCPUFA	Long-Chain Polyunsaturated Fatty Acid
LCT	Long-Chain Triglyceride

LDL	Low-Density Lipoprotein
MS/MS	Mass Spectrometry/Mass Spectrometry
PERT	Pancreatic Enzyme Replacement Therapy
P*f*ND	Pre-hydrolyzed Fortified Nutritional Drink (Post exposure to ALCT-460)
PI	Principal Investigator
RBC	Red Blood Cells
RD	Registered Dietitian
RO	*Rhizopus oryzae*
SAE	Serious Adverse Event
TG	Triglycerides
UADE	Unanticipated Adverse Device Effects
ULN	Upper Limit of Normal
UPLC-MS/MS	Ultra-high Performance Liquid Chromatography–Tandem Spectrometer

1.0 STUDY OVERVIEW

This is a multicenter open label study to evaluate the effect of sustained Relizorb™ use during enteral tube feeding on fat absorption, as well as safety and tolerability of sustained Relizorb use, in patients with cystic fibrosis (CF) with exocrine pancreatic insufficiency (EPI) who are receiving enteral nutrition as part of their nutrition care plan. An estimated 35-40 male and female subjects will be recruited to yield 30 evaluable subjects who complete the study through at least Visit 4 at 60 days. Subjects must be ≥4 years of age but there is no upper age limit. After a 7 day observation period when subjects will follow their usual care plan, subjects will begin a 7 day run in period when they will receive a standard semi-elemental formula (Peptamen® 1.5) and use of pancreatic enzyme replacement therapy (PERT) with enteral tube feeding will be recorded. Following the run in period, subjects will use Relizorb while receiving a semi-elemental formula (Impact® Peptide 1.5) with a relatively increased ratio of long chain triglycerides (LCT) to medium chain triglycerides (MCT) for 90 days. Use of PERT in conjunction with enteral tube feeding will be discontinued during this 90 day period. Plasma concentration of relevant long-chain polyunsaturated fatty acid (LCPUFA) such as docosahexaenoic acid (DHA; C:22:6n-3) and eicosapentaenoic acid (EPA; C20:5n-3) will be measured as a biomarker of fat absorption, along with tissue accretion of DHA and EPA assessed by measurement of erythrocyte membrane levels, determination of changes in the plasma fatty acid profile, plasma fat soluble vitamin and serum protein concentrations, at study entry (Day -14), at baseline (Day 0), and during Relizorb use at 30 day intervals (Days 30, 60, and 90).

2.0 SCIENTIFIC AND CLINICAL BACKGROUND

A decrease in pancreatic lipase secretion associated with impaired exocrine pancreatic function results in maldigestion and malabsorption of fats and reduced total calorie intake.[1] EPI includes acute conditions or chronic diseases, such as CF, pancreatitis, pancreatic cancer as well as in elderly patients and preterm infants.[2,3,4,5]

Compromised exocrine pancreatic output leads to a lack of pancreatic enzymes, including but most notably lipase. Lipase function is considered critical to maintain caloric intake, since 9 kcal of energy is derived per gram of fat, versus 4 kcal of energy per gram of protein or carbohydrate. Fats varying in fatty acid carbon chain lengths are hydrolyzed (digested) and metabolized differently. Short chain triglycerides (C:2 – C:4) and MCTs (C:6-C:12) are absorbed directly through the villi of the intestinal mucosa. MCTs can be readily absorbed due to their shorter chain-length and the residual activity of gastric lipase, even in pancreatic compromised patients. LCTs have fatty acids of >12 carbons (C:14-C:24). LCTs are not directly absorbed but instead must first be hydrolyzed into fatty acids and monoglycerides by pancreatic lipase before absorption can take place in the small intestine. Once fatty acids and monoglycerides are absorbed, they are transported to the liver and, ultimately, to tissues in the body for various physiological purposes.[6] Since long chain fatty acids, in particular LCPUFAs,

are the most difficult to digest and absorb, plasma concentrations and tissue accretion of LCPUFAs are informative biomarkers of fat absorption in general in people with fat malabsorption such as patients with CF and EPI. DHA in particular is known to be deficient in people with cystic fibrosis, leading to an imbalance of the omega-6 to omega-3 ratio.

It is important to note that fatty acids with different carbon chain lengths have different impacts on physiologically functions.[7] While both LCTs and MCTs provide calories, only long chain fatty acids from LCTs such as omega-3 fatty acids DHA and eicosapentaenoic acid (EPA) and omega-6 fatty acid arachidonic acid (AA) are structural components of membranes and also biological mediators involved in the regulation of various physiological functions. MCTs, when substituted for LCTs, have been shown to increase energy expenditure and satiety leading to reduced overall caloric intake and reduced body fat mass, making them a poor long-term energy source for nutritionally compromised patients.[8] LCPUFAs have been recommended for management of people with pancreatic insufficiency due to specific deficiencies. [4,9]

Reduced digestion and absorption of LCPUFA results in lower baseline serum levels and altered metabolism of some important omega-3 and omega-6 fats, such as DHA, EPA and AA. These fatty acids have a critical role in the composition, development and function of heart, liver, and neural (retina and brain) tissues and inflammatory and immunological systems.[6] Proper tissue levels of LCPUFAs, such as DHA and EPA, have been linked to optimal brain and vision development, cognition improvement, improved immunity and cardiac health.[9,10] LCPUFAs, and omega-3 fatty acids DHA and EPA in particular, have been shown to have important anti-inflammatory properties by suppressing inflammatory cytokines.[10]

Specific fatty acid alterations, imbalances and deficiencies have been identified in the blood and tissues of people with CF with decreased levels of DHA as well the essential long-chain fatty acid linoleic acid (LA), and increased levels of AA, as well as elevated levels of MCTs.[11] Fatty acid imbalances in the omega-3 (DHA, EPA) to the omega-6 (AA) ratio may contribute to the inflammatory characteristics of CF lung disease and gastrointestinal pathology.[12,13] Improving dietary fat intake or reducing fat malabsorption with pancreatic enzymes has failed to normalize the deficiency of DHA. While most people with CF seem to achieve adequate protein intake and absorption, they have significant deficiencies in the absorption of beneficial long-chain fatty acids that are important for achieving adequate weight gain and critical to correcting fatty acid imbalances, as well as maintaining good overall health.[11,12,13]

To improve caloric intake and avoid malnutrition, many individuals with EPI utilize enteral feeding as a supplement to daily dietary intake. Due to incomplete fat hydrolysis, current enteral feeding practice relies on large volumes (1,000 mL or more) of high calorie, nutrient-dense liquid formula delivered over 8-16 hours or longer. The

large volume requirements, coupled with poor fat hydrolysis and absorption, causes bloating in the morning that results in poor caloric intake at breakfast. The high volume of enteral formula also adds a significant carbohydrate load (~200 g of carbohydrates for typical 1,000 mL of enteral formula) that may contribute to the development or exacerbation of CF related diabetes (CFRD).

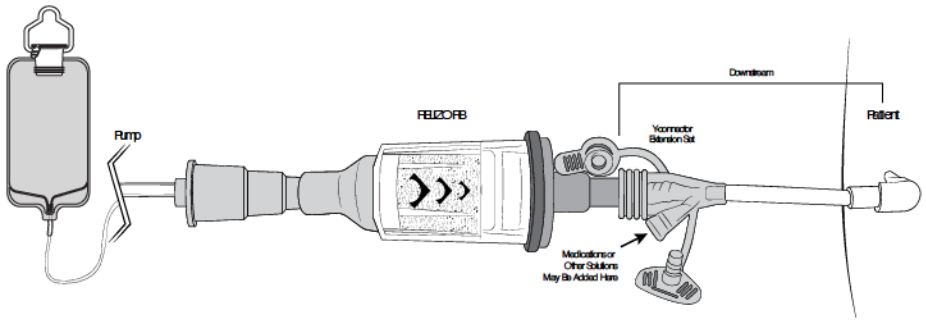
For patients with EPI who receive enteral nutrition, proteins can be provided pre-hydrolyzed in easily absorbed peptide form in semi-elemental formulas. Unfortunately, fatty acids are inherently unstable, so fat in enteral formulas are provided in the stable triglyceride form. As previously noted, LCTs must be hydrolyzed by lipase to form monoglycerides and fatty acids, before normal absorption and utilization in the body.

Alcresta Pharmaceuticals, Inc. (Alcresta) has developed Relizorb to consistently and efficiently hydrolyze the fats in enteral tube feeding in order to provide the benefit of readily absorbable fats from a given enteral formula, in their fatty acid and monoglyceride form, to patients with EPI or lipid malabsorption. Relizorb is a single-use, *ex-vivo*, point-of-care device designed to mimic the function of pancreatic lipase by pre-hydrolyzing fats from their natural triglyceride form, as contained in enteral formula, into their absorbable free fatty acid and monoglyceride forms, minimizing the burden of enteral feeding to caregivers and patients.

2.1 Description of Relizorb

Relizorb is a single-use, point-of-care digestive enzyme cartridge that connects in-line with existing enteral pump feed sets and pump extension sets. Relizorb is designed to hydrolyze fats contained in the enteral formulas. By hydrolyzing fats from enteral formulas, Relizorb allows for the delivery of absorbable fatty acids and monoglycerides for patients who rely on supplemental enteral (tube) feeding.

Figure 1: Relizorb Device



Relizorb (center) connecting with a pump feed tube (left) and the tube to the patient (right).

with a summary of the

Relizorb is comprised of a clear cylindrical, plastic cartridge with a single inlet connection port and a single purple outlet connection port (Figure 1). The inlet and outlet ports of Relizorb are intended to connect in-line with enteral pump feed sets and pump extension sets. Inside the cartridge, there are small white beads. The digestive enzyme, lipase, is covalently bound to polymeric beads. The lipase-bead complex, iLipase™ (immobilized lipase), is retained within the cartridge during use by filters on both ends of the cartridge. The fat in enteral formulas is hydrolyzed as it comes in contact with iLipase as the formula passes through the cartridge. The iLipase is retained within the cartridge and it is important to note that only minute quantities of the lipase have the potential to exit Relizorb. Relizorb was cleared by the US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) as a Class 2 low-risk device and is indicated for use in adults to hydrolyze fats in enteral formula.

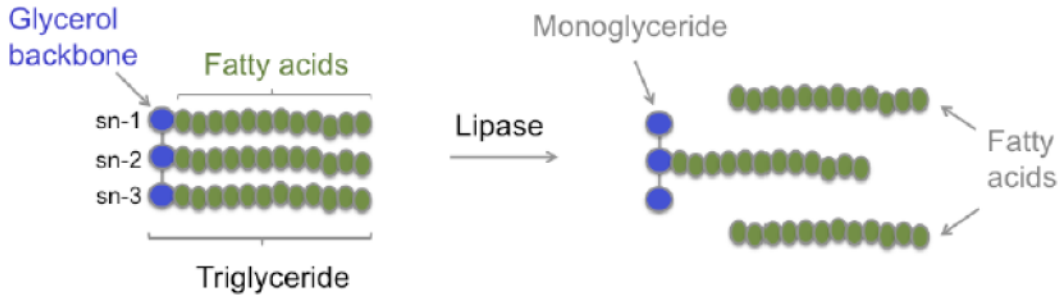
2.2 Active Component and Mechanism of Action

The active component of Relizorb is a lipase enzyme that is immobilized on polymeric beads, collectively called iLipase.

A volume of 500 mL of enteral formula used for overnight feeding will typically provide 600 kilocalories and 27 g of fat. Relizorb is designed to consistently and efficiently hydrolyze approximately 90% of available fats into absorbable fatty acids and monoglycerides.

A sensitive enzyme-based free fatty acid quantification assay for detecting medium and long-chain free fatty acids was used to measure fatty acid release resulting from the action of Relizorb over a range of conditions. Based on this method, *in vitro* analysis demonstrates that for most enteral formula tested, approximately >90% of fat will be hydrolyzed after passing through Relizorb.

Figure 2: Enzyme Hydrolysis



2.1 Clinical Labeling

One Relizorb is packaged in a single foil pouch with an investigational use label customized to this study. Each subject and/or parent/caregiver will receive Instructions For Use (IFU) that provides detailed instructions on the operational setup and use of Relizorb.

2.2 Storage Conditions

Storage conditions require temperatures of 2 °C to 27 °C (36 °F to 80 °F) according to product labeling. Relizorb is not to be frozen (-20 °C or -4 °F). Specifications regarding storage conditions are included in the IFU.

2.3 Study Rationale and Purpose

Enteral nutrition supplements, usually delivered as a nocturnal tube feeding, are provided for nutritionally challenged patients with EPI to support nutritional status and maintain or gain weight. There are well-accepted benefits associated with enteral nutrition, especially in CF, but use varies dramatically among centers, ranging from 0% to 33% of patients utilizing enteral nutrition to supplement daily caloric intake. Current enteral nutrition practice relies on large volumes of a nutrient dense liquid formula delivered over 8 to >12 hours. Common challenges in the current practice include duration of feeding, clogging of lines resulting in pump alarms, sleep interruption, the inability to administer PERT during continuous overnight delivery of the enteral formula. PERT is sometimes administered before, during, and/or after enteral tube feeding sessions. However, it is impractical to administer PERT products overnight that would provide for adequate hydrolysis of fat. Moreover, the efficacy and safety of PERT product use in conjunction with enteral nutrition has not been established. PERT product manufacturer prescribing information warns against crushing the product or adding it to formula, and the FDA advises that pancreatic enzyme products are not approved for administration via gastrostomy tubes. Symptoms of fat malabsorption such as nausea, bloating and steatorrhea due to incomplete hydrolysis of fats are often reported to be increased in patients with CF who receive enteral nutrition.

Some macronutrients in enteral formulas, such as protein, can be prepared pre-hydrolyzed in a peptide form that is stable and available to be readily absorbed. In addition, hydrolysis of protein occurs in the stomach independent of pancreatic enzymes. Therefore, patients with EPI theoretically should not need protease to achieve adequate absorption of peptides and amino acids in enteral formulas, although this has not been investigated. Due to poor stability of fatty acids, no enteral formula containing hydrolyzed fat has been manufactured to date. However, hydrolyzing fats at the time of consumption (point-of-care) avoids this problem. Thus, the intended benefit of this point-of-care approach with Relizorb is that fats in enteral formula, including

LCTs, are pre-hydrolyzed *ex-vivo* just before ingestion and provided in a form readily available for absorption in individuals who lack pancreatic lipase or the physiological capacity to digest fat.

The objectives of this study are as follows:

1. Demonstrate that sustained use of Relizorb in conjunction with enteral tube feeding without concomitant use of PERT results in an increase in fat absorption as evidenced by increased plasma concentrations of LCPUFAs such as DHA and EPA, tissue accretion (RBC) of omega-3 fatty acids such as DHA and EPA, and increased concentrations of fat soluble vitamins;
2. Show that serum protein levels are maintained despite withdrawal of PERT use associated with enteral tube feeding with sustained use of Relizorb in conjunction with enteral tube feeding using a semi-elemental formula;
3. Demonstrate the safety and tolerability of sustained use of Relizorb in conjunction with enteral tube feeding;
4. Explore the potential immunomodulatory effect of increased plasma concentrations of DHA and EPA as evidenced by changes in the omega-6 to omega-3 fatty acid ratio and urinary leukotriene concentrations.

2.4 Potential Benefits and Risks

This open-label study is the companion study to Protocol 0000497, an ongoing study enrolling patients from the same population. In both studies it is expected that, with Relizorb use, patients will experience a decrease in symptoms associated with fat malabsorption, improved fat absorption and calorie intake, and uptake of physiologically relevant fatty acids like DHA and EPA. Since fat hydrolysis occurs ex-vivo in-line with the enteral feeding circuit, patients will not be exposed to the enzyme but only to formula, with fat in a readily absorbable form (fatty acids and monoglycerides).

The porcine model of EPI is a well-established surgical model where ligation of pancreatic ducts causes a total lack of pancreatic enzymes, including lipase, diminished levels of bicarbonate, and reduced pH in the duodenum. Like EPI in humans, residual gastric lipase remains. EPI pigs have steatorrhea, arrested growth, fatty acid deficiencies, as well as common gastrointestinal symptoms seen in people with pancreatic insufficiency.[17] In four pre-clinical studies using this model, use of Relizorb and its prototypes was associated with improved growth as well as laboratory nutritional parameters. Improved total and LCPUFA fat absorption was demonstrated, especially increases in plasma and tissue levels of omega-3 and omega-6 fats, normalization of blood fat profile and increases in other nutritional parameters (e.g., fat soluble vitamins, proteins). There was also a decrease in signs of malabsorption in animals treated with Relizorb, and there were no observed adverse events associated

with Relizorb use. There were no observed adverse events associated with use of the Relizorb.[17, 18]

The safety and tolerability of iLipase is also supported by two clinical studies. In a study in normal, healthy volunteers, subjects orally consumed a single bottle of BOOST® Original fortified with 10 mL of algae oil, either as a pre-hydrolyzed drink (P*f*ND) after exposure to iLipase contained within a mesh bag or as a non-hydrolyzed nutritional drink (*f*ND). No serious adverse events occurred when a single P*f*ND and *f*ND were consumed. Adverse events were similar among the two groups; one mild headache (≤24h) in the *f*ND group, and three unrelated study events (dental infection-1, headache-1, vomiting-1) in the P*f*ND group. Compliance with the protocol was 100% with both nutritional drinks consumed within two minutes. No subsequent GI issues were reported at the 24h safety follow-up call in either group.

In a second study, patients with presumed EPI orally consumed a single bottle of BOOST® Original fortified with 10 mL of algae oil, either as a pre-hydrolyzed drink (P*f*ND) after exposure to iLipase contained within a mesh bag or as a non-hydrolyzed nutritional drink (*f*ND). There was 100% compliance, with all subjects consuming the full volume of P*f*ND and *f*ND. The hydrolyzed drink and non-hydrolyzed drink were both well tolerated by all subjects. There was no difference in palatability between hydrolyzed and non-hydrolyzed drink. Three subjects experienced a study event following consumption of *f*ND and 3 subjects experienced a study event after consumption of P*f*ND. Headache occurred in one subject in each treatment group. One instance each of fatigue, dizziness and nausea were reported. Two study events were considered treatment-related: abdominal pain (*f*ND) and throat irritation (P*f*ND). There were no SAEs in the study.

To date, the observed risks of Relizorb use are determined to be low based on preclinical validation, including safety evaluation in animal models as well as clinical studies in healthy volunteers and people with EPI. Relizorb is cleared by the FDA as a Class II (low risk) device for use in adults to hydrolyze fats in enteral formula. Nonclinical data is available in the Investigator's Brochure in Section 11.0 that supports continuation of further studies.

In summary, the potential benefits of participation in this open label study include the possibility of improved fat absorption and decrease in gastrointestinal symptoms related to fat malabsorption. Based on available preclinical and clinical data, the risk profile associated with participation in this open label study is low.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The overall objective of the study is to demonstrate improved fat absorption with sustained use of Relizorb in patients with CF who have EPI and are receiving enteral tube feeding. In this study, subjects will be receiving an enteral formula that has a high content of long chain triglycerides (Impact® Peptide 1.5) and will be using Relizorb during their enteral feeding in place of other therapies currently used to aid in fat absorption, such as pancreatic enzyme replacement therapy (PERT). Plasma concentration of relevant LCPUFAs such as DHA and EPA will be measured as a biomarker of fat absorption. Tissue accretion of fatty acids DHA and EPA assessed by measurement of erythrocyte membrane levels and the plasma fatty acid profile will be evaluated as additional biomarkers of fat absorption. Plasma fat-soluble vitamin and serum protein concentrations will also be measured. All fatty acid, fat-soluble vitamin, and protein concentrations will be assessed in relation to values obtained at study entry (Day -14), at baseline (Day 0), and during Relizorb use (Days 30, 60, and 90). Safety and tolerability of sustained use of Relizorb will also be assessed during use and compared with gastrointestinal symptoms recorded during the observation phase of the study (Day -14 through Day -8).

Efficacy

- Evaluate effect of sustained Relizorb use during enteral feedings on fat absorption through serial measurements of plasma and tissue (erythrocyte membrane) concentrations of physiologically relevant LCPUFAs such as DHA and EPA, as well as the plasma fatty acid profile changes, as biomarkers of fat absorption.
- Evaluate effect of sustained Relizorb use during enteral feedings on plasma fat-soluble vitamin concentrations.
- Evaluate effect of sustained Relizorb use on the ratio of omega-6 to omega-3 fatty acids as a potential indicator of immunomodulation
- Evaluate effect of sustained Relizorb use on urinary leukotriene levels
- Evaluate effect of sustained Relizorb use on serum protein levels
- Evaluate effect of sustained Relizorb use on growth.

Safety

- Evaluate the safety and tolerability of sustained use of Relizorb as part of a enteral feeding regimen.

3.2 Endpoints

Efficacy

- Change over time in plasma concentrations of LCPUFAs such as DHA and EPA
- Change over time in tissue (erythrocyte membrane) fatty acid concentrations such as DHA and EPA

- Change over time in plasma fatty acid profile of LCPUFAs
- Changes over time in the ratio of omega-6 to omega-3 fatty acids in plasma and in tissue (erythrocyte membrane) levels
- Change over time in plasma concentrations of fat soluble vitamins
- Change over time in body weight, BMI, and weight and BMI standard scores
- Change over time in serum protein concentrations (total protein, prealbumin, albumin, transferrin)
- Change over time in markers of inflammation (urinary leukotrienes)

Safety

- Frequency and severity of adverse events and unanticipated adverse device effects (UADEs)
- Evaluation of clinical and laboratory findings
- Concomitant medication assessment
- Frequency and severity of gastrointestinal signs and symptoms (abdominal pain, vomiting, loss of appetite, bloating, flatulence and steatorrhea)

4.0 STUDY DESIGN AND PROCEDURES

4.1 Enrollment Goals

Male and female patients with CF and EPI will be screened for the study from approximately 10 investigative centers in the United States. Approximately 35 subjects will be enrolled in the study with the goal of having at least 30 evaluable subjects completing the study through at least Visit 4 (Day 60).

4.1.1 Representative Age Groups

This study will enroll patients with CF who are 4 years of age or older without an upper age limit. Since median predicted survival age for patients with CF is approximately 40 years, it is expected that the majority of patients enrolled will be less than 40 years old.

To obtain a diverse age range in the study population, the PIs will be encouraged to recruit patients along the age continuum. Since study sites are pediatric centers, it is expected that the majority of subjects will be in the pediatric age range. However, PIs at study sites will be encouraged to collaborate with affiliated adult CF centers to allow for the recruitment of adult patients with CF.

Subjects discontinuing study participation may need to be replaced to achieve the minimum total number of 30. All available data for subjects who were enrolled and discontinued will be captured in data reports. Patients who participated in Protocol 0000497 and considered to be protocol compliant will be eligible for enrollment in

Protocol 0000498. In addition, Relizorb naïve patients that meet eligibility criteria may enroll. It is anticipated that active enrollment will last approximately three and a half months.

4.2 Study Duration

The anticipated study duration is approximately 104 days. This includes a 7 day observation period when the subject is maintaining their usual care routine, a 7 day run in period, and a 90 day open label treatment period. Subjects who experience a UADE during the last 29 days of the open label period will be followed for 30 days following the occurrence of the UADE or until resolution, whichever comes first.

4.3 Study Periods

The study will have three periods: a 7 day observation period that will establish a baseline, a 7 day run in period that will normalize the enteral formula type and volume of the feeding, and a 90 day treatment period. Study visits and the attendant tests and procedures should be performed according to schedule. However, changes in scheduled study visits are allowed with permission from the site for holidays, vacations, etc. For these exceptions, the study visit should occur within 4 days (4) of the scheduled day. There will be five study visits as described below:

Visit 1: Study Entry *(Day -14)*

On Visit 1 (Day -14), subjects (or legally authorized parent or guardian) will sign a written informed consent, or assent when applicable. Baseline procedures will include evaluation of eligibility criteria and recording or obtaining demographics, medical history, physical examination, height, weight, body mass index, vital signs, standard clinical laboratory tests (hematology, clinical chemistry, urinalysis), blood lipids, urine sample for urinary leukotriene evaluation, plasma fatty acid sample, pregnancy test for childbearing females and concomitant medications. Collected results on Day -14 will be used to screen patients for eligibility and characterize the study population. Study staff will also review the medical records and obtain up to four body weight measurements recorded at 3 month intervals over the previous 12 months. Historical average daily PERT use with meals and snacks and with enteral nutrition will be recorded. Study staff will provide detailed instructions for subjects to maintain a gastrointestinal symptom diary for 7 consecutive days.

During the observation period (Day -14 to Day -8), subjects will maintain their usual care plan. The brand, volume, and administration rate of the enteral formula used in the enteral feeding will be recorded, along with the usual dose of PERT use associated with the enteral feeding. Crushing of PERT products and adding to the enteral feeding bag is prohibited. Subjects will make entries into a 7-day gastrointestinal symptom

diary each day. PERT use with meals and snacks and with enteral tube feeding will be recorded each day by the subject.

During the run in period (Day -7 to Day -1), subjects will maintain their usual enteral feeding volume up to a maximum volume of 1000 mL and administration rate using Peptamen 1.5 for at least 5 days preceding the treatment period between Day -7 and Day -1. The usual dose of PERT use associated with the enteral feeding will be allowed, but crushing of PERT products and adding to the enteral feeding bag is prohibited. Subjects will make entries into a 7-day gastrointestinal symptom diary each day. PERT use with meals and snacks and with enteral tube feeding will be recorded each day by the subject. Peptamen 1.5 for use during the run in period will be shipped to the subject's home prior to Day -7.

Visit 2: Baseline *(Day 0)*

During Visit 2, as well as each subsequent visit, the study staff will collect the completed gastrointestinal symptom diary. Blood samples will be collected for fatty acid, protein, and fat-soluble vitamin analysis during these visits. In addition, a urine sample will be collected for urinary leukotriene analysis. Body weight and height will be measured and recorded, and BMI will be calculated and recorded. Each subject and/or parent(s) will receive verbal instructions on the temperature storage, setup and operation of Relizorb with Impact Peptide 1.5. Study staff will physically demonstrate setup and operation of Relizorb so that subjects/parents receive hands-on training prior to leaving the clinic. Study staff will instruct subjects/parents/caregivers on recording the use of Relizorb between study visits. Subjects and parents will have the opportunity to ask questions to ensure familiarity with the principles of operation. This will ensure that subjects/parents are knowledgeable regarding the proper use of formula with either the Covidien Kangaroo™ ePump or MOOG Enteral Lite® Infinity® pumps. Instructions For Use (IFU) will be provided to subjects/parents to take home.

Impact Peptide 1.5 is the only enteral formula allowed for use for enteral tube feedings in this part of the study. Subjects will maintain their usual enteral feeding volume up to a maximum volume of 1000 mL and administration rate using Impact Peptide 1.5. Study staff will inform subjects/parents that any use of PERT in association with the enteral tube feeding is strictly prohibited.

On or before Day 0, all subjects will receive outpatient study supplies, such as the Relizorb investigational device, Impact Peptide 1.5, Relizorb Accountability Log, 7-day gastrointestinal diary and specific written instructions. Subjects/parents/caregivers will be informed that they should start a 7-day gastrointestinal diary one week before the next study visit so it is completed the day before the next study visit. Subjects will be instructed to maintain their normal CF treatment regimen and usual diet throughout the study. No dietary restrictions exist during the outpatient period. Subjects should follow

dietary recommendations from their registered dietitian (RD), nutritionist or healthcare professional.

Visits 3, 4, and 5: Treatment Period *(Days 30, 60, and 90)*

Approximately one week before visits 3, 4, and 5, study staff will contact subjects/parents/caregivers and remind them to start a 7-day gastrointestinal diary such that it is completed the day before the study visit, and also remind them to bring the completed diary with them to the clinic visit along with all used and unused Relizorb cartridges. During these visits study staff will collect the completed 7-day gastrointestinal symptom diary. Blood samples will be collected for fatty acid, protein, and fat-soluble vitamin analysis during these visits. In addition, a urine sample will be collected for urinary leukotriene analysis. Body weight and height will be measured and recorded, and BMI will be calculated and recorded. Study staff will assess UADEs and concomitant procedures and medication use.

Study staff will review the Relizorb Accountability Log for completeness, collect all used Relizorb cartridges, and provide subjects with additional unused Relizorb cartridges for at home use until the next scheduled visit. Concomitant medications and UADEs will be assessed.

Subjects who experienced a new or ongoing UADE within the previous 29 days will receive a follow-up safety contact until 30 days after the occurrence of the UADE or until the UADE has resolved, whichever comes first. Therefore the duration of the study may be extended if a subject has a new or ongoing UADE between Day 60 and Day 90.

On the final clinic visit (Day 90), the majority of baseline procedures will be repeated. End of study procedures will include standard laboratory testing (clinical chemistry, hematology and urinalysis), blood lipids, vital signs, weight, and height measurement, and BMI calculation.

Subjects will be instructed to bring to the clinic all used and unused devices to enable study staff to check administration compliance. All used and unused cartridges will be inventoried and returned to the Sponsor, unless destruction at the study site is authorized.

4.4 Selection of Patients

4.4.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 4 years of age or older
2. Confirmed diagnosis of CF defined as two clinical features consistent with CF and have either:
   a. Genotype with two identifiable mutations consistent with CF, determined using diagnostic devices that have been cleared by the US FDA (the FDA clearance requirement does not apply if the test was performed prior to 2005, the year the US FDA first started evaluating genetic tests for CF), or
   b. Sweat chloride >60 mEq/L by quantitative pilocarpine iontophoresis
3. Documented history of exocrine pancreatic insufficiency due to CF (e.g., historical fecal elastase test, genotype consistent with exocrine pancreatic insufficiency, etc.)
4. Enteral formula user a minimum of four to five times per week, using PERT, consuming an unrestricted fat diet, and willing to use Peptamen 1.5 and Impact Peptide 1.5
5. Clinically stable with no significant changes in health status within 14 days of Day -14
6. Written informed consent obtained from patient, or, if the patient is a minor, from the patient's legal representative with assent from the minor when applicable.

4.4.2 Exclusion Criteria

Each patient who meets any of the following exclusion criteria will be excluded from the study:

1. Uncontrolled diabetes mellitus
2. Signs and symptoms of liver cirrhosis or portal hypertension (e.g., splenomegaly, ascites, esophageal varices) or significant liver disease. Significant liver disease is defined as liver transaminases >3x upper limit of normal (ULN) or total bilirubin 1.5x ULN at baseline (or based upon the discretion of the Principal Investigator (PI)
3. Lung or liver transplant
4. Active cancer disease currently receiving cancer treatment
5. Known small intestinal inflammatory diseases such as Crohn's or Celiac disease, or diarrheal illness unrelated to EPI (e.g., infectious gastroenteritis, sprue, lactose intolerance, inflammatory bowel disease)
6. History of fibrosing colonopathy or recurring distal intestinal obstructive syndrome (e.g. more than three occurrences per year)
7. CF respiratory exacerbations within 2 weeks prior to study entry

8. Oral glucocorticoid therapy or intravenous glucocorticoids within 2 weeks prior to baseline; patients who are receiving low dose alternate day corticosteroid therapy for lung disease may be enrolled in the study subject to consultation between the site PI and the Alcresta Chief Medical Officer
9. Major surgery or serious lung infection within 2 weeks prior to study entry
10. Acute life-threatening or uncontrolled medical illness
11. Known alcohol, drug or medication abuse
12. Any condition, in the judgment of the site PI, which would interfere with the intent of the study or make participation not in the best interest of the patient
13. For females of childbearing potential:
    a. Positive pregnancy test at study entry
    b. Lactating
    c. Unwilling to use an effective medically acceptable form of contraception (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, an intrauterine device, NuVaRing®, diaphragm with spermicide or abstinence) from baseline to the end of the study.
14. Treatment with investigational study agents (drug, biologic or device) other than Relizorb within 30 days of study entry
15. Adult subjects who lack the capacity to provide individual informed consent.

4.5 Patient Enrollment and Replacement Criteria

Approximately 30 to 35 patients will be enrolled in the study. Protocol compliant patients from Protocol 0000497 are eligible for this study, unless clinical changes have occurred in which the patient no longer meets the initial eligibility criteria. All eligible patients willing to continue in this study will be accepted. Every reasonable attempt should be made by study staff to assist eligible patients interested in participating in this study.

Any subject who withdraws from the study before Study Visit 3 on Day 30 will be replaced by an eligible patient.

Any subject who withdraws from the study before Study Visit 4 on Day 60 must be replaced by an eligible patient.

Any subject who withdraws from the study before Study Visit 5 on Day 90 may be replaced by an eligible patient unless the sum of completed subjects and currently enrolled and active subjects is greater than 30, in which case the subject will not be replaced unless the sum of completed subjects and currently enrolled and active

subjects drops below 30 before the thirtieth enrolled and active subject completes Study Visit 4 on Day 60 with the intention of finishing the study out to Day 90.

Every effort should be made to collect information regarding UADEs from subjects who drop out or are removed or excluded from the study. Data collected up to the point of withdrawal will be used in the analysis of the appropriate time point but will not be carried forward.

4.6 Allowed Concomitant Medications

Subjects should continue all prescribed medications and supportive therapies. Concomitant medications taken for current medical history and birth control are all allowed. Prescription and over-the-counter medications for the treatment of AE/UADEs are permitted.

All supportive therapies and concomitant medications taken by the subject will be recorded in the source documents and entered on the electronic case report form (eCRF). Any dosage changes to concomitant medications required during the study must be recorded in the eCRF.

4.7 Prohibited Medications

There are currently no known interactions to other medications with Relizorb. Treatments with any investigational drug, biologic or medical device are prohibited during the study.

Subjects may use oral PERT with meals and snacks during the day but are prohibited from using PERT or any other medication intended to hydrolyze fat if associated with administration of enteral tube feeding.

4.8 Safety Monitoring

4.8.1 Study Safety Procedures

Safety data will be monitored on a continual basis throughout the study and clinical changes evaluated. Safety monitoring will include safety follow-up contacts, monitoring AE/UADE, subject withdrawals and safety data. The site monitor will advise the Chief Medical Officer of the frequency and severity of UADEs. The Alcresta Chief Medical Officer will evaluate all UADEs within 24 hours of notification.

4.9 Study Procedures

Table 1 lists the timing of assessments and study procedures. If a subject misses a scheduled study visit within the ±4 day window, the visit should be rescheduled as soon as possible.

4.9.1 Informed Consent

Each patient must provide written informed consent, as well as assent, when applicable, before any study-related procedure is conducted.

4.9.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be reviewed to determine patient eligibility.

4.9.3 Demographics

Subject demographics will document age, gender, and ethnicity.

4.9.4 Medical History

On Day -14, a relevant medical history dating back at least 1 year will be obtained. The medical history will emphasize CF disease characteristics, prior therapy, surgery, allergies and assess the patient for any disqualifying medical conditions as specified in the exclusion criteria.

4.9.5 Physical Examination

Complete physical examinations are required for all patients entering the study. A qualified member of the study staff (e.g., physician, physician's assistant) will perform a complete physical examination.

4.9.6 Height, Weight, and BMI

Height, weight and BMI will be assessed at the time points outlined in Table 1. In addition, study staff will review the medical record and record up to 4 body weights at 3 month intervals recorded over the previous12 months.

4.9.7 Vital Signs

After a minimum resting period of 15 minutes, vital signs (heart rate, respiratory rate and sitting blood pressure) will be measured. Oral or tympanic temperature will also be collected.

4.9.8 Clinical Laboratory Tests

Blood sample collections will be obtained at the time points outlined in Table 1. Subjects will be in a seated or supine position during blood sample collection.

The clinical laboratory tests to be performed are listed in Table 2 (Clinical Laboratory Tests) below. Handling and shipment of clinical laboratory samples will be analyzed by a central laboratory and be outlined in the laboratory manual.

4.9.9 Pregnancy Test

A serum β-hCG pregnancy test will be performed only for females of childbearing potential. Negative results must be available four days prior to the first Relizorb usage on Day 0. If a female subject becomes pregnant while participating in the study, the site is responsible for notifying the Alcresta Chief Medical Officer as soon as possible.

4.9.10 Enteral Tube Feeding

During the treatment period (Days 0 to 90), subjects will receive enteral feedings using the same enteral formula, Impact Peptide 1.5. The volume of enteral tube feeding should be 500 to 1000 mL; subjects who routinely receive more or less volume may be enrolled only if approved by the Alcresta Chief Medical Officer. The enteral formula should be delivered using a compatible pump that has a no flow/low flow alarm at a flow rate set between 24 and 120 mL.

Table 2: Clinical Laboratory Tests

Clinical Chemistry	Hematology	Lipids	Urinalysis
Albumin	Complete blood count and white blood cell differential	Total cholesterol	Bilirubin
Alkaline phosphatase		Triglycerides	Ketones
ALT		HDL	Leukocyte esterase
AST		LDL	pH
Bicarbonate			Protein
BUN			Specific gravity
Calcium			Urinary creatinine
Chloride			Urinary uric acid
Cholesterol			
Creatine phosphokinase			
Creatinine			
Glucose			
Lactate dehydrogenase			
Magnesium			
Phosphorus			
Potassium			
Prealbumin			
Sodium			
Total and direct bilirubin			
Total protein			
Uric acid			
A1C levels			
Transferrin			

4.9.11 Gastrointestinal Symptom Diary

Detailed verbal instructions on how to record entries in the gastrointestinal symptom diary should be conducted by study staff on Day -14 and again as a subsequent reminder on Days 0, 30, and 60. The gastrointestinal symptom diary will also include a brief instruction. Entries need to occur on a daily basis for 7 consecutive days. The completed symptom diary will be entered into the eCRF and regarded as a source document. Diary data will be used for the primary safety study endpoint to determine the frequency and severity of gastrointestinal symptoms.

4.9.12 Plasma and Tissue Fatty Acid Samples

Blood samples will be collected on Day -14 and Day 0 as baseline measures of fatty acid levels. The other fatty acid blood samples will be obtained at the time points specified in Table 1.

4.9.13 Fat Soluble Vitamin Samples

Blood samples will be collected on Day -14 and Day 0 to measure baseline fat-soluble vitamin (A, D, and E) levels. The other fat-soluble vitamin blood samples will be obtained at the time points specified in Table 1.

4.9.14 Serum Protein Samples

Blood samples will be collected on Day -14 and Day 0 as baseline measures of serum protein (total protein, prealbumin, albumin, transferrin) levels. The other serum protein blood samples will be obtained at the time points specified in Table 1.

4.10 Removal of Subjects from the Study

During the course of this study, subjects will be withdrawn and their participation terminated if any of the following occurs:

- Any UADE severe enough in nature to warrant discontinuation in the study
- Withdrawal of consent
- The site PI, in consultation with the Alcresta Chief Medical Officer, believes the subject should be removed from the study for safety reasons
- Subject is non-compliant with study requirements.

5.0 DATA ACQUISITION, TRANSFER AND ANALYSIS

5.1 Data Acquisition

Electronic case report forms (eCRF) are considered confidential data. The Alcresta data management vendor will provide user access and training to investigative sites on the use of the eCRF system. Subject data will be entered into the eCRF by site staff using a secure, web-based electronic data capture application. Clinical data required by the protocol will be captured on the eCRF and supported by source documentation at site. The site PI will prepare and maintain adequate and accurate medical histories designed to record all observations and pertinent study data for each subject.

To ensure data accuracy, eCRF entry for individual subjects should be completed as soon as possible after the study visit. Site staff should enter information on the eCRF according to the completion guidelines provided by the Alcresta data management vendor. The site PI is ultimately responsible for all information collected on enrolled subjects and must ensure data is reviewed and verified for completeness and accuracy. The signature of the site PI or subinvestigator indicates formal approval of all data entered on the eCRF.

The Alcresta data management vendor will retain eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the Investigator Site File.

5.2 Data Transfer

Alcresta, in collaboration with the data management vendor, will be responsible for the electronic transfer of external laboratory data according to fully executed data transmission agreements, data management plans or other study documentation.

5.3 Analysis of Fatty Acid Absorption

The concentration of LCPUFAs such as DHA and EPA in plasma is the primary determination supporting the primary endpoint of fat absorption and will be analyzed using UPLC-MS expressed as ug/mL. The relative levels of LCPUFAs such as DHA and EPA in erythrocyte membrane and the overall plasma fatty acid profile also support the primary endpoint and will be analyzed using GC/MS expressed as g/100 g FA.

6.0 SAFETY OVERVIEW

6.1 Monitoring of Adverse Events

All study staff are responsible for ensuring that complete safety data has been recorded on the eCRF. Medical assessments must be performed during each scheduled study visit and serve as the primary basis for identifying an UADE. Although spontaneous or elicited medical complaints will likely constitute the majority of UADEs, any non-scheduled visit to a healthcare provider, or the initiation of a new medication, should trigger additional questioning as to the occurrence of an AE or UADE.

6.2 Adverse Events

An adverse experience (AE) is defined as any untoward medical occurrence in a subject, regardless of its causal relationship to the investigational device. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory

findings), symptom or disease experienced with use of the product, whether or not it is related to the product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the use of Relizorb.

6.2.1 Causal Relationship

All AE must be assessed for causality in reference to Relizorb use. When entering data for a reported AE, the site PI will be asked to assess the relationship of Relizorb use to the AE. Causality will be categorized according to the following criteria:

Not Related: There is no medical evidence to suggest the event may be related to Relizorb use, or there is another more probable medical explanation.

Possibly Related: An event, including laboratory test abnormality, with a temporal relationship to Relizorb use that makes a causal relationship improbable and which other medications, events or underlying disease provide a plausible explanation.

Probably Related: The event occurred within a reasonable time sequence to using Relizorb, but could be explained by concurrent disease or other medications or events.

Related: There is strong medical evidence to suggest that the AE is related to Relizorb use.

6.2.2 Anticipated Adverse Events in Subjects

Due to the GI complications inherent in CF patients, the identified risks are upper abdominal pain, bloating, constipation, diarrhea, flatulence, heartburn, indigestion, nausea, steatorrhea (fatty stool), vomiting, weight decrease and headache.

6.3 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An UADE is analogous to a serious adverse event (SAE), defined as any AE, occurring at any exposure to the therapeutic agent, that results in any of the following outcomes:

death, life-threatening AE, inpatient hospitalization or prolonged existing hospitalization, a persistent or significant disability or incapacity or a congenital anomaly/birth defect.

An UADE is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" according to 21 Code of Federal Regulations Part 812.3.

As provided by the International Conference of Harmonization (ICH) criteria, a serious adverse effect (event) is any clinical event or condition that is:

- Fatal
- Life-threatening
  (Note: The term "life-threatening" refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.)
- Requires hospitalization or prolonged current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject's underlying medical condition prior to entry into the study)
- Results in persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Judged to be medically significant by the Investigator
  (Note: A medically significant AE is a medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the outcomes listed above).

6.4 Reporting Unanticipated Adverse Device Effects

A sponsor who conducts an evaluation of an UADE under §812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 business days after the sponsor first receives notice of the UADE. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests. The site will complete an UADE event eCRF form within 24 hours of the Investigator being notified of the UADE. The report will be scanned and emailed to clinical@alcresta.com and then forwarded for Alcresta Chief Medical Officer review.

In addition, any event that results in a subject's withdrawal from the study must be reported directly to the Alcresta Chief Medical Officer as soon as possible but no later **than 24 hours.**

7.0 STATISTICAL PROCEDURES AND DATA ANALYSIS

7.1 General Considerations

Data collected in this study will be presented using summary tables, subject data listings and figures. Summary tables will present data by subject and, if applicable, by study visit. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum values. Categorical variables will be summarized by frequencies and percentages. Figures may be used to support the presentation of certain data.

All available data will be included in data listings. No imputation of values for missing data will be performed, unless otherwise specified. The relevance of missing sample data will be assessed. In the case of subject withdrawal from the study, data collected at the Day 30 and Day 60 time point will be employed in the analysis of that time point but those values will not be carried forward. Data that are potentially spurious or erroneous will be examined according to data management standard operating procedures.

Qualitative or descriptive data will be analyzed to evaluate against safety and tolerability endpoints. The potential influence of other covariates such as age, gender, ethnicity, height and weight will be examined.

7.2 Determination of Sample Size

The proposed study with 30 complete and evaluable subjects would have 80% power to detect a minimum effect size of 0.53. Based on literature reviews using 1.5% as the maximum standard deviation expected when measuring DHA levels, the study should be able to detect an absolute increase of at least 0.8% from the baseline DHA value after 90 days of Relizorb use (i.e., a change from 3.0% at baseline to 3.8% after 90 administration days or a 27% relative increase). This sample size will be adequate to detect the desired 30% relative increase in DHA levels.

7.2.1 Stopping Rules

Relizorb is a low risk medical device, and the patient population under study is at relatively low risk for a severe adverse experience. Therefore, there are no prospective stopping rules for this study.

The Alcresta Chief Medical Officer will review all UADEs as they occur. In addition, every 30 days all UADEs will be reviewed in aggregate starting from the first subject enrolled until the last subject has completed the study. Based on this planned surveillance, the Alcresta Chief Medical Officer will convene a teleconference with the chair of the Data Safety Monitoring Board (DSMB) as soon as possible if any of the following occur:

- Death of any subject in the study, regardless of causality,
- Two occurrences of the same UADE where causality has been assigned to Relizorb use by the site PI, or more than three occurrences of the same UADE regardless of causality,
- A trend emerges in the occurrence of similar UADEs.

If either the Alcresta Chief Medical Officer or the chair of the DSMB has a concern regarding the safety of study subjects, the Chief Medical Officer will convene a teleconference with the DSMB and the site PIs as soon as possible to discuss the potential safety issue. Possible outcomes of the teleconference include:

- Continuation of the study with no change in study conduct if it is determined that there is no safety issue,
- Placing the study on clinical hold until the study protocol can be modified to mitigate the safety issue,
- Termination of the study.

7.3 Randomization

Randomization will not be used in this open label study.

7.4 Populations for Analysis

7.4.1 Per Protocol Population

The per protocol population consists of all subjects who met the inclusion criteria, used Relizorb as stated in the protocol and IFU through at least Visit 3 (Day 30) and has not been the subject of any major protocol deviation.

7.4.2 Safety Population

The safety population includes all subjects who received at least one Relizorb exposure. For subjects who withdraw from the study, every effort will be made to retrieve all relevant safety information.

7.5 Procedures for Handling Missing, Unused and Spurious Data

All available safety and tolerability data will be presented in data listings and tabulations. No data imputation will be applied for missing values. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

In the case of subject withdrawal from the study, data collected at the Day 30 and Day 60 time point will be employed in the analysis of that time point but those values will not be carried forward.

7.6 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized and presented overall. Demographic data to be evaluated will include age, sex, ethnicity, height, weight and BMI. Demographic data will be presented in a by-subject listing. Age will be calculated from date of birth to date informed consent was obtained.

7.7 Safety Analysis

Safety will be assessed based on the incidence, severity, and type of AE and UADE, clinically significant changes or abnormalities in the subject's clinical laboratory results and vital signs. For clinical laboratory tests, descriptive summaries of actual values and changes from the baseline will be presented. Descriptive statistics will be provided for vital sign measurements collected during clinic visits.

AE and UADEs will be recorded throughout the study and listed in summary tables in terms of severity and causal relationship to Relizorb use. Relationship assessments that indicate the AE is "Not Related" is an event related to etiology, rather than from Relizorb use. "Related" is defined as an association between the AE or UADE and Relizorb use. Other selections include "Possibly Related" and "Probably Related".

The gastrointestinal symptoms recorded in the 7 day gastrointestinal symptom diary during the run in period will be compared with the symptoms recorded three separate times during the treatment period. Each symptom will be categorized as a) occurring or not occurring b) rated as a 1,2, or 3 in severity, and lasting in duration for less than 15 minutes, 15 to 30 minutes, 31 to 60 minutes, or greater than 60 minutes.

For the comparison between symptoms recorded during the run in period and the treatment period, the following analyses will be performed:

- Number of days where any symptom occurred;

- Number of days each symptom occurred;
- For each symptom, number of days when the severity was a 1, 2, and 3
- For each symptom, number of days when the symptoms lasted in duration for less than 15 minutes, 15 to 30 minutes, 31 to 60 minutes, or greater than 60 minutes.

Comparison of these values during the run in and treatment periods will be performed using analysis of variance (ANOVA).

7.8 Efficacy Analysis

The measurement of the absorption of fats is an important efficacy endpoint, using absorption of fatty acids as surrogate biomarkers for fat absorption. LCPUFA plasma concentrations such as DHA and EPA will be an outcome variable, along with tissue accretion of LCPUFAs, measured as relative levels in erythrocyte membrane, and the profile of fatty acids in plasma. The fatty acid profile will also be used to calculate the ratio of omega-6 to omega-3 fatty acids, another outcome variable. Fat-soluble vitamin (A, D, and E) concentration is an additional efficacy endpoint and will be used as a laboratory outcome variable. Serum protein (total protein, prealbumin, albumin, and transferrin) concentrations and urinary leukotriene concentrations are additional endpoints and also represent laboratory outcome variables.

For all laboratory outcome variables, mean values from samples obtained on Day -14 and Day 0 will be compared using a two-sided test for comparison. The mean value from samples obtained on Day 0 will be used as the baseline for comparison with mean values from samples obtained on Days 30, 60, and 90 using ANOVA.

Body weight, height, and BMI are endpoints and clinical outcome variables. Absolute change in body weight from Day 0 through Days 30, 60, and 90 will be analyzed using ANOVA. To evaluate the effect of Relizorb use on weight and BMI, up to 4 weight and BMI recordings obtained from the medical record at 3 month intervals over the previous 12 months. The historical weight recordings will be used to calculate historical weight gain velocity, expressed as grams of body weight per kilogram of body weight per day. The study weight gain velocity will be similarly calculated by using the body weight values obtained on Days 0, 30, 60, and 90. The historical weight gain velocity will be compared to the study weight gain velocity using a two-sided test for comparison. In addition, the historical weight and BMI recordings, along with the weight and BMI values recorded on Day 0, will be used to calculate a standard score for weight and BMI values recorded on Days 30, 60, and 90.

8.0 STUDY COORDINATION AND MONITORING

8.1 Site Principal Investigators and Study Administrative Structure

The site PI will ensure that all persons assisting with the study are adequately qualified, informed about the protocol and any amendments to the protocol, the study treatments and their study-related duties and functions. The site PI must maintain a list of subinvestigators and other appropriately qualified and trained individuals to whom significant study-related duties have been delegated.

The site PI also certifies licensure to practice medicine in the state in which the study is conducted. Investigators are responsible for providing documentation of qualifications, GCP training, and current medical licensure and filing in a regulatory file.

8.2 Institutional Review Board / Independent Ethics Committee

The site PI will not begin the research study until the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) that governs their participation has approved the protocol and ICF. The IRB/IEC will also review and approve all advertisements, if applicable. The site PI will forward a copy of the IRB/IEC approval document to Alcresta. Any protocol amendments must also be approved in writing by the IRB/IEC, prior to implementation by the site PI, except where necessary to eliminate an immediate hazard to study participants.

The site PI will submit a progress report to the IRB/IEC at intervals of one year or less, as established by review committees. The site PI will retain a copy of this report in the Investigator's Site File.

8.3 Study Monitoring

The monitoring plan and auditing procedures developed or approved by Alcresta will be followed to comply with current good clinical practices (cGCP) guidelines and applicable regulations. The site monitor will visit the site PI and study site at periodic intervals and maintain regular site communication. The site PI and study staff is expected to contact the site monitor directly, regarding clinical questions or clarification of protocol language.

The site PI will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject. The Investigator will allow the Sponsor's representatives, contract designees and authorized regulatory authority inspectors to have direct access to all source documents and medical records pertaining to the subject prior to and during the conduct period of the study. Access to patient records after participation in the study is complete may be required to follow resolution of AEs and UADEs.

8.4 Onsite Audits

Regulatory authorities, the IRB/IEC, and Alcresta (or Alcresta's contract vendor) may request access to all source documents, eCRFs and other study documentation for on-site audit or inspection. The site PI must guarantee direct access to these documents. Medical records and other study documents may be copied during an audit or inspection, provided that subject names are obliterated on the copies to ensure confidentiality.

8.4.1 Study Device Accountability

Alcresta or its contracted vendor will arrange for shipments of the investigational device to the study sites and Peptamen 1.5 and Impact Peptide 1.5 to the subject's home. An inventory of package contents will accompany each shipment of clinical research materials and ancillary supplies. The study coordinator or designee must receive the study material delivery, review the inventory, complete the record of receipt and ensure clinical research materials are properly stored in a secure, controlled, environmentally appropriate location and safely handled. Copies of all shipping receipts and dispensing records for the cartridges must be retained at site as part of required device accountability.

Accountability for the number of investigational devices dispensed at the study site is the responsibility of the site PI and study staff. Accountability records must indicate delivery to the site, a record of inventory, use by each subject and amount returned to Alcresta or designee. Study staff must provide the site monitor with records of the disposition of all investigational devices. The site monitor will account for the dispensation of clinical research study materials at the site and review Relizorb accountability. Accountability of all used and unopened Relizorb packages should occur on an ongoing basis. The site monitor will attempt to resolve any discrepancies of clinical research materials with the study coordinator or designee. On-site disposal of Relizorb will not be permitted unless previously authorized by Alcresta.

8.5 Patient Information and Informed Consent

The site PI will obtain IRB/IEC written approval of the ICF (including approval of revisions) to be provided to the patients, inclusive of assent for minors 7 to 17 years of age. Prior to study entry, the site PI or an authorized staff member will inform patients about the nature of the study. Patients and/or parent/caregivers will have the opportunity to inquire about details of the study and to decide on participation. Patients will be instructed that they are free to withdraw from study participation at any time, without penalty or loss of benefits to which they are otherwise entitled.

Patients will also be given information regarding Health Insurance Portability and the Accountability Act, either in a separate consent form or as a separate section contained within the ICF. The Investigator will inform patients of new information that may be relevant to their willingness to continue study participation. The Investigator will provide each patient with a copy of the signed and dated ICF and record it was given to the patient in the source documents.

8.6 Patient Confidentiality

To maintain patient privacy, all eCRFs, device accountability records, study reports and communications will identify the patient by initials and assigned identification number. The patient's confidentiality will be maintained and their identity will not be made publicly available, to the extent permitted by applicable laws and regulations.

Patient data stored on a computer will be handled in accordance with local data protection laws. Patients will be informed that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

8.7 Investigator Compliance

The site PI will not alter/modify this clinical study protocol without obtaining appropriate prior written agreement from Alcresta and the IRB/IEC. In the event of an emergency, the site PI shall implement any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor and appropriately documented in the source documents for this study.

By signing the Investigator's Agreement page of this protocol, the site PI confirms in writing that he/she has read, understands and will strictly adhere to the study protocol, and will conduct the study in accordance with ICH Guidelines for GCP and applicable regulatory requirements. By signing page 2, the site PI commits to ensuring that all site staff involved in the execution of this study are qualified and properly trained to perform their assigned responsibilities.

9.0 STUDY COMPLETION PROCEDURES

9.1 Completion of Study

At the end of the study, Alcresta will provide written documentation to all investigative sites and central IRBs that the study is closed. The site monitor will conduct close-out visits and ensure that IRB/IEC are notified of study closure.

9.2 Records Retention

The site PI must maintain all study records, according to ICH-GCP, and applicable regulatory requirements. Records will be retained and preserved until:

- At least two years after the last marketing application approval or Alcresta has discontinued research with Relizorb or
- At least two years since the formal discontinuation of clinical development of Relizorb.

These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution or private practice in which the study is being conducted. At the end of the above periods, the site PI will notify Alcresta in writing of the intent to destroy study records. Alcresta shall have 30 days to respond to the site PI's notification and may assume payment for continued record retention.

Custody of the records may be transferred to another responsible site PI, deemed acceptable to Alcresta, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor and to the site's IRB/IEC. The site PI must contact Alcresta prior to disposing of any study records.

9.3 Communication of Study Results

All information regarding use of Relizorb, the protocol and all other study materials are privileged and confidential information. The site PI agrees to use this information to execute the study and will not use it for other purposes, without consent from Alcresta.

It is anticipated that the results of this study will be presented at medical conferences and will be available in scientific publications or medical journals.

Publication by the site of any data from this study is strictly prohibited. Any exceptions must be carried out in accordance with the Clinical Trial Agreement.

9.4 Ethics

This study will be conducted in accordance with applicable standards of GCP (21 Code of Federal Regulations Part 812), in agreement with the Declaration of Helsinki and in keeping with federal and local regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety and well being of patients. This study will only be conducted at sites where IRB/IEC approvals have been obtained. The site PI will be thoroughly familiar with the proper use of Relizorb as described in the protocol, and the corresponding Investigator's Brochure.

10.0 REFERENCES

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11.0 APPENDICES

11.1 Peptamen® 1.5 Nutrition Information - *Unflavored* (Nestle Health Science)

One bottle equals 250 mL (1Carton)

Amount Per Serving	Unit	Amount	Amount per Serving	Unit	Amount
Calories	Kcal	375	Total Fat *	g	14
Sodium	mg (mEq)	255 (11.1)	Potassium	mg (mEq)	465 (12)
Total Carbohydrate	G	46	Protein	g	17
Vitamin A**	IU	1615	Vitamin C	mg	128
Calcium	Mg	250	Iron	mg	6.75
Vitamin D	IU	200	Vitamin E	IU	11.3
Vitamin K	Mcg	30	Thiamin	mg	0.75
Riboflavin	Mg	0.9	Niacin	mg	10.5
Vitamin B_6	Mg	1.5	Folic Acid	mcg	200
Vitamin B_{12}	Mcg	3	Biotin	mcg	150
Pantothenic Acid	Mg	5.25	Phosphorus	mg	250
Iodine	Mcg	56	Magnesium	mg	100
Zinc	Mg	9	Selenium	mcg	19
Copper	Mg	0.75	Manganese	mg	1
Chromium	Mcg	15	Molybdenum	mcg	45
Chloride	mg (mEq)	435 (12.3)	L-Carnitine	mg	37.5
Taurine	Mg	37.5	Choline	mg	170
Water	mL	193			

* MCT provides 10 g/250 mL

** Includes 37% of vitamin A activity from beta-carotene

Ingredients of Peptamen® 1.5 (*Unflavored*):
Water, Maltodextrin, Enzymatically Hydrolyzed Whey Protein (from Milk), Medium Chain Triglycerides (from Coconut and/or Palm Kernel Oil), and less than 2% of Cornstarch, Soybean Oil, Soy Lecithin, Magnesium Chloride, Sodium Ascorbate, Sodium Phosphate, Calcium Phosphate, Guar Gum, Calcium Citrate, Choline Chloride, Potassium Chloride, Salt, Sodium Citrate, Taurine, L-Carnitine, Magnesium Oxide, Alpha-Tocopheryl Acetate, Zinc Sulfate, Ferrous Sulfate, Niacinamide, Calcium Pantothenate, Vitamin A Palmitate, Potassium Citrate, Manganese Sulfate, Pyridoxine Hydrochloride, Vitamin D_3, Copper Sulfate, Thiamine Mononitrate, Riboflavin, Beta Carotene, Folic Acid, Biotin, Citric Acid, Potassium Iodide, Chromium Chloride, Sodium Selenate, Sodium Molybdate, Phytonadione, Vitamin B_{12}.

11.2 Impact Peptide 1.5 Nutrition Information - *Unflavored* (Nestlé Healthcare Nutrition)

One bottle equals 250 mL (1 Carton is 8.45 ounces)

Amount Per Serving	Unit	Amount	Amount per Serving	Unit	Amount
Calories	cal	375	Total Fat *	g	15.9
MCT	g	7.8	MCT/LCT ratio	50:50	
DHA+EPA	g	1.225	Sodium	mg	292
Potassium	mg	468	Carbohydrate	g	35
Protein	g	23.5	Vitamin A	IU	3750
Vitamin C	mg	250	Calcium	mg	250
Iron	mg	4.5	Vitamin D	IU	200
Vitamin E	IU	25	Vitamin K	mcg	18.7
Thiamine (Vitamin B_1)	mg	0.75	Riboflavin (Vitamin B_2)	mg	0.6
Niacin	mg	7	Vitamin B6	mg	1
Vitamin B12	mcg	2	Biotin	mcg	100
Pantothenic Acid	mg	3.5	Phosphorus	mg	250
Iodine	mcg	40	Magnesium	mg	105
Zinc	mg	9	Selenium	mcg	25
Copper	mg	0.75	Manganese	mg	1
Chromium	mcg	35	Molybdenum	mcg	55
Chloride	mg	435	Choline	mg	138
Folic Acid	mcg	135	L-Carnitine	mg	37.5
Taurine	mg	70			

Ingredients of Impact® Peptide 1.5 (*Unflavored*):
Water, Maltodextrin, Enzymatically Hydrolyzed Whey Protein (from Milk), Medium Chain Triglycerides (from Coconut and/or Palm Kernel Oil), contains less than 2% of L-Arginine Cornstarch, Refined Fish Oil (Anchovy, Sardine), Soybean Oil, Citric Acid, Calcium Citrate, Yeast Extract, Magnesium Chloride, Potassium Phosphate, Ascorbic Acid, Salt, Hdroxylated Soy Lecithin, Sodium Citrate, Choline Chloride, Guar Gum, Xanthan Gum, Potassium Citrate, Taurine, Magnesium Oxide, Sodium Ascorbate, Alpha-Tocopheryl Acetate, L-Carnitine, Zinc Sulfate, Ferrous Sulfate, Niacinamide, Vitamin A Palmitate, Calcium Pantothenate, Manganese Sulfate, Vitamin D_3, Copper Sulfate, Pyridoxine Hydrochloride, Beta Carotene, Thiamine Mononitrate, Riboflavin, Folic Acid, Chromium Chloride, Biotin, Sodium Molybdate, Potassium Iodide, Sodium Selenate, Phytonadione and Vitamin B_{12}.