# Statistical Analysis Plan

| | |
|---|---|
| Protocol Title: | Absorption and Safety with Sustained Use of RELiZORB® Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding |
| Protocol Number: | 0000498-02 (07-MAR-2016) |
| Investigational Device: | RELiZORB immobilized lipase (iLipase™) cartridge |
| Sponsor: | Alcresta Therapeutics, Inc.<br>One Newton Executive Park, Suite 100<br>Newton, MA 02462, USA |
| SAP Authors: | [redacted] |
| SAP Version: | Final 3.0 |
| SAP Date: | 29 Jun 2017 |

**CONFIDENTIAL**

## DOCUMENT HISTORY

| Version | Date |
|---|---|
| 0.1 | 02-May-2016 |
| 1.0 | 10-May-2016 |
| 1.1 | 16-Dec-2016 |
| 1.2 | 10-Mar-2017 |
| 2.0 | 28-Mar-2017 |
| 3.0 | 29-Jun-2017 |

# TABLE OF CONTENTS

## ABBREVIATIONS

| ABBREVIATION | DEFINITION OR DESCRIPTION |
|---|---|
| AE | adverse event |
| ALA | alpha linolenic acid |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| ASSURE | Absorption and Safety with Sustained Use of RELiZORB™ |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| β-hCG | Beta-Human Chorionic Gonadotropin pregnancy test |
| BMI | body mass index |
| CDC | Center for Disease Control and Prevention |
| CF | cystic fibrosis |
| CI | confidence interval |
| CRF | case report form |
| CSR | Clinical Study Report |
| DGLA | dihomo-g-linolenic acid |
| DHA | docosahexaenoic acid |
| DPA | docosapentaenoic acid |
| eCRF | electronic case report form |
| EMA | European Medicines Agency |
| EPA | eicosapentaenoic acid |
| EPI | exocrine pancreatic insufficiency |
| FDA | Food and Drug Administration |
| GCMS | gas chromatography-mass spectrometry |
| GI | Gastrointestinal |
| GLA | gamma-linolenic acid |
| HDL | high-density lipoprotein |
| HR | heart rate |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IFU | Instructions for Use |
| ITT | Intent To Treat |
| LA | linoleic acid |
| LCFA | long chain fatty acid |
| LCPUFA | long chain polyunsaturated fatty acid |
| LDL | low-density lipoprotein |
| LOD | limit of detection |
| LLOQ | lower limit of quantitation |
| LSMeans | least squares means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed model repeated measures |
| PERT | pancreatic enzyme replacement therapy |
| PP | Per Protocol |

| | |
|---|---|
| PT | preferred term |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SE | standard error |
| SOC | system organ class |
| TG | Triglycerides |
| UADE | unanticipated adverse device effect |
| ULOQ | upper limit of quantitation |
| WCV | Weight change velocity |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |
| z-score | z-score |

# 1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Alcresta Therapeutics, Inc., protocol 0000498 (Absorption and Safety with Sustained Use of RELiZORB® Evaluation (ASSURE) Study in Patients with Cystic Fibrosis Receiving Enteral Feeding), dated 07-MAR-2016.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3] for statistical practice.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analysis not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol 0000498-02 dated 07-MAR-2016
- Electronic case report form (eCRF) for Protocol 0000498
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Study Objectives

The overall objective of the 90-day study is to assess safety, tolerability and to demonstrate improved fat absorption with sustained use of RELiZORB in patients with CF who have EPI and are receiving enteral tube feeding.

The efficacy objectives include:

- Evaluate effect of sustained Relizorb use during enteral feedings on fat absorption through serial measurements of plasma and tissue (erythrocyte membrane) physiologically relevant LCPUFAs such as DHA & EPA as biomarkers of fat absorption.
- 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 during enteral feedings on plasma fat-soluble vitamin concentrations
- Evaluate effect of sustained Relizorb use on growth
- Evaluate effect of sustained Relizorb use on urinary leukotriene levels
- Evaluate effect of sustained Relizorb use on serum protein levels

The Safety Objective is to:

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

## 2.2 Safety, Efficacy and Exploratory Endpoints

### 2.2.1 Safety Endpoints

The safety and tolerability endpoints include the following:

- Frequency and severity of adverse events
- Incidence of gastrointestinal symptoms.
- Unanticipated adverse device effects (UADE)
- Evaluation of clinical and laboratory findings
- Vital signs
- Concomitant medications

### 2.2.2 Efficacy Endpoints

The primary efficacy variable is the composition changes (%) of total DHA plus EPA (omega-3 index) in erythrocyte membranes.

The secondary efficacy endpoints include changes in:

- Erythrocyte membrane composition (%) of total DHA
- Erythrocyte membrane composition (%) of total EPA
- Erythrocyte membrane composition (%) ratio of omega-6 to omega-3 fatty acids
- Plasma concentration of total DHA concentration (µg/mL)
- Plasma concentration of total EPA concentration (µg/mL)
- Plasma concentration of total DHA+EPA concentration (µg/mL)
- Plasma composition (%) ratio of omega-6 to omega-3 fatty acids

The exploratory efficacy endpoints include:

- Plasma concentrations of fat soluble vitamins A, D and E
- Serum protein concentrations (total protein, pre-albumin, albumin, transferrin)
- Marker of inflammation (urinary leukotriene $LTE_4$)
- Weight gain velocity versus historical comparison
- Standardized Body weight and BMI expressed as age-specific z-score via CDC reference.

Plasma concentrations (µg/mL) of total DHA and total EPA measured by ultra high performance liquid chromatography (UHPLC) will be provided by [redacted] Total EPA+DHA will be calculated as the sum of the concentrations of total DHA and total EPA. Fatty acid composition (%) in both plasma and erythrocytes is measured by gas chromatography-mass spectrometry (GCMS) and is provided by [redacted]

## 3. OVERALL STUDY DESIGN AND PLAN

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 cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI) who are receiving enteral tube feeding.

During an initial 7-day observation period (Day -14 to Day -8) subjects will receive their usual enteral nutrition regimen. If subjects use pancreatic enzyme replacement therapy (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 7-day observation period 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, and PERT use will be recorded. Individualized patient standard use of PERT with daily meals, snacks, and enteral nutrition will continue during the run in period. The subject will also record gastrointestinal symptoms daily during the 7-day run in period in a gastrointestinal symptom diary.

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 subject standard use of oral PERT is allowed with daily meals and snacks, but use of therapeutic agents currently used to aid in fat absorption, such as PERT, will not be used with RELiZORB during enteral feedings. The subject will also record gastrointestinal symptoms in a gastrointestinal symptom diary during the 7-day period prior to scheduled study visits on Day 30, Day 60 and Day 90.

The complete study schedule of events is presented in Table 1.

## 3.1 Schedule of Events

### Table 1: Schedule of Events

| Evaluation | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 * |
|---|---|---|---|---|---|
| | **Day -14** *Study Entry* | **Day 0** *Baseline* | **Day 30** *Treatment* | **Day 60** *Treatment* | **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 1.5 500 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 alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen, calcium, chloride, cholesterol, creatinine phosphokinase, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, and uric acid.
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, pre-albumin, 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 0.
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

### 3.2 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 in plasma, 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.

The primary efficacy endpoint for this study is the sum of DHA+EPA. The sample size was based on a literature review of DHA assuming an effect size of 0.53. Assuming the same effect size for measuring erythrocyte tissue composition of the total of DHA plus EPA is consistent with that of DHA, the current sample size will provide 80% power.

### 3.3 Subject Replacement

Approximately 30 to 40 subjects were to be enrolled in the study. Protocol compliant subjects from Protocol 0000497 were eligible for this study, unless clinical changes had occurred in which the patient no longer met the initial eligibility criteria.

Any subject who withdrew from the study before Study Visit 4 on Day 60 was to be replaced by an eligible subject unless enrollment was closed.

## 4. ANALYSIS AND REPORTING

### 4.1 Interim Analysis

No interim analysis is planned for this study.

### 4.2 Final Analysis

All final, planned analysis identified in the protocol and in this SAP will be performed after the last subject has completed the end of study visit (or early termination) and all relevant study data have been processed and integrated into the analysis data base (database lock). Any post-hoc, exploratory analysis completed to support planned study analysis, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified as such.

## 5. ANALYSIS POPULATIONS

The following analysis populations are planned for this study

- **Safety Population:** The safety population includes all subjects who received at least one Relizorb exposure.
- **Intent to Treat Population (ITT):** The ITT population, includes all subjects who received at least one RELiZORB exposure. This population is the same as safety, and will be used for efficacy analyses.
- **Per Protocol Population (PP):** The per protocol population consists of all subjects who met the inclusion criteria, used RELiZORB as stated in the protocol and Instructions For Use (IFU) through at least Visit 3 (Day 30) and had not been the subject of any major protocol deviation(s).

# 6. GENERAL ISSUES FOR STATISTICAL ANALYSIS

## 6.1 General Statistical Methodology

The primary population for safety is the safety population. For the efficacy analysis, the primary endpoint will be conducted on both the per protocol (PP) and ITT populations. All secondary efficacy analyses will be conducted on the ITT population unless otherwise specified.

Continuous variables will be summarized using descriptive statistics, including number of non-missing values, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using the number and proportion of each possible value.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places with a maximum of 1 decimal place) as the raw data. Measures of location (mean and median) will be reported to 1 degree of precision (with a maximum of 2 decimal places) more than the raw data and the measure of spread (standard deviation) will be reported to 2 degrees of precision (with a maximum of 3 decimal places) more than the raw data. All efficacy endpoints in section 8.1 will use a maximum of two decimal places.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category. The denominator for the percentage calculation will be based upon the total number of subjects in the relevant study population unless otherwise specified.

Assessments done on unscheduled visits will not be summarized but will be listed. If any assessments are repeated on the same day and/or time point, the last non-missing assessment will be summarized and/or analyzed.

Statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and nominal p-values will be reported. SAS software (SAS, Inc., Cary, NC) will be utilized for statistical analysis (version 9.3).

Subject level information presented in a listing will include subject identification number as well gender, age (examples: F/23, M/37). All listings will be sorted by subject identification numbers.

## 6.2 Handling of Missing Data

Available subject data will be used in the statistical analysis. For the MMRM analysis, subjects who lack all post-baseline measures, the baseline efficacy outcome will be imputed for all post-baseline responses (i.e., no change from baseline).

To handle missing or partial AE and medication dates, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value
2. If the month is unknown, then:
    a. If the year matches the year of the first RELiZORB administration date, then impute the month and day of the first RELiZORB administration date.
    b. Otherwise, assign "January."
3. If the day is unknown, then:

a. If the month and year match the month and year of the first RELiZORB administration date, then impute the day of the first RELiZORB administration date.
b. Otherwise, assign "01."

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

### 6.3 Derived Variables

The following derived variables have been initially identified as important for the analysis of the safety and efficacy endpoints. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

- Baseline = the last non-missing measurement before the date of RELiZORB administration for safety assessments. For efficacy assessments, baseline will be the assessment collected at Visit 2 (Day 0). However, if the result from Visit 2 is missing and the result from Visit 1 is available, the result from Visit 1 will be used.
- Study Entry = Day -14, which occurs during Study Visit 1.
- Study day = Assessment Date - Date of first RELiZORB administration (+ 1 if assessment date is on or after date of first RELiZORB administration).
- Change from Baseline = Value at Post Baseline - Value at Baseline.
- % Change from Baseline = 100 * Change from Baseline / Value at Baseline.
- "End of Study" is the point at which the last contact with the subject during the protocol-specified schedule is made.
- "Screen Failure" is a subject who has not met eligibility criteria.

The years of enteral tube feeding will be calculated from the first date of gastrostomy tube placement in the medical history to the Visit 1 date. For partial dates, if the day is missing, the first will be used. If the month and day are missing, January 1 will be used. The years will be calculated as (Visit 1 date – date of gastrostomy tube placement)/365.25.

The following subgroups will be used for subgroup analyses of selected endpoints:

- Age Categories: <=12 years, 13-18 years, and >=19 years.
- CFRD Categories: CRFD and non-CFRD. CFRD will include all subjects who reported "cystic fibrosis related diabetes", "CFRD", "type 1 diabetes mellitus", "diabetes mellitus related to cystic fibrosis" in their medical history.

### 6.3.1 Weight and BMI Derived Variables

Up to 4 weight, height, and body mass index (BMI), (and BMI percentile for subjects of age ≤18 years) recordings will be obtained from the medical record at approximately 3 month intervals over the previous 12 months prior to Visit 1 on Day -14. Weight and BMI will be collected at Visit 1 (study entry; Day -14) and at study visits on Day 0 (Visit 2), Day 30 (Visit 3), Day 60 (Visit 4), and Day 90 (Visit 5).

#### 6.3.1.1 Weight Gain Velocity

Weight gain velocity (WGV) is defined as the rate of change in body weight per initial body weight per time period. The quantity will be expressed in units of g/kg/90 days.

The formula to calculate WGV between two dates Date1 and Date2 is:

90 x [weight (g) at Date2 – weight (g) at Date1] / [weight (kg) at Date1] / (Date2 – Date1 + 1)

The factor of 90 converts the rate from per day to per 90 days.

The WGV can be considered the slope as the change in weight (Δw) divided by the change in days plus 1 (Δt). This quantity is multiplied by 90 and then divided by the subject weight at interval start (kg) to express the results as 90-day changes for each kilogram of weight. For example, if a patient is 62.0 kg on January 1, 2016 and 63.5 kg on April 1, 2016, the slope is 1.5 kg/92 days = 1.5 kg/92 days = 1500 g/92 days = 16.3 grams per day. Equivalently, 90 days x 16.3 g/day equals 1467.4 g / 90 days. Expressed per kg body weight, the WGV equals 23.7 g/kg/90 days. Equivalently, as above, 90*(63500-62000)/62.0/92 = 23.7

WGV will be calculated from the date of Visit 2 to the date of Visit 5, or the last visit at which a weight is available.

The historical weight recordings will be used to calculate historical WGV. Any weights recorded more than 12 months before Study Entry and weights recorded before the date of tube placement indicated in medical history will be excluded. The selection of the appropriate medical indications and date imputations for this are described in Section 6.3 for the calculation of duration of enteral feeding. The historical WGV will be determined by first calculating the change in weight between each consecutive historical weight recorded before Study Entry and thus providing up to 3 values for change in weight. WGV will then be calculated from these weight changes as described above. The average of these values will be determined and identified as the average historical WGV.

#### 6.3.1.2 Weight and BMI Z-scores and Percentiles Derived Variables

Weight and BMI values from baseline (Visit 2 or Visit 1 if Visit 2 is missing) and Visit 3 to Visit 5 will be normalized to Z-scores based on age- and sex-specific data from the Centers for Disease Control and Prevention (CDC). A SAS program and dataset obtained from the CDC website will be used to calculate the values for healthy subjects aged 2-20 years, with age expressed in months with decimal. The CDC data is provided in half month intervals for age.

### 6.4 Lower and Upper Limit of Quantification

For analysis, all laboratory values will be presented in standard (SI) units.

In general, for quantitative laboratory values reported as "<" or "≤" the lower limit of

quantitation (LLOQ) or limit of detection (LOD), one-half of the reported value (i.e., LLOQ/LOD) will be used for analysis.

For quantitative laboratory values reported as ">" or "≥" the upper limit of quantitation (ULOQ), the reported value (i.e., ULOQ) will be used for analysis.

# 7. STUDY SUBJECTS AND DEMOGRAPHICS

## 7.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study. The total number of subjects screened, screen failures and enrolled will be summarized.

In addition, tabulations of the number of subjects who completed the study, and discontinued early from the study (along with the reasons for withdrawal) will be provided. The subject disposition tabulation will also include the number of subjects in each of the analysis populations.

## 7.2 Protocol Violations and Deviations

Protocol violations and deviations will be recorded in the CRF and reviewed prior to database lock.

Violations and deviations will be categorized into the following categories:

- Inclusion/exclusion criteria
- Informed consent form (ICF)
- Missed study procedure or visit
- Out of window procedure or visit
- Investigational product noncompliance
- Other

Other protocol deviation categories may be identified during the study. Protocol deviations and violations will be recorded and referenced to determine the subjects to be excluded from the per protocol population. The final decision regarding inclusion and exclusion of subjects from the analysis populations will be based on a listing of protocol deviations. This will be determined during a data review meeting before database lock, with input from Clinical and Biostatistics team members and approval from the Sponsor.

Protocol deviations will be summarized by type (deviation or violation), major or minor, and by category for all enrolled subjects.

## 7.3 Demographics and Other Baseline Characteristics

Baseline demographics and characteristics (age, age category, gender, race, ethnicity, height, weight, and BMI) duration (years) of enteral tube feeding (EF) prior to study entry, females of child bearing potential, physical exam (normal, abnormal), and CFRD subgroup will be presented. Subjects reporting more than 1 race will be counted in a "Multiple" category.

The years of enteral tube feeding will be calculated from the first date of gastrostomy tube placement in the medical history to the Visit 1 date. For partial dates, if the day is missing, the first will be used. If the month and day are missing, January 1 will be used. The years will be calculated as (Visit 1 date – date of gastrostomy tube placement)/365.25.

Subject demographics and baseline characteristics will also be presented in a subject listing.

Whether a subject met all inclusion/exclusion criteria will be included in a listing. Any criteria not met will be included.

### 7.4 Medical History

All medical history information will be presented in a subject listing.

## 8. EFFICACY ANALYSIS

The primary analysis population for all efficacy analyses will be the ITT population. The analysis of erythrocyte membrane composition (%) of DHA+EPA will be repeated using the PP population.

### 8.1 Primary Efficacy Endpoint

Fatty acid erythrocyte tissue composition of the total of DHA plus EPA is the primary efficacy endpoint and is measured at visits 1 through 5 on days -14, 0, 30, 60, and 90, respectively. The primary efficacy endpoint (actual values) will be analyzed by a mixed model repeated measures (MMRM) model to test for LS Mean differences relative to baseline (as defined in Section 6.3) among the post-baseline visits. For this analysis, study visit 2 (day 0), 3 (day 30), 4 (day 60), 5 (day 90) is a categorical effect and subject is a random effect. The primary study population compares baseline to Day 90 in the ITT population. For subjects who lack visit 2, the value at visit 1 will be used.

An unstructured within-subject covariance matrix will be used. If the model does not converge, auto-correlated, and compound symmetry will be explored and the model resulting in the lowest Akaike information criterion value will be presented. LS Means, standard errors (SE), and 95% confidence intervals will be reported by visit. Contrasts in LS Means at each visit against baseline will also be reported with SE and 95% confidence intervals with p-values for differences from zero. A sensitivity analysis of the primary efficacy endpoint will be conducted in the PP population.

Summary statistics for actual values at each visit and changes from baseline will be presented.

The primary endpoint analysis will be repeated by age subgroups and by CFRD subgroups separately.

### 8.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed using the same analysis as the primary analysis for the ITT population:

- Erythrocyte membrane composition (%) of total DHA
- Erythrocyte membrane composition (%) of total EPA
- Erythrocyte membrane composition (%) ratio of omega-6 to omega-3 fatty acids
- Plasma concentration of total DHA concentration (µg/mL)
- Plasma concentration of total EPA concentration (µg/mL)
- Plasma concentration of total DHA+EPA concentration (µg/mL)
- Plasma composition (%) ratio of omega-6 to omega-3 fatty acids

The following secondary endpoints will be repeated by age subgroups and CRFD subgroups separately.

- Erythrocyte membrane composition ratio of omega-6 to omega-3 fatty acids
- Plasma concentration of total DHA+EPA concentration (μg/mL)
- Plasma composition ratio of omega-6 to omega-3 fatty acids

### 8.3 Exploratory Efficacy Endpoints

The values for the following endpoints will be analyzed using the same MMRM comparing baseline to Day 90 on the ITT population as described in Section 8.1.

- Serum protein concentration (total protein, pre-albumin, albumin, transferrin)
- Plasma concentration of fat soluble vitamins (A, D and E)
- Urinary leukotriene $E_4$ ($LTE_4$)

The analysis for plasma concentration of vitamins A, D, and E will also be repeated by age subgroups.

#### 8.3.1 Weight Gain Velocity

Weight gain velocity changes from historical average (baseline) to 0-90 days by age subgroup will be assessed by a one-sample t-test if the test for normality by Shapiro-Wilkes is met, or otherwise by the Wilcoxon signed rank test.

#### 8.3.2 Weight and BMI Z-scores

Age-specific z-scores for weight and BMI are obtained (via CDC standard tables) at each study visit and at quarterly intervals in the year prior to baseline. For weight and for BMI, the average historical distribution percentile (mean of historical values) and the z-scores (and distribution percentile) at 30, 60 and 90 days will be presented. The change in percentile of the distribution from historical average to 90 days will be tested by a one-sample t-test or Wilcoxon signed rank test. This analysis will be performed by age subgroup only.

## 9. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety assessments in this study will include the following categories of safety and tolerability data collected for each subject:

- Adverse Events (AEs)
  - Serious Adverse Events
  - Unanticipated adverse device effect (UADEs)
  - UADEs leading to discontinuation of enteral feeding
  - Any deaths
- 7 day gastrointestinal symptom diary
- Clinical laboratory investigations
- Vital signs
- Concomitant medications

- Exposure to treatment

Safety data will be summarized descriptively on the safety population.

### 9.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0 or most recent version).

AEs will be summarized by MedDRA system organ class and preferred term. Separate columns will be included in the AE summary table for AEs starting under the treatment by Standard of Care, and starting during RELiZORB treatment.

For all AEs, the event will be summarized under the treatment (Standard of Care, RELiZORB) the event started in and in the total column. The AE is assigned to the standard of care or RELiZORB based on the start date of the adverse event.

- If the start date of the event is before the first administration of RELiZORB, the event will be summarized under Standard of Care.
- If the start date of the event is on or after the first administration of RELiZORB, the event will be summarized under RELiZORB.
- If the start and end date of the event are both missing, the event will be summarized under both SOC and RELiZORB.

In a general overview of AEs, events will be summarized by treatment for the following items:

- All AEs
- Serious Adverse Events (SAEs)
- AEs by relationship
- AEs leading to discontinuation of enteral feeding
- AEs by maximum severity
- UADEs
- UADEs by relationship
- UADEs leading to discontinuation of enteral feeding
- UADEs by maximum severity

Missing and partially missing AE start and/or stop dates will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.2.

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA System Organ Class and preferred term will be prepared. UADEs and SAEs will not be included in summaries of AEs, but will be summarized separately. Each subject will be counted only once within each level of summary (system organ class and preferred term).

Adverse events that lead to discontinuation of enteral feeding will be summarized and listed separately.

### 9.1.1 Unanticipated Adverse Device Effects

UADEs will be summarized separately for all UADEs, UADEAEs by maximum intensity, UADEAEs by strongest relationship to study device. Each subject will be counted only once within each level of summary (system organ class and preferred term). If a subject experiences more than one AE in each level, the AE with the strongest relationship or the maximum severity, as appropriate, will be included in each summary for AE relationship and severity.

All UADES and UADEs leading to discontinuation of Enteral Feeding will be presented in a listing.

### 9.1.2 Serious adverse events

Serious Adverse Events (SAEs) will be listed separately but not summarized.

### 9.1.3 Deaths

All deaths that occur during the study will be presented in a subject listing.

## 9.2 Gastrointestinal (GI) Symptom Diary

The gastrointestinal symptoms recorded in the 7 day gastrointestinal symptom diary during the observation and run in periods will be compared with the symptoms recorded three separate times during the treatment period.

The following descriptive summaries will be provided for each period: Visit 1 (Days -14 to -8), Visit 2 (Days -7 to -1), and Visit 3 (Days 23 to 30), Visit 4 (Days 53 to 60), and Visit 5 (Days 83 to 90) under RELiZORB:

- Number of subjects who experienced a symptom at least once during the period (incidence) overall and for each symptom
- Number of days each symptom occurred within a period.

## 9.3 Clinical Laboratory Evaluations

Laboratory data for Chemistry, Hematology, Urinalysis, and Blood lipids will include the following analytes:

- **Chemistry**: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen, calcium, chloride, cholesterol, creatinine phosphokinase, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, uric acid
- **Hematology:** basophils, eosinophils, hematocrit, hemoglobin, white blood cell count, lymphocytes, monocytes, neutrophils, platelet count, red blood cell count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration
- **Urinalysis:** bilirubin, blood, glucose, ketones, leukocyte esterase, pH, protein, specific gravity, urinary creatinine and uric acid
- **Blood Lipids**: total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)

Laboratory data will be summarized separately for each category by visit for the safety population. Descriptive summaries of actual values and changes from Baseline will be presented by study visit.

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged as normal, high or low, along with corresponding normal ranges (if available).

Pregnancy test results will be listed separately.

### 9.4 Vital Signs

Descriptive summaries of actual values and changes from baseline to each scheduled visit will be calculated for vital signs including heart rate (HR), respiratory rate (RR), temperature (Temp), systolic and diastolic blood pressure.

A listing of all vital signs will be provided.

### 9.5 Physical Examination

All physical examination results will be listed only.

### 9.6 Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) (Version March 2015 or most recent version) and summarized by ATC Level 3 term and preferred term on the safety population.

### 9.7 Exposure to Treatment

The number of days of RELiZORB use for the overall treatment period, between Visits 2 and 3 (including Visit 2), between Visits 3 and 4 (including Visit 3), and between Visits 4 and 5 (including Visit 4 and 5) will be calculated. The average weekly number of days of RELiZORB use between these visits will be determined by first taking the number of days between Visits (date of last Visit – date of current visit +1) and dividing by 7. This will give us the number of weeks between Visits. Next, the number of days of RELiZORB use will be divided by the number of weeks between Visits to provide the average weekly RELiZORB use between Visits. Average weekly number of days of RELiZORB use for the overall treatment period will be calculated in the same manner.

Average volume of formula administered (mL/day) for the overall treatment period via RELiZORB is defined as the total volume of formula administered via RELiZORB across study / Number of days a RELiZORB administration occurred. Average volume between Visits 2 and 3 (including Visit 2), between Visits 3 and 4 (including Visit 3), and between Visits 4 and 5 (including Visit 4 and 5) will be calculated in the same manner as average volume for total study period except that the total volume of formula administered via RELiZORB / the number of days a RELiZORB administrations occurred between visits will be used.

Study treatment adherence will be calculated for each subject and summarized descriptively. Adherence will be defined as the number of days the RELiZORB is used divided by the number of days inclusive from Visit 2 through Visit 5, multiplied by 100. Adherence between visits will be summarized and defined as the number of days the RELiZORB is used between Visits (as defined in the first paragraph) divided by the number of days between Visits (Visits 2 and 3,

Visits 3 and 4, Visits 4 and 5), multiplied by 100.

The analysis will be completed using the safety population.

All RELiZORB usage information will be included in a subject listing.

### 9.8 Equipment Adverse Experience (RELiZORB Usage)

The number of subjects who experienced at least one operational problem with the device along with the reported problem will be summarized for the overall treatment period including for the following periods: between Visits 2 and 3 (including Visit 2), between Visits 3 and 4 (including Visit 3), and between Visits 4 and 5 (including Visit 4 and 5). The number of times each problem was reported will also be summarized. Only problems due to the investigational device will be summarized.

A listing including the details for the equipment adverse experience will be included.

## 10. CHANGES FROM PLANNED ANALYSIS

The following items were changed from the planned analysis specified in the protocol:

| Protocol Version 2.0 | Updated Planned Statistical Analysis Changes From the Protocol | Justification For Change |
|---|---|---|
| **7.4.2 Safety Population**<br>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 safety information. | **7.4.2 Intent to Treat**<br>The ITT population, includes all subjects who received at least one RELiZORB exposure. This population is the same as safety and will be referenced as ITT for efficacy analysis. | To clarify study populations for safety and for efficacy analysis. |
| **Section 7.5 Procedures for Handling Missing, Unused and Spurious Data**<br>All available safety and tolerability data will be presented in data listings and tabulations. No data imputation will be applied for missing values. | **Section 6.2 Handling of Missing Data**<br>Available subject data will be used in the statistical analysis. For the MMRM analysis, subjects who lack all post-baseline measures, the baseline efficacy outcome will be imputed for all post-baseline responses (i.e., no change from baseline). | There really is no change for subjects who are missing post-baseline data. |

| | | |
|---|---|---|
| **Section 7.7 Safety Analysis** (paragraph 3)<br>For the comparison between GI symptoms recorded during the run in period and the treatment period, the following analyses will be performed:<br>• No. of days where any symptom occurred;<br>• No. of days each symptom occurred;<br>• No. of days when severity was 1, 2 or 3<br>• Symptom duration of <15min, 15-30min, 31-60min or >60min. | Removal of GI symptoms analysis:<br>• No. of days when severity was 1, 2 or 3<br>• Symptom duration<br>• Any GI comparisons using ANOVA | Based on the fact that the GI symptom diary is a self-reporting diary, where collection of input like severity of symptoms is not validated, analysis is descriptive. |
| **Section 7.8 Efficacy Analysis**<br>Comparison of these values during the run in and treatment periods will be performed using analysis of variance (ANOVA). | Analysis updated to a repeated measures analysis to compare mean values at baseline to Days 30, 60, and 90. | The MMRM statistical model in the SAP is an extension of the proposed model and accommodates random and fixed effects in the context of repeated measures. |

## 11. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999

RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.

## 12. TABLES, LISTINGS, AND FIGURES

All listings, tables, and figures will have a header showing the sponsor company name [Alcresta Therapeutics, Inc.], protocol number, output version, and a footer showing the filename and path, date of output generation, and date of data cut. All tables and figures will have a "SOURCE: Listing(s) xxxx" line that indicates which data listing contains the underlying data.

### 12.1 Planned Table Descriptions

The following are planned summary tables for protocol 0000498:

| Table Number | Population | Title | Listing Reference |
|---|---|---|---|
| 14.1.1 | All Subjects | Subject Disposition | 16.2.1.1, 16.2.1.2 |
| 14.1.2 | All Enrolled Subjects | Protocol Deviations/Violations | 16.2.2.1 |
| 14.1.3 | Safety | Demographics and Baseline Characteristics | 16.2.3.1 |
| 14.1.4 | Safety | RELiZORB Administration | 16.2.4.1, 16.2.4.2, 16.2.4.3 |
| 14.1.5 | Safety | Equipment Adverse Experience | 16.2.4.4 |
| 14.2.1.1a | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) for EPA+DHA (omega-3 index): Primary Efficacy Endpoint | 16.2.5.1.1 |
| 14.2.1.1b | Per Protocol | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) for EPA+DHA (omega-3 index) | 16.2.5.1.1 |
| 14.2.1.1c | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) for EPA+DHA (omega-3 index) by Age Subgroup | 16.2.5.1.1 |
| 14.2.1.1d | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) for EPA+DHA (omega-3 index) by CFRD Subgroup | 16.2.5.1.1 |
| 14.2.1.2 | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) for EPA and DHA | 16.2.5.1.1 |
| 14.2.1.3a | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids | 16.2.5.4.1 |
| 14.2.1.3b | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids by Age Subgroup | 16.2.5.4.1 |
| 14.2.1.3c | ITT | Changes over Time in Tissue (Erythrocyte Membrane) Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids by CFRD Subgroup | 16.2.5.4.1 |
| 14.2.1.4a | ITT | Changes over Time in Plasma Fatty Acid Concentration (µg/mL) of Total EPA+DHA | 16.2.5.2.1 |
| 14.2.1.4b | ITT | Changes over Time in Plasma Fatty Acid Concentration (µg/mL) of Total EPA+DHA by Age Subgroup | 16.2.5.2.1 |

| Table Number | Population | Title | Listing Reference |
|---|---|---|---|
| 14.2.1.4c | ITT | Changes over Time in Plasma Fatty Acid Concentration (µg/mL) of Total EPA+DHA by CFRD Subgroup | 16.2.5.2.1 |
| 14.2.1.5 | ITT | Changes over Time in Plasma Fatty Acid Concentration (µg/mL) of Total EPA and Total DHA | 16.2.5.2.1 |
| 14.2.1.6a | ITT | Changes over Time in Plasma Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids | 16.2.5.3.1 |
| 14.2.1.6b | ITT | Changes over Time in Plasma Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids by Age Subgroup | 16.2.5.3.1 |
| 14.2.1.6c | ITT | Changes over Time in Plasma Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids by CFRD Subgroup | 16.2.5.3.1 |
| 14.2.1.7 | ITT | Changes over Time in Serum Protein Concentrations (Total Protein, Prealbumin, Albumin, and Transferrin) | 16.2.5.6.1 |
| 14.2.1.8 | ITT | Changes over Time in Urinary Leukotriene $E_4$ | 16.2.5.7.1 |
| 14.2.1.9a | ITT | Changes over Time in Plasma Concentrations of Fat Soluble Vitamins (A, D, and E) | 16.2.5.5.1 |
| 14.2.1.9b | ITT | Changes over Time in Plasma Concentrations of Fat Soluble Vitamins (A, D, and E) by Age Subgroup | 16.2.5.5.1 |
| 14.2.1.10 | ITT | Weight and Body Mass Index (BMI) Z-scores by Age Subgroup and Comparison to Historic Z-score | 16.2.5.10.1 |
| 14.2.1.11 | ITT | Changes over Time in Weight Gain Velocity (g/kg/90 days) Compared to Historical by Age Subgroup | 16.2.5.9.1 |
| 14.3.1.1 | Safety | Summary of Adverse Events | 16.2.6.1, 16.2.6.2, 16.2.6.3, 16.2.6.5 |
| 14.3.1.2 | Safety | Adverse Events by System Organ Class and Preferred Term | 16.2.6.1 |
| 14.3.2.1 | Safety | Unanticipated Adverse Device Effects by System Organ Class and Preferred Term | 16.2.6.3 |
| 14.3.2.2 | Safety | Unanticipated Adverse Device Effects by System Organ Class, Preferred Term, and Relationship | 16.2.6.3 |
| 14.3.2.3 | Safety | Unanticipated Adverse Device Effects by System Organ Class, Preferred Term, and Severity | 16.2.6.3 |

| Table Number | Population | Title | Listing Reference |
|---|---|---|---|
| 14.3.3.1 | Safety | Gastrointestinal Symptom Diary: Frequency and Incidence – Overall and by Symptom | 16.2.7.1 |
| 14.3.4.1 | Safety | Summary of Clinical Chemistry Measurements: Results and Change from Baseline | 16.2.8.1 |
| 14.3.4.2 | Safety | Summary of Hematology Measurements: Results and Change from Baseline | 16.2.8.2 |
| 14.3.4.3 | Safety | Summary of Numeric Urinalysis Measurements: Results and Change from Baseline | 16.2.8.3 |
| 14.3.4.4 | Safety | Summary of Blood Lipids: Results and Change from Baseline | 16.2.8.4 |
| 14.3.5.1 | Safety | Summary of Vital Sign Measurements: Results and Change from Baseline | 16.2.9.1 |
| 14.3.6.1 | Safety | Concomitant Medications | 16.2.3.3 |

### 12.2 Planned Listing Descriptions

The following are planned data and patient data listings for protocol 0000498:

| Listing Number | Population | Title |
|---|---|---|
| 16.2.1.1 | All Subjects | Analysis Populations |
| 16.2.1.2 | All Enrolled Subjects | Patient Disposition |
| 16.2.1.3 | All Subjects | Inclusion and Exclusion Criteria |
| 16.2.2.1 | All Subjects | Protocol Deviations/Violations |
| 16.2.3.1 | All Subjects | Demographics and Baseline Characteristics |
| 16.2.3.2 | All Subjects | Medical History |
| 16.2.3.3 | All Subjects | Concomitant Medications |
| 16.2.4.1 | Safety | Enteral Tube Feeding Pre-Baseline and Baseline before Start of RELiZORB |
| 16.2.4.2 | Safety | RELiZORB Usage Log |
| 16.2.4.3 | Safety | RELiZORB Administration and Study Treatment Adherence |
| 16.2.4.4 | Safety | Equipment Adverse Experience |
| 16.2.5.1.1 | ITT | Composition (%) of EPA, DHA and DHA plus EPA (%) in Erythrocyte Membranes<br>Gas Chromatography/Mass Spectrophotometry (GCMS) |
| 16.2.5.1.2 | Subjects Excluded from Per Protocol | Composition (%) of EPA, DHA and DHA plus EPA (%) in Erythrocyte Membranes<br>Gas Chromatography/Mass Spectrophotometry (GCMS) |
| 16.2.5.2.1 | ITT | Concentrations (µg/mL) of Total DHA, Total EPA, and Total EPA+DHA<br>Ultra High Performance Liquid Chromatography (UHPLC) |
| 16.2.5.2.2 | Subjects Excluded from Per Protocol | Concentrations (µg/mL) of Total DHA, Total EPA, and Total EPA+DHA<br>Ultra High Performance Liquid Chromatography (UHPLC) |
| 16.2.5.3.1 | ITT | Plasma Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids<br>Gas Chromatography/Mass Spectrophotometry (GCMS) |
| 16.2.5.3.2 | Subjects Excluded from Per Protocol | Plasma Composition (%) Ratio of Omega-6 to Omega-3 Fatty Acids<br>Gas Chromatography/Mass Spectrophotometry (GCMS) |
| 16.2.5.4.1 | ITT | Tissue (Erythrocyte Membrane) Composition (%) |

| | | |
|---|---|---|
| | | Ratio of Omega-6 to Omega-3 Fatty Acids<br>Gas Chromatography/Mass Spectrophotometry (GCMS) |
| 16.2.5.4.2 | Subjects Excluded from Per Protocol | Tissue (Erythrocyte Membrane) Composition (%)<br>Ratio of Omega-6 to Omega-3 Fatty Acids<br>Gas Chromatography/Mass Spectrophotometry (GCMS) |
| 16.2.5.5.1 | ITT | Plasma Concentrations of Fat Soluble Vitamins (A, D and E) |
| 16.2.5.5.2 | Subjects Excluded from Per Protocol | Plasma Concentrations of Fat Soluble Vitamins (A, D and E) |
| 16.2.5.6.1 | ITT | Serum Protein Concentrations |
| 16.2.5.6.2 | Subjects Excluded from Per Protocol | Serum Protein Concentrations |
| 16.2.5.7.1 | ITT | Urinary Leukotriene $E_4$ (LTE4) |
| 16.2.5.7.2 | Subjects Excluded from Per Protocol | Urinary Leukotriene $E_4$ (LTE4) |
| 16.2.5.8.1 | ITT | Weight, Height, and Body Mass Index |
| 16.2.5.8.2 | Subjects Excluded from Per Protocol | Weight, Height, and Body Mass Index |
| 16.2.5.9.1 | ITT | Weight Gain Velocity |
| 16.2.5.9.2 | Subjects Excluded from Per Protocol | Weight Gain Velocity |
| 16.2.5.10.1 | ITT | Weight and Body Mass Z-scores |
| 16.2.5.10.2 | Subjects Excluded from Per Protocol | Weight and Body Mass Z-scores |
| 16.2.6.1 | All Enrolled Subjects | Adverse Events |
| 16.2.6.2 | All Enrolled Subjects | Adverse Events Leading to Discontinuation of Enteral Feeding |
| 16.2.6.3 | All Enrolled Subjects | Unanticipated Adverse Device Effects |
| 16.2.6.4 | All Enrolled Subjects | Unanticipated Adverse Device Effects Leading to Discontinuation of Enteral Feeding |
| 16.2.6.5 | All Enrolled Subjects | Serious Adverse Events |
| 16.2.6.6 | All Enrolled Subjects | Deaths |
| 16.2.7.1 | All Enrolled Subjects | Gastrointestinal Symptom Diary |
| 16.2.8.1 | All Enrolled Subjects | Clinical Laboratory Tests: Chemistry |
| 16.2.8.2 | All Enrolled Subjects | Clinical Laboratory Tests: Hematology |
| 16.2.8.3 | All Enrolled Subjects | Clinical Laboratory Tests: Urinalysis |
| 16.2.8.4 | All Enrolled Subjects | Clinical Laboratory Tests: Blood Lipids |
| 16.2.9.1 | All Enrolled Subjects | Vital Signs |
| 16.2.9.2 | All Enrolled Subjects | Physical Examination |
| 16.2.10.1 | All Enrolled Subjects | Telephone Contact Log |

### 12.3 Planned Figure Descriptions

The following are planned summary figures for protocol 0000498:

| Figure Number | Population | Title | Reference Table |
|---|---|---|---|
| 14.2.1.1 | Per Protocol | Boxplot of Erythrocyte Membrane Fatty Acid Composition (%) for EPA, DHA and DHA plus EPA (%) | 14.2.1.1a |
| 14.2.1.2 | Per Protocol | Boxplot of Plasma Fatty Acid Concentration (µg/mL) for Total EPA, Total DHA, and Total EPA+DHA (µg/mL) | 14.2.2.1b |
| 14.2.1.12 | Per-Protocol | Boxplot of Weight and Body Mass Index (BMI) Z-scores | 14.2.1.10 |
| 14.2.1.13 | Per-Protocol | Boxplot of Weight Gain Velocity (g/kg/30 days) | 14.2.1.11 |