Statistical Analysis Plan:

SPAN: A Phase 2, Open Label, Multicenter, **P**ilot Study to **A**ssess Safety and Efficacy of an E**n**teric Microgranule Formulation of Adrulipase in Patients with Exocrine Pancreatic Insufficiency (EPI) due to Cystic Fibrosis (CF)

Protocol Number: FWB-CF-2.03

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE 2, OPEN LABEL, MULTICENTER, PILOT STUDY TO ASSESS SAFETY AND EFFICACY OF AN ENTERIC MICROGRANULE FORMULATION OF ADRULIPASE IN PATIENTS WITH EXOCRINE PANCREATIC INSUFFICIENCY (EPI) DUE TO CYSTIC FIBROSIS (CF)

PROTOCOL NUMBER: FWB-CF-2.03

SHORT TITLE: Adrulipase in Patients with EPI Due To CF

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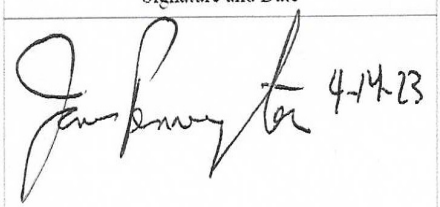 4-14-23
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VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	2023-04-13	Final version	Final version

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CDC	Centers for Disease Control
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFF	Cystic Fibrosis Foundation
CFFT	Cystic Fibrosis Foundation Therapeutics
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval(s)
CNA	coefficient of nitrogen absorption
CRF	case report form
CSR	clinical study report
EPI	exocrine pancreatic insufficiency
ICH	International Conference on Harmonisation
mITT	Modified Intent-to-treat
IP	investigational product
IR	immediate release
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PERT	pancreatic enzyme replacement therapy
PP	per-protocol
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
U	units

ULN	upper limit of normal
USP	United States Pharmacopeia

2. PURPOSE OF THE ANALYSES

The statistical analysis plan (SAP) is being developed after review of the First Wave Biopharma, Inc. (First Wave), protocol number FWB-CF-2.03 (Version 1.0), but before any analyses of the data. The SAP contains detailed information to aid in the implementation of the statistical analyses and reporting of the study data for use in the clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be analyzed, the subject characteristics parameters, the efficacy parameters, and the safety parameters that will be evaluated. The details of the specific statistical methods that will be used will be provided in this SAP. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR. Table and listing specifications are provided in a separate document.

3. PROTOCOL SUMMARY

3.1. Study Objectives

3.1.1. Primary Objectives

The Primary objective of this pilot study is to establish safety and efficacy of a new enteric microgranule formulation of adrulipase in patients with EPI due to CF.

The primary safety objective of this study is to assess the safety and tolerability of optimized dose of either 1.2 g/day, 1.95 g/day or 2.4 g/day of adrulipase provided in size 00 capsules containing ~150 mg adrulipase. Efficacy will be evaluated by comparing CFA values during treatment with patient-specific optimized dose of adrulipase versus baseline CFA obtained during screening of the patient's pre-study porcine PERT.

3.2. Overall Study Design and Plan

This is a Phase 2, single arm pilot study assessing the safety and efficacy of adrulipase in an enteric microgranule formulation. Patients with a confirmed diagnosis of cystic fibrosis who are 18 years of age or greater will be screened for eligibility if they have been clinically controlled on a stable dose of commercial pancreatic enzyme replacement therapy (PERT) for at least one month. Patients on cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies must have been on a stable dose for at least 3 months prior to study entry, and no dose changes will be made during the study. Patients receiving gastric acid suppressants must have been on a stable dose for at least one month prior to study entry and no dose changes will be made during the study. Upon obtaining an informed consent, potentially eligible patients will receive dietary counselling during the week prior to the scheduled date of confinement for collecting stool samples for calculation of baseline coefficient of fat absorption (CFA). This counselling will emphasize the importance of dietary stability during the study. Patients found to have a CFA of 80% or greater while receiving their commercial PERT and meeting the other eligibility criteria will be enrolled into the study.

Upon study enrolment, the patient will be switched from their commercial PERT to receive adrulipase. The patient will remain on study for approximately three weeks, after which a repeat CFA will be obtained. A dose titration scheme will be used for determining whether a low, medium, or high dose of adrulipase may succeed in controlling signs and symptoms of exocrine pancreatic insufficiency (EPI) and provide a CFA of 80% or greater. Patients will initially receive a low dose of adrulipase. Upon the appearance of EPI symptoms, lasting at least three days, and upon discussion with the investigator, the patient will be switched to the medium dose of adrulipase. If signs and symptoms of EPI persist for three or more days, the patient will be switched to the high dose of adrulipase. After patients reach 3 weeks of study and complete their end of study CFA, they will be returned to their pre-study commercial PERT. An end of study safety visit will be scheduled for one week after finishing adrulipase therapy.

Safety assessments will be made by collecting adverse events, safety lab assessments, and immunologic assays to assess drug induced immune responses.

3.3. Study Population

Subjects that are ≥ 18 years of age with EPI due to CF and with CFA ≥ 80% at screening while on stable PERT will be enrolled. The inclusion and exclusion criteria for the study are enumerated in Sections 8.3.2 and 8.3.3 of the protocol, respectively.

3.4. Sample Size

Based upon CFA data obtained in the recently completed Phase 2 studies (OPTION, OPTION 2), 12 patients using a dose titration scheme should provide sufficient point estimates of CFA and all other secondary efficacy endpoints. Given the acceptable safety profile obtained in the previous Phase 2 OPTION studies, a sample of 12 patients should be adequate for observation of safety.

4. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)." If a count is 0, 0% will be shown for the percentage. To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no subjects had a response in a particular category.

Continuous variables will be summarized using mean, SD, minimum, maximum, median and number of subjects. The 25th and 75th percentiles will be provided for distributions that are known to be skewed. The mean, median, 25th percentile, 75th percentile, and confidence intervals (CI) will be reported to 1 more level of precision than the original observations, and the SD will be reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.

When p-values are provided, they will be rounded to 3 decimal places; p-values that round to "0.000" will be presented as "<0.001." Unless otherwise stated, all statistical tests of treatment effects will be conducted at a 2-sided alpha level of 0.05.

All analysis will be performed using SAS® System version 9.4 or later.

Dates in listings will be displayed as yyyy-mm-dd (e.g., 2023-01-24).

The baseline value is defined as the last non- missing value on or before the first dose of study treatment.

Select displays will be presented by dose (1.2 g/day, 1.95 g/day, 2.4 g/day). Subjects will be classified by the maximum dose of adrulipase received during the study.

5. ANALYSIS SAMPLES

The following 3 analysis populations will be identified for this study:

5.1. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all enrolled patients receiving at least one dose of treatment and having at least one valid stool collection and CFA post baseline while receiving their assigned study drug.

A stool sample will be considered valid if the date and time associated with the second blue dye marker is recorded, indicating that the stool sample collection is complete.

The mITT population will be used for all analyses of efficacy endpoints.

5.2. Per-Protocol Population

The per-protocol (PP) population is a subset of the mITT population and includes all mITT subjects without major protocol deviations that could impact the efficacy analyses. Protocol deviations will be captured throughout the study and classified as minor or major prior to database lock. Each major deviation will be categorized as either important or not important with respect to the effect on the primary endpoint analysis.

Subjects who are found to be <80% compliant with adrulipase will also be excluded from the PP population. The PP population will be used as supportive to the mITT population.

Prior to database lock, the protocol deviations will be reviewed and the PP Population will be determined.

5.3. Safety Population

The safety population will include all enrolled subjects who receive at least 1 dose of treatment.

The safety population will be used for all analyses of safety endpoints unless specified otherwise and for the summaries of patients in listings related to dosing of study drug.

6. STUDY SUBJECTS

6.1. Disposition of Subjects

The disposition of subjects will be summarized for all subjects screened in the study. The following disposition information will be summarized overall:

- The number of subjects screened.
- The number of subjects who failed screening and the reason for screen failure.

All percentages will use the number of screened subjects as the denominator.

The following disposition information will be summarized for all subjects enrolled.

- The number of subjects enrolled.
- The number and percentage of subjects in the mITT population, PP population, and safety population.
- The number and percentage of subjects who completed the study (through Visit 7)
- The number and percentage of subjects who withdrew from the study and the reason for withdrawal

All percentages will use the number of enrolled subjects as the denominator.

A data listing of subject disposition for all enrolled subjects and a data listing of screen failures will also be provided.

6.2. Demographic and Other Baseline Characteristics

Subject demographics and other baseline characteristics will be summarized descriptively for the safety population for each dose (1.2 g/day, 1.95 g/day, 2.4 g/day) and overall. Summaries by dose classify subjects according to the maximum dose of adrulipase received during the study.

Demographic data will include:

- age
- sex
- race
- ethnicity

Age (years) will be age at screening, as collected on the CRF.

Baseline characteristic data will include:

- gastric acid suppression use at screening
- CFTR (cystic fibrosis transmembrane conductance regulator) modulator use at screening (yes, no)
- name of pre-study PERT

- pre-study PERT dose (lipase units/kg/day)
- weight
- height
- body mass index (BMI)
- years since diagnosis of EPI.

Descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum values) will be presented for continuous variables. For qualitative or categorical variables, the number and percentage of subjects within each category will be presented.

Individual data for demographics, baseline characteristics, and medical history will be presented in the data listings for subjects in the safety population. A data listing of any inclusion/exclusion criteria not met will also be presented for all screened subjects.

Partial missing dates will be imputed for the purposes of determining time since diagnosis of EPI as follows:

- For a partially missing diagnosis date where the day is missing, but the month and year are present, the day will be set to the first day of the month.
- For a partially missing diagnosis date where the day and the month are missing, but the year is present, the month and day will be set to January 1st.

Years since diagnosis of EPI will be calculated in years using the imputed diagnosis date and the date of screening as [(date of screening – diagnosis date)]/365.25, rounded to one decimal place.

6.3. Prior and Concomitant Medications

The prior and concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary (WHODrug) Global Version (2022-SEP) to identify the drug class and preferred drug name.

Concomitant medications will include all medications that started on or after day of first dose of the study treatment or that stopped on or after day of first dose of study treatment. Prior medications will include all medications that started and stopped prior to the day of first dose of the study treatment.

The number and percentage of subjects using prior and concomitant medications will be displayed overall and by maximum dose of adrulipase received during the study and will be tabulated by Anatomical Therapeutic Chemical (ATC) level 1 term, ATC level 2 term, and preferred drug name for all subjects in the safety population. If a subject has more than 1 medication within an ATC level 1 term, the subject will be counted only once in that ATC level 1 term. Similarly, if a subject has more than 1 medication within an ATC level 2 term, the subject will be counted only once in that ATC level 2 term. If a subject has more than 1 medication that codes to the same preferred drug name, the subject will be counted only once for that preferred drug name. All percentages will use the number of subjects in the safety

population as the denominator. The tabular summary will be sorted by descending frequency by ATC level 1 term, ATC level 2 term, and preferred drug name.

Prior and concomitant medication data will also be presented in a data listing for subjects in the safety population.

6.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 25.1. Medical history data will be listed for the safety population including the condition, start date, end date and whether the condition is ongoing.

7. STUDY OPERATIONS

7.1. Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the study team.

The number and percentage of subjects with:

- at least 1 protocol deviation;
- at least 1 major protocol deviation;
- at least 1 protocol deviation for each protocol deviation type

will be summarized overall and by maximum dose of adrulipase received during the study for the mITT population.

Line listings will be provided to the study team for the manual classification of major vs. minor protocol deviations and the FirstWave study team will confirm classification of major vs. minor at a data review meeting prior to database lock. Each major deviation will be categorized as either important or not important with respect to the effect on the primary endpoint analysis.

All subjects in the safety population having a protocol deviation and the details for the protocol deviation will be identified in a subject-level data listing. The listings will include the date of the deviation, protocol deviation type, if it was IRB reportable, date reported to IRB, any noted comments, and the deviation corrective and preventative action (CAPA).

7.2. Randomization

Not applicable.

7.3. Measures of Treatment Compliance

Treatment compliance will be summarized in terms of g/day using a compliance rate and will be displayed overall and by maximum dose of adrulipase received during the study.

The compliance rate will be calculated as:

[Actual Dose g/day / Expected Dose g/day]*100

The actual dose (g/day) a subject received will be calculated as:

[(number pills dispensed – number of pills returned)*0.15 g]/number of actual study days on adrulipase,

where the number of actual study days on adrulipase is calculated as:

((date/time of last adrulipase dose – date/time of first adrulipase dose) / 86400) + 1.

The expected dose for adrulipase depends on whether the subject titrated to a higher dose during the study, e.g. low dose (1.2 g/day), medium dose (1.95 g/day), high dose (2.4 g/day), and is calculated as:

1.2 g/(days on low dose) + 1.95 g/(days on medium dose) + 2.4 g (days on high dose)

Treatment compliance will be summarized using descriptive statistics.

As described in Section 5.2, subjects found to be <80% compliant with adrulipase will be excluded from the PP population.

Individual data for study drug (number of capsules) dispensed and returned, and treatment compliance will be listed for subjects in the mITT population. a

Note that since capsules are dispensed at one visit and returned at one visit (e.g. not separately b

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

All safety analyses will be performed using the safety population.

Safety measures summarized will include AEs, laboratory data, and vital signs. Additionally, exposure to study treatment during the study will be displayed.

Key adverse event summaries will also be presented by dose as described in Section 8.3.

Safety data will not be imputed, except for partial and missing dates, which will be imputed only for defining treatment-emergent AEs (TEAEs) and concomitant medications. Imputed dates will not be presented in data listings.

TEAEs will be defined as any AEs that occur or are reported to worsen in severity on or after the date of first dose of study treatment. Partial dates will be imputed for the purposes of defining TEAEs as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless 1) the first day of the month is before the date of first dose of study treatment and the month and year are the same as the month and year of the date of first dose of study treatment, and 2) the end date is on or after the date of first dose of study treatment or the end date is completely missing, in which case the start day will be set to the first day of first dose of study treatment.
- For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless 1) January 1st is before the date of first dose of study treatment and the year is the same as the year of the date of first dose of study treatment, and 2) the end date is on or after the date of first dose of study treatment or the end date is completely missing, in which case the start day and month will be set to that of the date of first dose of study treatment.
- For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the subject, in which case the end day will be set to that of the subject's last contact date.
- For a missing end day and month where the year is present, the end day and month will be set to the subject's last contact date, unless the year of the subject's last contact date is greater than the end year, in which case the end day and month will be set to December 31st.

Partial and completely missing dates will be imputed for the purposes of classifying concomitant medications as follows:

- Partial dates will be imputed following the same algorithm as above for TEAEs.

- For a missing start date (i.e., day, month, and year are missing), the start date will be set to the date of first dose of study treatment, unless the stop date is prior the date of first dose of study treatment, in which case the start date will be set to the stop date.

- For a missing stop date (i.e., day, month, and year are missing), the medication will be treated as ongoing.

8.2. Extent of Exposure

The following summaries will be displayed overall and by maximum dose of adrulipase received during the study.

Time on treatment (days) will be calculated as: date of last dose of study drug – date first dose of study drug + 1. Time on treatment will be summarized using descriptive statistics for subjects in the safety population. Time on treatment will also be displayed separately for each dose (e.g. time on low dose [1.2 g/day], time on medium dose [1.95 g/day], time on high dose [2.4 g/day].

For each dose, whether the subject started dosing at that dose level, reason for dose increase (for doses after initial dose), and date/time of first and last dose at that dose level will be listed for all subjects in the safety population.

8.3. Adverse Events

Summaries will be presented overall and by dose. Subjects are classified by maximum dose of adrulipase received during the study.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 to identify the system organ class and preferred term.

Adverse events that occur or are reported to worsen in severity on or after date of first dose of study treatment will be considered TEAEs. Adverse events that occurred after the end date of the end of the treatment period will be classified as follow-up adverse events.

TEAEs will be summarized for all subjects in the safety population. The total number of TEAEs occurring will be shown. The number and percentage of subjects experiencing any TEAE will also be provided. In addition, summary tables will reflect a count and percentage of subjects experiencing at least 1 TEAE in each system organ class and preferred term. All percentages will use the number of subjects in the safety population as the denominator. Therefore, if a subject has more than 1 AE within a system organ class, the subject will be counted only once in that system organ class. If a subject has more than 1 AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Tabular summaries will be sorted by descending frequency by system organ class and by preferred term.

TEAEs will also be summarized by maximum relationship to study drug and maximum severity. Relationship to study treatment will be scored as Related or Unrelated. Severity will be rated as Mild, Moderate, or Severe. Summary tables will reflect a count and percentage of subjects experiencing at least 1 TEAE in each system organ class, preferred term and either relationship or severity. If a subject experiences more than 1 AE within a system organ class or preferred term, that subject will be counted only once for that event under the maximum severity or most

related category for the study drug. Similarly, if relationship or severity data are missing, the study analysis will follow the assumption of maximum relationship or severity in the summary tables. These summaries will be presented with percentages that use the number of subjects in the safety population as the denominator. The tabular summaries will be sorted by descending frequency by system organ class and by preferred term.

AE duration (days) is calculated as AE end date – AE start date + 1. Imputed AE start dates and imputed AE end dates as defined in Section 8.1 are used in the case of partially missing dates. AE duration will be presented in the listings.

All AEs will be presented in data listings for subjects in the safety population.

8.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Summaries will be presented overall and by dose. Subjects are classified by maximum dose of adrulipase received during the study.

Treatment-emergent SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation and TEAEs resulting in death will be summarized for all subjects in the safety population.

Summary tables will reflect a count and percentage of subjects experiencing at least 1 TEAE in each system organ class and preferred term within each AE subset (serious, leading to treatment discontinuation, leading to study discontinuation, resulting in death). These tabular summaries will be sorted by descending frequency by system organ class and by preferred term.

SAEs, adverse events leading to treatment discontinuation, adverse events leading to study discontinuation, and AEs resulting in death will be presented in data listings for subjects in the safety population.

8.5. Clinical Laboratory Evaluation

All summaries except for the shift tables will be presented overall and by dose. Subjects are classified by maximum dose of adrulipase received during the study.

Values at Screening (Visit 1) and at 3 weeks post first dose, as described in Section 3, for laboratory parameters for hematology, clinical chemistry, and urinalysis will be summarized for the safety population using descriptive statistics.

Shift tables based on classification of values with respect to the reference range (low, normal, high) will be summarized for the safety population for critical clinical chemistry and hematology laboratory tests.

Post-baseline elevations in alanine aminotransferase (≥3 times the upper limit of normal [ULN]), aspartate aminotransferase (≥3 times ULN), total bilirubin (≥1.5 times ULN) will be summarized at Screening and at 3 Weeks Post First Dose. Hematology, clinical chemistry, hepatic monitoring, urinalysis, lipids, and pregnancy results will be presented in data listings for subjects in the safety population.

8.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.6.1. Vital Signs

Summaries will be presented overall and by dose. Subjects are classified by maximum dose of adrulipase received during the study.

Values at Screening (Visit 1), Screening (Visit 2, during supervised confinement), and at 3 Weeks Post First Dose (Visit 6), as described in Section 3, of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature will be summarized for the safety population using descriptive statistics.

Vital sign values will be presented in a data listing for all subjects in the safety population.

8.6.2. Physical Examinations

A focused physical examination evaluating gastrointestinal tract, heart, and lungs will be performed at study visits 2, 6, and 9. An indication of whether the examination was performed (yes/no), date of the examination, and an indication of whether abnormal findings that were clinically significant were found (yes/no) will be collected. Because details of clinically significant abnormal findings will be entered on the medical history or AE form as appropriate, this data will be summarized with medical history and AEs, respectively.

9. ENDPOINT EVALUATION

9.1. Overview of Efficacy Analysis Methods

9.1.1. Multicenter Studies

Data from all sites will be pooled for the purpose of analyses.

9.1.2. Assessment Time Windows

No assessment time windows will be used for analyses.

9.1.3. Timing of Analyses

The final analysis will occur after last subject completes Visit 7 (follow-up) or terminates early from the study.

9.1.4. Multiple Comparisons/Multiplicity

No statistical testing is planned for the efficacy endpoints for this single arm study. Thus, no adjustments are needed for multiplicity.

9.2. Primary Endpoint

The primary endpoint analyses will be presented overall and by dose. Subjects are classified by maximum dose of adrulipase received during the study.

9.2.1. Computation of the Primary Endpoint

The primary efficacy endpoint is defined as the CFA assessed at the end of the 3-week treatment period (Visit 6, on adrulipase). CFA is evaluated by the 72-hour marker-to-marker stool sample collection at Visit 6 and standardized high-fat diet during supervised confinement. Coefficient of fat absorption represents the percentage of fat absorbed from the diet by the subject and is calculated from the results of the quantitative fecal fat measurement in conjunction with the dietary fat intake.

CFA will be calculated by using 2 data points:

- Fat consumption in grams/24h (converted from fat consumption in grams/72h as provided by the qualified dietician at each site).
- Fat excretion in grams/24h as provided by the central laboratory.

CFA will be calculated as follows:

$$\frac{\text{(Grams/24h of fat consumed – Grams/24h of fat excreted) x 100}}{\text{Grams/24h of fat consumed}}$$

9.2.2. Primary Analysis of the Primary Endpoint

The primary analysis of the primary endpoint will be a comparison of the mean CFAs from the adrulipase treatment vs the PERT treatment (screening), using descriptive statistics. The primary efficacy endpoint analysis will use the mITT population. For the summary of CFA, if a subject switches back to PERT during the confinement period, prior to the end of the stool collection, then the CFA value will be excluded from the summary.

Values and change from baseline (Visit 2, on PERT) to end of treatment (Visit 6, on adrulipase) in stool weights will be summarized using descriptive statistics. Summaries will be performed for the overall group and by maximum dose of adrulipase received using descriptive statistics.

In addition, the number and percentage of subjects in the mITT population who have a CFA ≥ 80% based on the CFA at week 6 (3-week post dose) will be summarized.

Fat consumed (g/24h), fat excreted (g/24h), and CFA (%) at each visit as well as CFA change from baseline to end of treatment will be listed for all subjects in the mITT population.

Details of each supervised confinement, including controlled diet and marker-to-marker stool collection, will be listed for all subjects in the mITT population.

9.2.3. Secondary Analyses of the Primary Endpoint

A secondary (supportive) descriptive summary of the primary efficacy measure will be provided using the per-protocol population.

9.2.4. Sensitivity Analyses of the Primary Endpoint (Best Case/Worst Case Scenarios)

The primary analysis is based on the mITT population which requires a post-baseline CFA. A subject could receive adrulipase but dropout without providing a valid stool collection for a CFA. Reasons for dropout could be related to lack of symptom control indicating a failure or could be due to reasons unrelated to treatment.

The descriptive summary of CFA ≥ 80% (yes/no) at week 6 (3-week post dose) will be repeated in the safety population (1) assigning dropouts as ‘yes’ [best case scenario], and separately (2) assigning dropouts as ‘no’ [worst case scenario].

9.3. Secondary Endpoints

All secondary endpoint analyses except for the shift table of malabsorption signs and symptoms will be presented overall and by dose. Subjects are classified by maximum dose of adrulipase received during the study.

9.3.1. Stool Weight

Stool weight during the 72-hour marker-to-marker stool collections will be evaluated at Screening (Visit 2) and at the end of Treatment (Visit 6). All collected stool will be shipped to

the central lab for determination of the stool weight as described under the primary efficacy measure.

Stool weight will be analyzed from stool samples collected during the 2 scheduled confinements (Visit 2 and Visit 6).

Change from baseline (Visit 2, on PERT) to end of treatment (Visit 6, on adrulipase) in stool weights will be summarized using descriptive statistics. If a subject switches to PERT during the confinement period, prior to the end of the stool collection, then the stool weight value during that confinement period will be excluded from the summary.

If a subject has more than one stool weight record for a given visit (Visit 2 or Visit 6) and the correct value is unknown, only the heaviest value will be included in the summary.

Stool weight at each visit and change from baseline to end of treatment will be listed for all subjects in the mITT population.

9.3.2. Malabsorption signs and symptoms

Signs and symptoms of malabsorption will be evaluated at Visits 2, 3, 4, 5, 6, and 7.

The EPI malabsorption symptoms will be evaluated according to the following measures:

- Stool frequency (number of bowel movements per day);
- Stool consistency (graded as 0 = hard, 1 = formed/normal, 2 = soft, 3 = watery, or 4 = overt diarrhea);
- Bloating (graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe);
- Abdominal pain (graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe);
- Flatulence (graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe);
- Incidences of visible oil/grease in stool (Yes/No).
- Increased stool quantity (graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe); and
- Worsening of overall bowel habit (graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe).

Stool frequency will be summarized for the mITT population using descriptive statistics. Stool frequency will be summarized at Visit 2 (Screening, on PERT), At First Dose (Visit 3), 1 Week Post First Dose, 2 Weeks Post First Dose, 3 Weeks Post First Dose, and End of Study/Early Termination (Visit 7).

The number and percentage of subjects within each category for stool consistency, bloating, abdominal pain, flatulence, incidence of visible oil/grease in stool, increased stool quantity, and worsening of overall bowel habit at each study visit will also be provided at Visit 2 (Screening, on PERT), At First Dose (Visit 3), 1 Week Post First Dose, 2 Weeks Post First Dose, 3 Weeks Post First Dose, and End of Study/Early Termination (Visit 7).

Shifts from Visit 2 will be presented for stool consistency, bloating, abdominal pain, flatulence, increased stool quantity, and worsening of overall bowel habit for the mITT population. This shift table for malabsorption signs and symptoms will also be presented by whether a subject achieved CFA ≥ 80% at 3 weeks post-dose (yes/no).

Signs and symptoms of malabsorption will be listed for all subjects in the mITT population.

9.3.3. Coefficient of Nitrogen Absorption

CNA at Screening (Visit 2, on PERT) and at the end of the 3-week treatment period (Visit 6, on adrulipase) will be analyzed.

CNA will be expressed as the percentage of nitrogen (protein) absorbed from the subject's diet.

CNA will be calculated using 2 data points:

- Nitrogen consumption in grams/24h (converted from fat consumption in grams/72h as provided by the qualified dietician at each site)
- Nitrogen excretion in grams/24h as provided by the central laboratory

CNA will be calculated as follows:

$$\frac{\text{(Grams/24h of nitrogen consumed – Grams/24h of nitrogen excreted) x 100}}{\text{Grams/24h of nitrogen consumed}}$$

Values and change from baseline (Visit 2, on PERT) to end of treatment (Visit 6, on adrulipase) in CNA will be summarized using descriptive statistics. For the summary of CNA, if a subject switches back to PERT during the confinement period, prior to the end of the stool collection, then the CNA value will be excluded from the summary. Missing CNA values will not be imputed.

A secondary (supportive) descriptive summary of CNA will be provided using the per-protocol population.

Nitrogen consumed (g/24h), nitrogen excreted (g/24h), and CNA (%) at each visit as well as CNA change from baseline to end of treatment will be listed for all subjects in the mITT population.

9.3.4. Body Weight and BMI

Body weight and BMI will be evaluated at Visits 1, 2 and 6.

Values and change from baseline in body weight and BMI will be summarized for the mITT population using descriptive statistics.

Body weight and BMI will be listed by visit for all subjects in the mITT population.

9.4. Examination of Subgroups

No subgroups are of interest for this study.

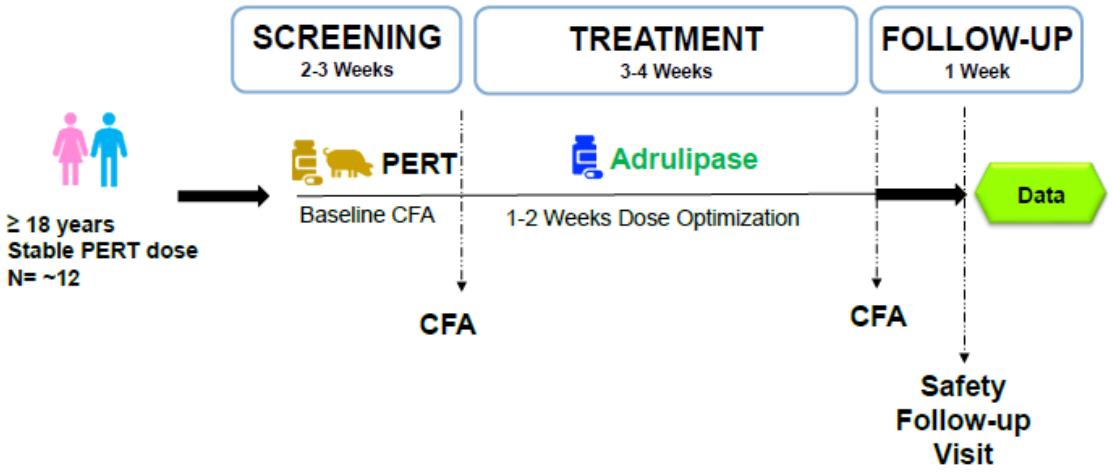
10. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

11. APPENDIX

11.1. Study Flow Chart



11.2. Schedule of Events

	SCREENING		ADRULIPASE TREATMENT				END OF
	Consent and Initial Evaluations	CFA on PERT	Dispense	Optimize	Optimize	CFA on Adrulipase	STUDY/EARLY TERMINATION
Visit Number	1[a]	2[b]	3	4 (T)[c]	5 (T)[c]	6[b]	7
Study Week	-3	-2	1	2	3	4	5
Study Days	-21	-14	0	5	10	16	28
Visit Window (days)	+7	±7	±2	±2	±2	+5	±7
Pre-Visit Instructions	X	X		X	X		
Supervised confinement		X				X	
Clinical Assessments							
Obtain informed consent	X						
Demographics	X						
Complete history and physical	X						
Focused physical exam[d]		X				X	X
Confirm CF diagnosis (Inclusion Criteria 4)	X						
Height/weight, vital signs (sitting)	X	X				X	
Inclusion/exclusion criteria review	X	X	X				
Concomitant medications	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

Confirm scheduled date for next supervised confinement visit	X				X		
Study Treatment							
Instruct regarding study drug Adrulipase (dose optimization, low, medium, or high)			X			X	
Full study drug accountability at the end of confinement						X	
Return Adrulipase at the end of confinement						X	
Record fat and protein intake and study drug taken at all meals and snacks			X			X	
Efficacy Measures							
Malabsorption signs & symptoms		X	X	X	X	X	X
72-hour controlled diet record		X				X	
Marker-to-marker stool collection and stool weight[f]		X				X	
Laboratory Tests							
Urinalysis	X					X	
Pregnancy test (serum for V1 screening and urine dipstick for other visits)[g]	X		X			X	X
Hematology, clinical chemistry, PT/INR, and aPTT [h]	X					X	
Fasting[i] lipids (patient to come in fasting status) and pre-albumin	X					X	

Serum samples for anti-adrulipase lipase antibodies and adrulipase concentrations		X				X	X
Fecal pancreatic elastase[j]	X						
Diagnostic Test							
Spirometry	X						
Switch back to Prescribed Porcine PERT							
Switch back to prescribed porcine PERT[k]						X	X

a Screening procedures can occur up to 14 days before the first day of supervised confinement (V2). As some lab assessments require fasting status, site may utilize a pre-screening telephone consent process to obtain agreement in advance for patients to adhere fasting for at least 8 hours. Patients will also be asked to bring a stool sample to V1

b Visit 2 and Visit 6 are the first and second scheduled confinement visits and can take up to 7 days. A 5-day window is permitted around the scheduled confinement for both V2 and V6 to accommodate for scheduling. Dosing must have occurred for at least 16 days prior to the start of the scheduled confinement.

c Visits 4 and 5 are telephone visits to assess any changes to AEs and concomitant medications in addition to confirming the visit date for the next scheduled supervised confinement.

d The Focused Physical Exam will evaluate gastrointestinal tract, heart, and lungs.

e At the end of V6 (after the last stool sample has been collected), Patients will begin treatment with their prestudy porcine PERT.

f The stool samples will be sent to the central laboratory and CFA, CNA, and stool weight will be measured.

g A serum pregnancy test must be conducted in females of reproductive potential at screening Visit 1. Pregnancy status will be re-evaluated via urine pregnancy test in these Patients at Visit 3, 6 and at the End-of-Study or Early Termination visit (Visit 7).

h On the basis of laboratory safety values, unscheduled hepatic monitoring testing may be performed in patients with new, clinically meaningful increases in liver function tests occurring during the study, in consultation with study designated Medical Monitor. These tests are to be done through the central labs.

i Fasting labs should be taken after patients have been in a fasting status for at least 8 hours at Visits 1 and 6.

j Fecal pancreatic elastase will be collected at Visit 1 and sent for analysis to the central laboratory.

k At the end of the supervised confinement (once the second blue dye marker sample has been collected), patients will return to their prestudy porcine PERT dose.