STATISTICAL ANALYSIS PLAN
21 May 2021
FINAL 1.0

A Phase 2, Open-Label, Multicenter, 2x2 Crossover Trial to assess the Safety and Efficacy of MS1819 in Enteric Capsules in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis; with an Extension Phase Evaluation of Immediate Release MS1819 Capsules

OPTION 2 Study
PROTOCOL NUMBER AZ-CF2002

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
0.1	22 January 2021	Draft 1 Creation
0.2	21 April 2021	Draft 2
1.0	21 May 2021	Final Version 1.0

APPROVALS

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LIST OF ABBREVIATIONS

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
DSMB	data safety monitoring board
EP	extension phase
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

1. PURPOSE OF THE ANALYSES

The statistical analysis plan (SAP) is being developed after review of the AzurRx Biopharma, Inc. (AzurRx), protocol number AZ-CF2002, 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.

2. PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of this study are to assess the safety and efficacy of MS1819 in enteric capsules vs porcine pancreatic enzyme replacement therapy (PERT) in patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF).

The primary safety objective of the study is to assess the safety and tolerability of doses of 2240 mg/day and 4480 mg/day of MS1819 provided in enteric capsules. The primary efficacy objective of the study is to assess the efficacy of MS1819 in enteric capsules vs. PERT.

2.1.2 Secondary Objectives

To evaluate and compare effects of MS1819 in enteric capsules and porcine PERT on other measures of digestion including the coefficient of nitrogen absorption (CNA), stool weight, body weight, body mass index (BMI), signs and symptoms of malabsorption, and serum liposoluble vitamins A, D, E, and K.

2.1.3 Exploratory Objective

The exploratory objective of the extension phase (EP) is to find a dose of MS1819 in immediate release capsules that is safe and results in CFA values in a therapeutic range.

2.2 Overall Study Design and Plan

This is a Phase 2, open-label, multicenter, 2, 2x2 crossover study assessing the safety and efficacy of MS1819, 2240 mg/day vs porcine PERT, and 4480 mg/day vs porcine PERT given at the same dose and dosing regimen that was being administered during the pre-study period. MS1819 will be administered in enteric capsules.

MS1819 will be first assessed in a 2x2 crossover including approximately 30 patients completing both periods. Fifteen patients will be randomized to the MS1819 2240 mg/day vs PERT arm, and 15 patients will be randomized to the MS1819 4480 mg/day vs PERT arm. Patients in each arm will further be randomized to receive either the sequence consisting of MS1819 for 3 weeks followed by PERT for another 3 weeks or the opposite sequence of treatments, PERT for 3 weeks followed by MS1819 for another 3 weeks.

Randomized patients will be males or females,18 years or older. Safety (adverse events [AEs], serious adverse events [SAEs], discontinuations due to adverse events, and safety laboratory values) will be assessed by descriptive methods. The primary efficacy endpoint is the coefficient of fat absorption (CFA) that will be assessed at the end of the 3-week period of treatment for each 2x2 crossover.

Patients enrolled into the extension phase (EP) will be composed of patients who have completed the crossover phase of OPTION 2. These patients must continue to comply

with the same inclusion and exclusion criteria as used in the crossover phase of the OPTION 2 trial (some screening tests may need to be repeated and all subjects must have completed an End of Study visit in the crossover phase).

Concomitant medications will be allowed as in the crossover phase. The Drug Product, immediate release capsules (MS1819 IR) each containing 140 mg of MS1819, will be the same as used in a previous OPTION trial (AZ-CF2001) of MS1819 in patients with EPI due to CF.

The EP will first enroll 9 patients, each receiving 4.4 grams/day of MS1819, for two weeks. At the end of 2 weeks, patients will enter confinement for a controlled diet, stool collection and CFA measurement. Data will be analyzed using descriptive statistics. Based upon resulting CFA and safety data, 5 additional patients may be enrolled at the 4.4 grams/day dose to better characterize the CFA following encouraging results from the initial 9 patients. If safety is satisfactory and the CFAs do not achieve values considered to be in the therapeutic range, 9 more patients will be enrolled and dosed at 6.7 grams/day for 2 weeks. These 9 patients may be patients who have participated in the 4.4 grams/day dose evaluation, as described above, or may be new patients from the OPTION 2 crossover phase. After treatment with MS1819 IR 6.7 grams/day for 2 weeks is completed, CFAs will be measured, and data assessed as before. Depending on safety and CFA analysis, either another 5 patients will be enrolled to better characterize encouraging initial results, or the study will be terminated.

Safety will be evaluated by the DMC Chairperson after the initial 9 patient phase of 4.4 grams/day, and again after the initial 9 patient phase of 6.7 grams/day, should that dose be studied.

A study flow chart is presented in Appendix 13.1 for the crossover phase and 13.2 for the extension phase, and a schedule of events is presented in Appendix 13.3 for the crossover phase and 13.4 for the extension phase.

2.3 Study Population

Subjects that are ≥18 years of age with EPI due to CF will be enrolled. The inclusion and exclusion criteria for the study are enumerated in Sections 7.3.2 and 7.3.3 of the protocol, respectively.

2.4 Treatment Regimens

At randomization for the crossover phase, subjects will be assigned in a 1:1:1:1 ratio to one of four arms:

- MS1819 (2240 mg/day) followed by prestudy porcine PERT
- Prestudy porcine PERT followed by MS1819 (2240 mg/day)
- MS1819 (4480 mg/day) followed by prestudy porcine PERT
- Prestudy porcine PERT followed by MS1819 (4480 mg/day)

MS1819 will be administered in enteric capsules for the crossover phase. Subjects will receive the same dose of PERT that was being administered during the prestudy period while in the porcine PERT period of their treatment sequence.

The extension phase will enroll patients as follows:

- 9 patients will be enrolled initially, each receiving 4.4 grams/day of MS1819 IR
- Based on resulting CFA data, 5 additional patients may be enrolled, each receiving 4.4 grams/day of MS1819 IR
- If safety in the 4.4 grams/day dose is found to be satisfactory and the CFAs do not achieve values in the therapeutic range, 9 patients will be enrolled, each receiving 6.7 grams/day of MS1819 IR
- Based on resulting CFA data, 5 additional patients may be enrolled, each receiving 6.7 grams/day of MS1819 IR

MS1819 will be administered in IR capsules for the extension phase.

2.5 Treatment Group Assignments or Randomization

Subjects who meet all of the enrollment criteria will be randomized to receive MS1819 (2240 mg/day) followed by PERT, PERT followed by MS1819 (2240 mg/day), MS1819 (4480 mg/day) followed by PERT, or PERT followed by MS1819 (4480 mg/day) using a 1:1:1:1 allocation ratio. MS1819 will be administered in enteric capsules.

The extension phase will include subjects that completed the crossover phase and will not be randomized. Subjects participating the extension phase will receive either the 4.4 grams/day or 6.7 grams/day dose of MS1819 IR capsules, depending on the part of the extension phase that subject is participating in, as detailed in the extension phase flow chart in Appendix 12.2.

2.6 Sample Size Determination

The primary objectives of this study are to assess the safety and efficacy of MS1819 in enteric capsules vs PERT in patients with EPI due to CF. The exploratory objective of the extension phase is to find a dose of MS1819 in immediate release capsules that is safe and results in CFA values in a therapeutic range. The sample size was selected to be sufficient to address the safety objectives of this trial.

Based upon CFA data obtained in the recently completed Phase 2a trial (OPTION), 15 patients per MS1819 dose should provide sufficient point estimates of CFA in each group in the crossover phase. Given the acceptable safety profile obtained in the OPTION trial a sample of 15 patients should be adequate for the observation of safety per dose of MS1819. This study will use descriptive analyses for both safety and efficacy analyses.

Likewise, in the EP, sample sizes are estimates based upon prior studies of similar design with CFA and safety endpoints.

3. 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 9.3 or later.

Dates in listings will be displayed as yyyy-mm-dd (e.g., 2015-01-24).

Separate displays will be produced for each crossover phase dose (2240 mg/day, 4480 mg/day) and each extension phase dose (4.4 grams/day, 6.7 grams/day), unless otherwise stated.

For the crossover phase, in order to present summaries by treatment group regardless of sequence, the following parameters will be summarized as described below: safety laboratory, vital signs, signs and symptoms of malabsorption, weight, BMI, and serum liposoluble vitamins A, D, E, and K. These endpoints will be summarized relative to the time of first dose on a given study treatment. All post-randomization measurements will be relative to the time of the first dose. For example, in the MS1819 treatment column, the measurement at first dose will be Visit 3 if a subject is randomized to the MS1819-PERT sequence, and Visit 6 if a subject is randomized to the PERT-MS1819 sequence.

4. ANALYSIS POPULATIONS

The following 3 analysis populations will be identified for this study for each the crossover phase and the extension phase:

4.1 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population for the crossover phase includes all randomized 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..

The mITT population for each stage of the extension phase includes all enrolled patients receiving at least one dose of treatment and having a valid stool collection and CFA during the relevant stage of the extension phase.

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 efficacy analyses. Subjects will be analyzed according to the treatment group to which they were randomized for the crossover phase, regardless of the actual treatment received, unless stated otherwise.

4.2 Per-Protocol Population

The per-protocol (PP) population for the crossover phase is a subset of the mITT population of the crossover phase and includes all mITT subjects without major protocol deviations that could impact the efficacy analyses. Subjects who are found to be <80% compliant with MS1819 during the crossover phase will be excluded from the PP population. The PP population will be used as supportive to the mITT population. Subjects will be included in the treatment sequence to which they were randomized regardless of the actual treatment sequence received.

The PP population for each stage of the extension phase is a subset of the mITT population of the extension phase and includes all mITT subjects without major protocol deviations that could impact the efficacy analyses. Subjects who are found to be <80% compliant with MS1819 during the relevant stage of the extension phase will 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 for each phase.

4.3 Safety Population

The safety population for the crossover phase, which will be used for all safety analyses of the crossover phase unless stated otherwise, will include all randomized subjects who receive at least 1 dose of treatment. Subjects in the safety population will be analyzed according to the actual treatment received regardless of their randomized assignment.

The safety population for each stage the extension phase, which will be used for all safety analyses of the extension phase unless stated otherwise, will include all subjects that enroll into the extension phase and receive at least 1 dose of treatment in the relevant stage of the extension phase.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Disposition will be summarized separately for each dose of the crossover phase and each dose of the extension phase, unless stated otherwise.

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 by treatment sequence for all subjects randomized in the study for the crossover phase:

- The number of subjects randomized.
- The number and percentage of subjects in the mITT population, PP population, and safety population.
- The number and percentage of subjects who completed the first treatment period (through Visit 6)
- The number and percentage of subjects who withdrew from the first treatment period and the reason for withdrawal
- The number and percentage of subjects who completed the second treatment period (through Visit 9)
- The number and percentage of subjects who withdrew from the second treatment period and the reason for withdrawal
- The number and percentage of subjects who completed the study (through Visit 10)
- The number and percentage of subjects who withdrew from the study and the reason for withdrawal

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

A data listing of subject disposition for all randomized subjects and a data listing of screen failures will also be provided for the crossover phase.

The following disposition information will be summarized for all subjects in the extension phase:

- The number and percentage of subjects in the mITT population, PP population, and safety population
- The number and percentage of subjects who were treated in the 2240 mg/day dose of the crossover phase

- The number and percentage of subjects who were treated in the 4480 mg/day dose of the crossover phase
- The number and percentage of subjects who were treated in both the 4.4 grams/day stage and the 6.7 grams/day stage of the extension phase
- The number and percentage of subjects who were treated in the 4.4 grams/day stage and not the 6.7 grams/day stage of the extension phase (4.4 grams/day summary only)
- The number and percentage of subjects who were treated in the 6.7 grams/day stage and not the 4.4 grams/day stage of the extension phase (6.7 grams/day summary only)
- The number and percentage of subjects who completed the extension phase treatment period
- The number and percentage of subjects who withdrew from the extension phase treatment period
- The number and percentage of subjects who completed the extension phase of the study (through Visit 17)
- The number and percentage of subjects who withdrew from the extension phase of the study and the reason for withdrawal

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

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

5.2 Protocol Deviations

Protocol deviations will be summarized separately for each dose of the crossover phase (by treatment sequence) and each dose of the extension phase.

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 for the mITT population. For subjects that participated in both the crossover phase and the extension phase of the study, any protocol deviation that occurred prior to the start date of the extension phase will be summarized in the crossover phase. Any protocol deviation that occurred on or after the start date of the extension phase will be summarized in the extension phase.

Line listings will be provided to the study team for the manual classification of major vs. minor protocol deviations and the AzurRx 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 for the crossover phase.

All subjects in the mITT 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).

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Subject demographics and other baseline characteristics will be summarized descriptively by treatment sequence and overall for the mITT population separately for each of the doses in the crossover phase, and for each of the doses for the mITT population in the extension phase. The demographic and baseline characteristic summaries will be used to describe the study population as well as to check for balance among the treatment groups.

Demographic data for both the crossover and extension phases will include age, sex, race, and ethnicity. Age (years) will be age at screening, as collected on the CRF.

Baseline characteristic data for the crossover phase will include gastric acid suppression use at randomization, CFTR (cystic fibrosis transmembrane conductance regulator) modulator use at randomization (yes, no), name of pre-randomization PERT, pre-randomization PERT dose (lipase units/kg/day), weight, height, body mass index (BMI), and years since diagnosis of EPI. Pre-randomization PERT dose (lipase units/kg/day) will also be summarized by region.

Baseline characteristic data for the extension phase will include gastric acid suppression use at randomization, CFTR (cystic fibrosis transmembrane conductance regulator) modulator use at the start of the extension phase (yes, no), name of PERT used at the start of the extension phase, PERT dose at the start of the extension phase (lipase units/kg/day), weight at the start of the extension phase, height at the start of the extension phase, body mass index (BMI) at the start of the extension phase, and 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 mITT 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 randomization as [(date of randomization – diagnosis date)]/365.25, rounded to one decimal place.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance will be summarized separately for each dose of the crossover phase and each dose of the extension phase.

For the crossover phase, treatment compliance will be summarized for MS1819 in terms of mg/day using a compliance rate. Given that subjects were to take the dose associated with their pre-study PERT during treatment with PERT, detailed pill information was not collected and thus compliance rate for PERT will not be summarized.

The compliance rate for MS1819 for the crossover phase will be calculated as:

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

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

[(number pills dispensed – number of pills returned)*280 mg]/number of actual study days on MS1819 in the crossover phase,

where the number of actual study days on MS1819 is calculated as:

((date/time of last MS1819 dose – date/time of first MS1819 dose) / 86400) + 1.

The expected dose for MS1819 is either 2240 mg/day or 4480 mg/day, depending on the randomized treatment assignment.

Treatment compliance will be summarized by each study period and overall for MS1819 using descriptive statistics.

As described in Section 4.2, subjects found to be <80% compliant with MS1819 during the crossover phase will be excluded from the PP population for the crossover phase.

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

For the extension phase, treatment compliance will be summarized for MS1819 in terms of mg/day using a compliance rate.

The compliance rate for MS1819 for the extension phase will be calculated as detailed above, replacing 280 mg with 140 mg for the dose of each capsule.

The expected dose for MS1819 is either 4480 mg/day (4.4 grams/day) or 6720 mg/day (6.7 grams/day), depending on the stage of the extension phase.

Treatment compliance will be summarized for the extension phase using descriptive statistics.

As described in Section 4.2, subjects found to be <80% compliant with MS1819 during a given stage of the extension phase will be excluded from the PP population for that stage of the extension phase.

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

8. SAFETY EVALUATION

8.1 Overview of Safety Analysis Methods

Unless otherwise stated, safety analyses will be presented separately for each dose of the crossover phase and each dose of the extension phase. For the crossover phase, all safety analyses will be performed using the safety population and summarized by actual treatment (MS1819 regardless of period vs. PERT regardless of period) allowing direct intrasubject comparison of the tolerability of MS1819 vs. PERT. For the extension phase, all safety analyses will be performed using the safety population and summarized for each dose. Safety measures summarized will include AEs, laboratory data, vital signs, and concomitant medications. Additionally, exposure to study treatment during the study will be displayed.

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 in crossover phase period 1. 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.

To categorize events with partial dates into their associated treatment periods, the imputation rules above will be defined relative to the first dose of the treatment period of interest separately (first treatment period of crossover, second treatment period of

crossover, 4.4 grams/day dose stage of the extension phase, 6.7 grams/day dose stage of the extension phase), as applicable. Thus, in the aforementioned rules, 'study treatment' refers to the treatment in the specified treatment period. Per the imputation rules, events with partial dates may require multiple imputed start dates to account for each treatment period. For example, an event with missing start day where the start month is the same as the treatment start month for both study treatments of the crossover period will have the start date imputed to both the treatment start date of the first crossover study period and the treatment start date of the second crossover study period.

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 for each period (first treatment period of crossover, second treatment period of crossover, first dose period of the extension phase, second dose period of the extension phase), as applicable, unless the stop date is prior the date of first dose of study treatment for a given period, 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

Time on treatment (weeks) will be calculated as (date of last dose of study drug – date first dose of study drug + 1)/7. Time on treatment will be summarized by treatment group for each period using descriptive statistics for all subjects in the safety population for the crossover phase. Time on treatment will be summarized using descriptive statistics for all subjects in the safety population for each dose in the extension phase. For subjects that paticipated in both the 4.4 grams/day period and the 6.7 grams/day period of the extension phase, time on treatment will also be summarized across both doses. Total time on treatment for MS1819 (across both doses of each the crossover phase and the extension phase) will also be summarized.

The date and time of the first and last dose of each study period will be presented in a data listing for all subjects in the safety population for each dose in the crossover phase. The date and time of the first and last dose will be presented in a data listing for all subjects in the safety population for each dose in the extension phase.

8.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 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 in crossover phase period 1 will be considered to be TEAEs.

TEAEs will be categorized as occurring in a given study period according to the following rules:

- Adverse events that occur or are reported to worsen in severity on or after date and time of start of crossover period 1 study treatment and on or before date and time of end of crossover period 1 study treatment will be attributed to crossover study period 1. Adverse events that occur or are reported to worsen in severity on the start date of crossover period 1 study treatment that do not have a time associated with the event will be attributed to crossover study period 1.

- Adverse events that occur or are reported to worsen in severity after the end date of crossover period 1 study treatment and on or before the date of end of crossover period 2 study treatment will be attributed to crossover study period 2. Adverse events that occur or are reported to worsen in severity on the date of end of crossover period 2 study treatment that do not have a time associated with the event will be attributed to crossover study period 2.

- Adverse events that occur on the crossover date between crossover study period 1 and crossover study period 2 that do not have a time associated with the event will be attributed to crossover study period 1.

- Adverse events that occur in both crossover study period 1 and crossover study period 2 will be attributed to both crossover study periods.

- Adverse events that occurred after the subject's last crossover study period will be classified as follow-up adverse events. If a subject entered both the first and second study periods, events occurring after the end date of the second study period will be considered as follow-up. If a subject discontinued prior to the start of the second crossover study period, any event occurring after the end date of the first crossover study period will be considered as follow-up. For subjects that did not enroll in the extension phase, any adverse event following the last crossover study period will be categorized as follow-up adverse events of the crossover phase. For subjects that did enroll in the extension phase, adverse events that occurred after the last crossover study period but before the start of the extension phase will be categorized as follow-up adverse events of the crossover phase.

The same period categorization rules will apply for the extension phase, where applicable, with the following exception. For the extension phase, if a subject only participates in the 4.4 grams/day dose stage of the extension phase, adverse events will only be categorized into the 4.4 grams/day treatment period or follow-up period within the extension phase. Otherwise, adverse events will be categorized into the 4.4 grams/day dose stage, the 6.7 grams/day dose stage, and follow-up as described above. For example, an adverse event that occurs in both the 4.4 grams/day dose period and the 6.7 grams/day dose period wll be attributed to both extension phase treatment periods.

TEAEs will be summarized for all subjects in the safety population. TEAEs will be summarized by treatment group for each dose in the crossover phase and for each dose in the extension phase. 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 in the MS1819 treatment group.

Treatment-emergent AEs will be presented by treatment group and overall for the crossover phase and overall for the extension phase with percentages that use the number of subjects in the safety population as the denominator.

Treatment-emergent AEs will also be summarized by maximum relationship to study drug and maximum severity. Relationship to each study treatment (MS1819 and prestudy PERT [crossover phase only]) will be scored as Related or Unrelated. Severity will be rated as Mild, Moderate, or Severe. All percentages will use the number of safety subjects as the denominator. Summary tables will reflect a count and percentage of subjects experiencing at least 1 TEAE in each system organ class, preferred term and grouping, 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, in the event that 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 by treatment group and overall in the crossover phase and overall in the extension phase 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 in the MS1819 treatment group.

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

Treatment-emergent SAEs, TEAEs leading to study discontinuation, TEAEs resulting in death, treatment-emergent SAEs by relatedness, treatment-emergent SAEs leading to discontinuation, and treatment-emergent SAEs resulting in death will be summarized for all subjects in the safety population for each study phase. 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 discontinuation, death). These summaries will be presented by treatment group and overall for each dose in the crossover phase and overall for each dose in the extension phase with percentages that

use the number of subjects in the safety population as the denominator. These tabular summaries will be sorted by descending frequency by system organ class and by preferred term in the MS1819 treatment group.

Adverse events leading to study discontinuation, AEs resulting in death, and SAEs will be presented in data listings for subjects in the safety population for each dose of the crossover phase and for each dose of the extension phase.

8.5 Clinical Laboratory Evaluation

8.5.1 Crossover Phase

Values at Screening and at 3 weeks post first dose, as described in Section 3, for laboratory parameters for hematology and clinical chemistry will be summarized by treatment group for the safety population using descriptive statistics. Values at Screening, Visit 3 (At Randomization), At First Dose, and at 3 Weeks Post First Dose, as described in Section 3, for laboratory parameters for urinalysis will be summarized by treatment group for the safety population using descriptive statistics.

Shift tables based on classification of values with respect to the reference range will be summarized for the safety population for critical clinical chemistry and hematology laboratory tests by treatment group. Critical clinical chemistry and hematology laboratory tests are listed in the appendix for Table Display Specifications.

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 by treatment group at Screening and at 3 Weeks Post First Dose.

Hematology, clinical chemistry, hepatic monitoring, urinalysis, lipids, coagulation, and pregnancy results will be presented in data listings for subjects in the safety population.

8.5.2 Extension Phase

Values for laboratory parameters for urinalysis, hematology and clinical chemistry will be summarized for the safety population using descriptive statistics.

Hematology, clinical chemistry, hepatic monitoring, urinalysis, lipids, coagulation, 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

8.6.1.1 Crossover Phase

Values at Visit 3 (At Randomization), At First Dose, and at 3 Weeks Post First Dose, as described in Section 3, of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature will be summarized by treatment group for the safety population using descriptive statistics.

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

8.6.1.2 Extension Phase

Values of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature will be summarized for the safety population using descriptive statistics for each dose of the extension phase.

Vital sign values will be presented in a data listing for all subjects in the safety population for each dose of the extension phase.

8.6.2 Physical Examinations

A physical examination will be performed at study visits 3, 6, 9, and 10 of the crossover phase and at study visits 11, 13, 14, 16 and 17 of the extension phase. An indication of whether the examination was performed, date of the examination, and an indication of whether abnormal findings that were clinically significant were found 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.

8.6.3 Other Safety Measures

8.6.3.1 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 (March 2020) 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 in the first crossover period or that stopped on or after day of first dose of study treatment in the first crossover period. Prior medications will include

all medications that started and stopped prior to the day of first dose of the study treatment in the first crossover study period.

For the crossover period, concomitant medications will be categorized as occurring in study period 1 or study period 2. Concomitant medications that started or stopped on or after day of first dose of study treatment in period 1 and before the start of period 2 are attributed to period 1. Concomitant medications that started prior to the first dose of study treatment in period 1 and stopped on or after day of first dose of study treatment in period 1, or are ongoing, are attributed to period 1. Concomitant medications that started or stopped on or after day of first dose of study treatment in period 2 are attributed to period 2. Concomitant medications that started prior to the study and are stopped on or after day of first dose of study treatment in period 2, or are ongoing, are attributed to period 2.

For the extension phase, concomitant medications will be categorized into period (4.4 grams/day, 6.7 grams/day) using the same rules described above.

The number and percentage of subjects using prior and concomitant medications will be tabulated for each study period for the crossover phase and overall for the extension phase 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 medications will be summarized separately for each dose of the crossover phase and for each dose of the extension phase.

Prior medications will be summarized overall (by planned treatment sequence for the crossover phase). Concomitant medications will be presented by actual treatment group and overall for the crossover phase and overall for the extension phase with percentages that use the number of subjects in the safety population as the denominator.

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

9. EFFICACY EVALUATION

9.1 Overview of Efficacy Analysis Issues

9.1.1 Handling of Dropouts or Missing Data

Missing data will not be replaced.

9.1.2 Assessment Time Windows

Rules for assessment time windows are addressed in Section 9.2 for each efficacy endpoint.

9.2 Analysis Methods

9.2.1 Crossover Phase: Primary Efficacy Analyses

The primary efficacy endpoint is the CFA assessed at the end of each 3-week treatment period (Visit 6 or Visit 9). CFA is evaluated by the 72-hour marker-to-marker stool sample collection (1 measure at Visit 6 and 1 at Visit 9) and standardized high-fat diet during each 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:

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

The primary efficacy endpoint analysis of the crossover phase will use the mITT population and be analyzed as randomized for each dose. For the summary of CFA, if a subject switches study treatments (i.e. MS1819 to PERT or PERT to MS1819) during the confinement period, prior to the end of the stool collection, then the CFA value during that confinement period will be excluded from the summary.

CFA at the end of the first period (Visit 6) and CFA at the end of the second period (Visit 9) will be summarized by treatment group for each dose using descriptive statistics.

Fat consumed (g/24h), fat excreted (g/24h), and CFA (%) will be listed by visit for all subjects in the mITT population for each dose.

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

9.2.1.1 Crossover Phase: Supportive Analyses of the Primary Efficacy Analysis

A secondary (supportive) descriptive summary of the primary efficacy measure will be provided using the per-protocol population, according to randomized treatment group for each dose.

9.2.1.2 Crossover Phase: Subgroup Analyses

Subgroup summaries comparing MS1819 to porcine PERT will be provided for:

- CFA level while receiving porcine PERT (<80%, ≥80%)

- Gastric acid suppression use (yes, no)

The descriptive summary will be repeated for each subgroup for each dose using the mITT population, according to randomized treatment group.

9.2.2 Crossover Phase: Secondary Efficacy Analyses

All secondary efficacy analyses will be presented separately for each dose of the crossover phase.

9.2.2.1 Coefficient of Nitrogen Absorption

CNA at the end of each treatment period (Visit 6, Visit 9) 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:

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

CNA at the end of the first period (Visit 6) and CNA at the end of the second period (Visit 9) will be summarized by treatment group for each dose using descriptive statistics.. For the summary of CNA, if a subject switches study treatments (i.e. MS1819 to PERT or PERT to MS1819) during the confinement period, prior to the end of the stool collection, then the CNA value during that confinement period 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, according to randomized treatment group.

Nitrogen consumed (g/24h), nitrogen excreted (g/24h), and CNA (%) will be listed by visit for all subjects in the mITT population.

9.2.2.2 Stool Weight

Stool weight during the 72-hour marker-to-marker stool collections will be evaluated at the end of each treatment period (Visit 6, Visit 9). 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 at the end of each treatment period will be analyzed from stool samples collected during the 2 confinement periods (Visit 6 and Visit 9).

Stool weight at the end of each treatment period (Visit 6, Visit 9) will be summarized by treatment group using descriptive statistics. If a subject switches study treatments (i.e. MS1819 to PERT or PERT to MS1819) 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 6 or Visit 9) and the correct value is unknown, only the heaviest value will be included in the summary.

Stool weight will be listed by visit for all subjects in the mITT population.

9.2.2.3 Malabsorption Signs and Symptoms

Signs and symptoms of malabsorption will be evaluated at Visits 3, 4, 5, 6, 7, 8, 9, and 10.

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 by treatment group for the mITT population using descriptive statistics. Stool frequency will be summarized at Visit 3 (At Randomization), At First Dose, 1 Week Post First Dose, 2 Weeks Post First Dose, and 3 Weeks Post First Dose, as described in Section 3.

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 and by treatment group will also be provided Visit 3 (At Randomization), At First Dose, 1 Week Post First Dose, 2 Weeks Post First Dose, and 3 Weeks Post First Dose, as described in Section 3. Shifts from Visit 3 will be presented for stool consistency, bloating, abdominal pain, flatulence, increased stool quantity, and worsening of overall bowel habit for the mITT population by treatment group.

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

9.2.2.4 Weight and BMI

Weight and BMI will be evaluated at Visits 1, 3, 6 and 9.

Weight and BMI at Visit 3 (At Randomization), At First Dose, and at 3 Weeks Post First Dose, as described in Section 3, will be summarized for the mITT population using descriptive statistics by treatment group.

Weight and BMI will be listed for all subjects in the mITT population.

9.2.2.5 Serum Liposoluble Vitamin (A, D, E, and K) Levels

Analyses of certain lab values will be undertaken to evaluate markers of nutritional status. Specifically, the laboratory parameters to be summarized will include blood levels of vitamin A, D, E, and K. Vitamin A, D, E, and K levels will be evaluated at Visits 1, 3, 6, 9, and 10.

Vitamin A, D, E, and K levels will be summarized by treatment group for Visit 3 (At Randomization), At First Dose, and at 3 Weeks Post First Dose, as described in Section 3, using descriptive statistics.

Vitamin A, D, E, and K levels will be listed for all subjects in the mITT population.

9.2.3 Extension Phase: Exploratory Efficacy Analyses

All efficacy analyses in the extension phase will be exporatory in nature as the extension phase is dose-finding and not intended to be powered for efficacy analyses. All exploratory efficacy analyses for the extension phase will be descriptive.

All exploratory efficacy analyses will be presented separately for each dose of the extension phase.

9.2.3.1 Coefficient of Fat Absorption

The exploratory endpoint of CFA will be assessed at the end of the 2-week treatment period (Visit 13 for the 4.4 grams/day dose or Visit 16 for the 6.7 grams/day dose). CFA is evaluated by the 72-hour marker-to-marker stool sample collection (1 measure at Visit 13 and 1 at Visit 16) and standardized high-fat diet during each supervised confinement. CFA is collected and calculated as described in Section 9.2.1.

CFA at the end of the treatment period (Visit 13 or Visit 16) will be summarized for using descriptive statistics.

The descriptive summary of CFA at the end of the treatment period (Visit 13 or Visit 16) will also be provided using the per-protocol population.

In addition, CFA at the end of the extension treatment period (Visit 13 or Visit 16) will be compared against each the CFA at the end of the PERT crossover study period and CFA at the end of the MS1819 study period for the subset of subjects participating in the extension phase using descriptive statistics.

Fat consumed (g/24h), fat excreted (g/24h), and CFA (%) will be listed by visit 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.

9.2.3.2 Coefficient of Nitrogen Absorption

CNA at the end of the treatment period (Visit 13 for the 4.4 grams/day dose or Visit 16 for the 6.7 grams/day dose) will be analyzed. CNA will be expressed as the percentage of nitrogen (protein) absorbed from the subject's diet. CNA is collected and calculated as described in Section 9.2.2.1.

CNA at the end of the treatment period (Visit 13 or Visit 16) will be summarized using descriptive statistics.

The descriptive summary of CNA at the end of the treatment period (Visit 13 or Visit 16) will also be provided using the per-protocol population.

Nitrogen consumed (g/24h), nitrogen excreted (g/24h), and CNA (%) will be listed by visit for all subjects in the mITT population.

9.2.3.3 Stool weight

Stool weight during the 72-hour marker-to-marker stool collections will be evaluated at the end of the treatment period (Visit 13 for the 4.4 grams/day dose or Visit 16 for the 6.7 grams/day dose). 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 at the end of the treatment period (Visit 13 or Visit 16) will be summarized using descriptive statistics.

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

Stool weight will be listed by visit for all subjects in the mITT population.

9.2.3.4 Signs and Symptoms of Malabsorption

Signs and symptoms of malabsorption will be evaluated at Visits 11, 12, and 13 (4.4 grams/day) and Visits 14, 15, 16 (6.7 grams/day), as well as at Visit 17.

The EPI malabsorption symptoms will be evaluated as described in Section 9.2.2.3.

Stool frequency will be summarized for the mITT population using descriptive statistics.

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 be summarized.

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

9.2.3.5 Weight and BMI

Weight and BMI will be evaluated at Visits 11 and 13 (4.4 grams/day) and Visits 14 and 16 (6.7 grams/day).

Weight and BMI will be summarized for the mITT population using descriptive statistics.

Weight and BMI will be listed for all subjects in the mITT population.

10. DATA MONITORING

10.1 Data Monitoring

An external, independent data safety monitoring board (DSMB) will monitor and protect the safety and risk/benefit of the study patients throughout the study duration and evaluate the risk/benefit of study drug. The DSMB will consist of suitably qualified individuals, including CF experts. After the study is complete, the DSMB will review the efficacy/safety data. Additional safety reviews may be conducted, at the request of the Data Safety Monitoring Board (DSMB) or DSMB Chair.

Since the planned DSMB review will occur after the completion of the study, the DSMB will review a subset of the analyses specified in the SAP and a separate DSMB analysis plan is not required.

Details are described in the DSMB charter.

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Section 10.7.1 of the protocol states that an exploratory analysis of non-inferiority between the MS1819 and PERT groups will be conducted for CFA (MS1819 minus porcine PERT) with a non-inferiority margin of 15%. Section 10.7.2 of the protocol states that CNA will be analyzed in the same manner as CFA. The non-inferiorty analyses for CFA and CNA will not be conducted.

12. REFERENCES

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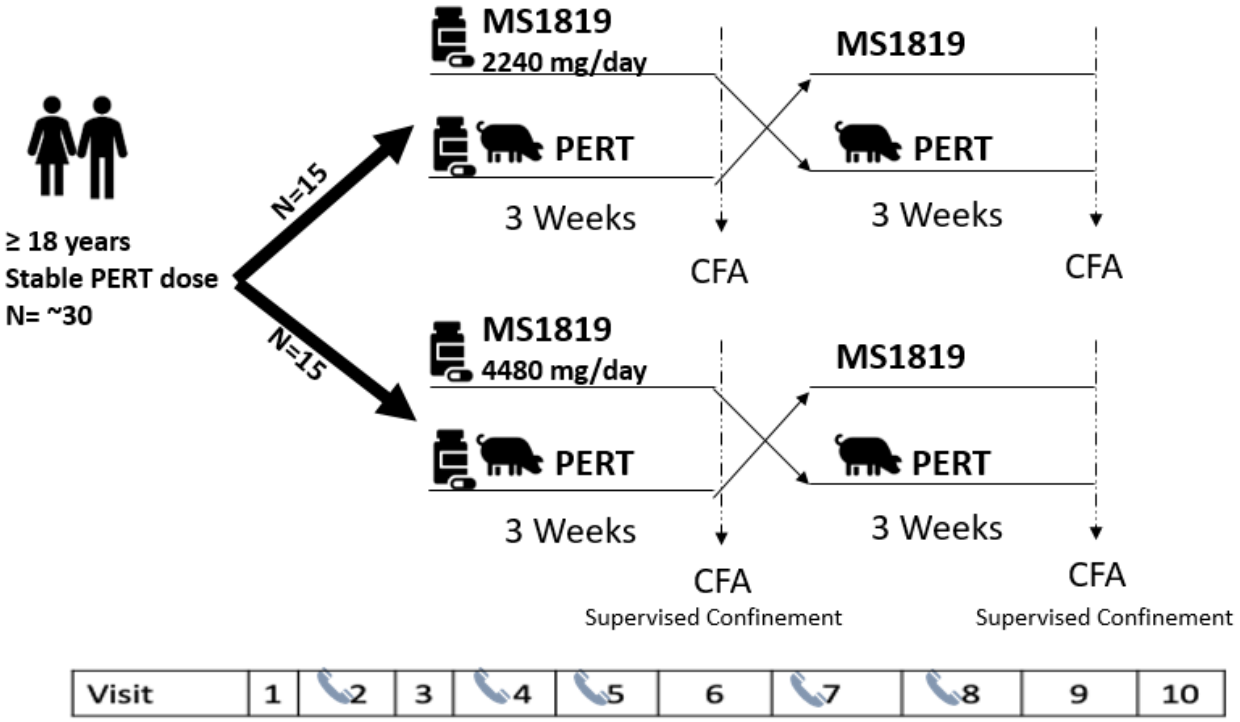
Kenward, M. G., and Roger, J. H. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. *Biometrics,* 53, 983–997.

Senn, S. & Barnett, V. (2002). *Cross-over Trials in Clinical Research* (2nd ed.). New York, NY: John Wiley & Sons, Ltd.

13. APPENDICES

13.1 Crossover Phase Study Flow Chart

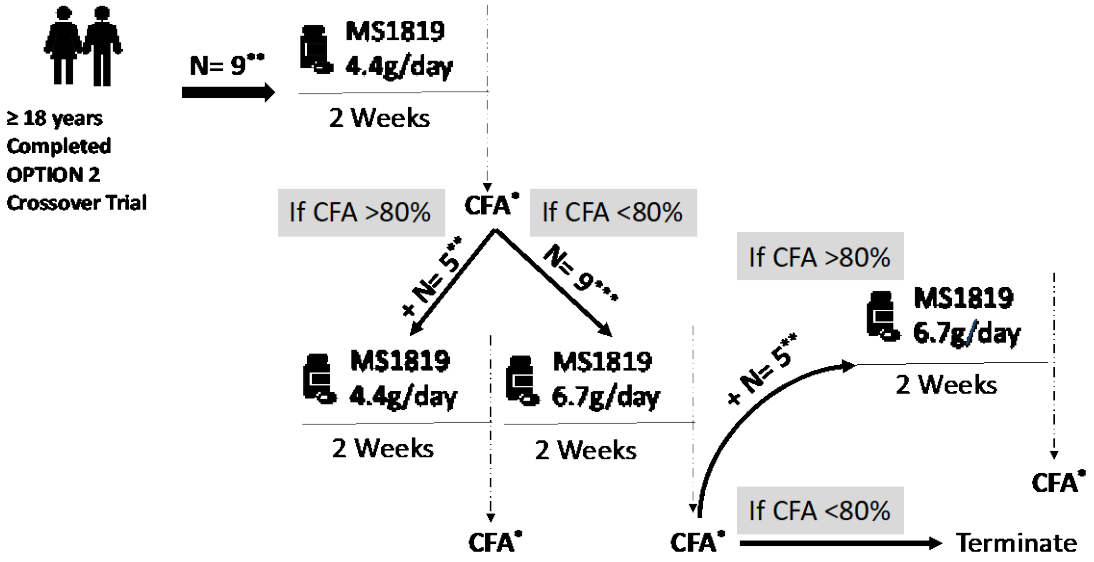
OPTION 2: A Phase 2, Open-Label, Multicenter, 2x2 Crossover Trial to assess the Safety and Efficacy of MS1819 in Enteric Capsules in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis



Visit	1	2	3	4	5	6	7	8	9	10

13.2 Extension Phase Study Flow Chart

Extension Phase Evaluation of Immediate Release MS1819 Capsules



*Supervised Confinement
**Eligible patients who completed crossover trial
***From 4.4g/day group or eligible patients who completed crossover trial

13.3 Crossover Phase Schedule of Events

	SCREENING		INITIAL TREATMENT PERIOD				SECOND TREATMENT PERIOD			END OF STUDY/EARLY TERMINATION
Visit Number	**1**[a]	**2 (T)**[b]	**3**	**4 (T)**[c]	**5 (T)**[c]	**6**[d]	**7 (T)**[c]	**8 (T)**[c]	**9**[d]	**10**
Study Week	**-3**		**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Study Days	**-21**		**1**	**8**	**15**	**17**	**29**	**36**	**38**	**56**
Visit Window (days)	**V1 to V2 interval ≤21 days**			**±2**	**±2**	**+5**	**±2**	**±2**	**+5**	**±2**
Pre-Visit Instructions		**X**								
Supervised confinement						**X**			**X**	
Clinical Assessments										
Obtain informed consent	**X**									
Demographics	**X**									
Complete history and physical	**X**									
Focused physical exam[e]			**X**			**X**			**X**	**X**
Confirm CF diagnosis (Inclusion Criteria 4)	**X**									
Height/weight, vital signs (sitting)	**X**		**X**			**X**			**X**	
Inclusion/exclusion criteria review	**X**		**X**							
Concomitant medications	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Confirm scheduled date for next supervised confinement visit				**X**	**X**		**X**	**X**		
Study Treatment										
Randomization			**X**							
Instruct regarding prestudy PERT/Dispense study drug			**X**			**X**			**X**	

	SCREENING		INITIAL TREATMENT PERIOD				SECOND TREATMENT PERIOD			END OF STUDY/EARLY TERMINATION
Visit Number	**1**[a]	**2 (T)**[b]	**3**	**4 (T)**[c]	**5 (T)**[c]	**6**[d]	**7 (T)**[c]	**8 (T)**[c]	**9**[d]	**10**
Study Week	**-3**		**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Study Days	**-21**		**1**	**8**	**15**	**17**	**29**	**36**	**38**	**56**
Visit Window (days)	**V1 to V2 interval ≤21 days**			**±2**	**±2**	**+5**	**±2**	**±2**	**+5**	**±2**
MS1819 (either 2240 or 4480 mg/day)										
Verify study drug count at the end of confinement						**X**			**X**	
Return MS1819 (only for those on MS1819) at the end of confinement						**X**			**X**	
Record fat and protein intake and study drug taken at all meals and snacks						**X**			**X**	
Cross over to alternative treatment[f]						**X**				
Efficacy Measures										
Malabsorption signs & symptoms			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
72-hour controlled diet record						**X**			**X**	
Marker-to-marker stool collection and stool weight[g]						**X**			**X**	
Laboratory Tests										
Urinalysis	**X**		**X**			**X**			**X**	
Pregnancy test (serum for V1 screening and urine dipstick for other visits)[h]	**X**		**X**			**X**			**X**	**X**

	SCREENING		INITIAL TREATMENT PERIOD				SECOND TREATMENT PERIOD			END OF STUDY/EARLY TERMINATION
Visit Number	**1**[a]	**2 (T)**[b]	**3**	**4 (T)**[c]	**5 (T)**[c]	**6**[d]	**7 (T)**[c]	**8 (T)**[c]	**9**[d]	**10**
Study Week	**-3**		**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Study Days	**-21**		**1**	**8**	**15**	**17**	**29**	**36**	**38**	**56**
Visit Window (days)	**V1 to V2 interval ≤21 days**			**±2**	**±2**	**+5**	**±2**	**±2**	**+5**	**±2**
Hematology, clinical chemistry, PT/INR, and aPTT[i]	**X**					**X**			**X**	
Fasting[j] lipids (patient to come in fasting status) and pre-albumin	**X**					**X**			**X**	
Vitamin A, D, E, and K	**X**		**X**			**X**			**X**	**X**
Serum samples for anti-LIP2 lipase antibodies and MS1819 concentrations			**X**			**X**			**X**	**X**
Fecal pancreatic elastase[k]	**X**									
Diagnostic Test										
Spirometry	**X**									
Resume Prescribed PERT										
Switch back to prescribed porcine PERT[l]									**X**	

A Screening procedures can occur up to 21 days before V1 through the first day of dosing (V3). 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 the screening visit.

B This first study telephone call will occur once eligibility for the patient is determined. Instructions on the randomization visit will also be communicated and patients will be told to bring in their prestudy porcine PERT with them for V3.

C Visits 4, 5, 7, and 8 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 Visit 6 and Visit 9 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 V6 and V9 to accommodate for scheduling. Dosing must have occurred for at least 16 days prior to the start of the scheduled confinement.

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

F At the end of V6 (after the last stool sample has been collected), Patients that were randomized to MS1819 (on either the 2240 or 4480 mg/day dose) will begin treatment with their prestudy porcine PERT. Patients that were randomized to their prestudy porcine PERT will begin treatment with MS1819.

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

H A serum pregnancy test must be conducted in females of reproductive potential at screening. Pregnancy status will be re-evaluated via urine pregnancy test in these Patients at Visit 3, 6, 9 and at the End-of-Study or Early Termination visit.

[I] 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.

[J] Fasting labs should be taken after patients have been in a fasting status for at least 8 hours.

[K] Fecal pancreatic elastase will be sent and analyzed by the central laboratory.

[L] At the end of V9, Patients should resume their prescribed porcine PERT. For Patients that were on their prescribed porcine PERT during V9 no change will be needed.

13.4 Extension Phase Schedule of Events

	4.4 g/day TREATMENT PERIOD			6.7 g/day TREATMENT PERIOD			END OF EXTENSION STUDY/EARLY WITHDRAWAL TERMINATION
Visit Number	**11[A]**	**12(T)[B]**	**13[C]**	**14[A]**	**15 (T)[B]**	**16[C]**	**17**
Study Week	**1**	**1**	**3**	**1**	**1**	**3**	**2 weeks after last dose of study drug**
Study Days	**E1**	**E5**	**E11**	**E1**	**E5**	**E11**	
Visit Window (days)		**±2**	**+4**		**±2**	**+4**	**±2**
Pre-Visit Instructions		**X**			**X**		
Supervised confinement			**X**			**X**	
Clinical Assessments							
Obtain informed consent	**X**			**X[D]**			
Focused physical exam[E]	**X**		**X**	**X**		**X**	**X**
Height/weight, vital signs (sitting)	**X**		**X**	**X**		**X**	
Inclusion/exclusion criteria review	**X**			**X[D]**			
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**		**X**	**X**		
Study Treatment							
Dispense study drug MS1819 (either 4.4 or 6.7g/day)	**X**			**X**			
Verify study drug count at the end of confinement			**X**			**X**	
Return MS1819 at the end of confinement			**X**			**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**	**X**
72-hour controlled diet record			**X**			**X**	
Marker-to-marker stool collection and stool weight[F]			**X**[G]			**X**[G]	
Laboratory Tests							
Pregnancy test (urine dipstick)[H]	**X**		**X**	**X**		**X**	**X**
Urinalysis			**X**			**X**	
Hematology, clinical chemistry, PT/INR, and aPTT[I]			**X**			**X**	
Fasting[J] lipids (patient to come in fasting status) and pre-albumin			**X**			**X**	
Serum samples for anti-LIP2 lipase antibodies and MS1819 concentrations	**X**		**X**	**X**		**X**	**X**
Diagnostic Tests							
Spirometry	**X**			**X**[D]			
Resume Prescribed PERT							
Switch back to prescribed porcine PERT[F]			**X**			**X**	

[A] Subjects do not need to go through full screening again.
[B] Visits 12, and 15 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.
[C] Visits 13 and 16 are scheduled confinement visits and can take up to 7 days. A +4-day window is permitted around the scheduled confinement for both V13 and V16 to accommodate for scheduling. Dosing must have occurred for at least 10 days prior to the start of the scheduled confinement.

[D] Only for patients that did not participate in first part of extension phase study
[E] The Focused Physical Exam will evaluate gastrointestinal tract, heart, and lungs.
[F] At the end of V13 and/or V16 (after the last stool sample has been collected), Patients will begin treatment with their prestudy porcine PERT.
[G] The stool samples will be sent to the central laboratory and CFA, CNA, and stool weight will be measured.
[H] Pregnancy status will be evaluated via urine pregnancy test
[I] 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.
[J] Fasting labs should be taken after patients have been in a fasting status for at least 8 hours.

14. ATTACHMENTS

- Table Display Specifications
- Listing Display Specifications