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Statistical Analysis Plan

A Phase 2, Open Label, Multicenter, 2 x 2 Crossover Trial to assess the Safety and Efficacy of MS 1819 SD in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis

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

OPTION Study
PROTOCOL NUMBER AZ-CF2001

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS 6

1. PURPOSE OF THE ANALYSES 7

2. PROTOCOL SUMMARY 8

2.1 Study Objectives 8
2.1.1 Primary Objective 8
2.1.2 Secondary Objectives 8
2.2 Overall Study Design and Plan 8
2.3 Study Population 9
2.4 Treatment Regimens 9
2.5 Treatment Group Assignments or Randomization 9
2.6 Sample Size Determination 9

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS 11

4. ANALYSIS POPULATIONS 12

4.1 Modified Intent-to-Treat Population 12
4.2 Per-Protocol Population 12
4.3 Safety Population 12

5. STUDY SUBJECTS 13

5.1 Disposition of Subjects 13
5.2 Protocol Deviations 14

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 15

7. MEASUREMENTS OF TREATMENT COMPLIANCE 16

8. SAFETY EVALUATION 17

8.1 Overview of Safety Analysis Methods 17
8.2 Extent of Exposure 18
8.3 Adverse Events 18
8.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events 20
8.5 Clinical Laboratory Evaluation 20
8.6 Vital Signs, Physical Findings, and Other Observations Related to Safety 20
8.6.1 Vital Signs 20
8.6.2 Physical Examinations 21
8.6.3 Other Safety Measures 21
8.6.3.1 Prior and Concomitant Medications 21

9. EFFICACY EVALUATION 23

9.1 Overview of Efficacy Analysis Issues 23
9.1.1 Handling of Dropouts or Missing Data 23
9.1.2 Assessment Time Windows 23
9.2 Analysis Methods 24
9.2.1 Primary Efficacy Analyses 24
9.2.1.1 Supportive Analyses of the Primary Efficacy Analysis 25
9.2.1.2 Subgroup Analyses 25
9.2.2 Secondary Efficacy Analyses 25
9.2.2.1 Coefficient of Nitrogen Absorption 25
9.2.2.2 Stool Weight 26
9.2.2.3 Malabsorption Signs and Symptoms 27

9.2.2.4 Weight and BMI 27
9.2.2.5 Serum Liposoluble Vitamin (A, D, E, and K) Levels 28

10. DATA MONITORING 29

10.1 Data Monitoring 29

11. DIFFERENCES BETWEEN THE SAP AND PROTOCOL AND CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL 30

11.1 Differences between the SAP and Protocol and Changes to the Analyses Planned in Protocol Version 2 30

12. REFERENCES 31

13. APPENDICES 32

13.1 Study Flow Chart 32
13.2 Schedule of Events 33
13.3 Protocol Deviation Types 36

14. ATTACHMENTS 37

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
EPI	exocrine pancreatic insufficiency
ICH	International Conference on Harmonisation
mITT	Modified Intent-to-treat
IP	investigational product
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-CF2001, 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-SD 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 a dose of 2240 mg/day of MS1819-SD in patients with EPI caused by CF. The primary efficacy objective of the study is to demonstrate the non-inferiority of MS1819-SD to porcine PERT for the coefficient of fat absorption (CFA) at the end of each treatment period in subjects with EPI due to CF.

2.1.2 Secondary Objectives

To evaluate and compare effects of MS1819-SD 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.

2.2 Overall Study Design and Plan

This is a Phase 2, open-label, multicenter, 2x2 crossover study assessing the safety and efficacy of MS1819-SD (2240 mg/day) in patients with EPI due to CF for male and female patients aged 18 years or older. Efficacy will be evaluated by comparing treatment with MS1819-SD to treatment with porcine PERT at the same dose that was being administered during the prestudy period.

MS1819-SD will be assessed in a 2x2 crossover including at least 30 patients completing both periods such that at least 15 patients will complete each sequence of treatments. Patients will be randomized to receive either the sequence consisting of MS1819-SD for 3 weeks followed by PERT for another 3 weeks or the opposite sequence of treatments (PERT for 3 weeks followed by MS1819-SD for another 3 weeks).

The study will not employ a washout period between the first treatment period and the second treatment period. Recent experience with crossover lipase enzyme treatment from commercial PERTs to investigational lipase has demonstrated that symptoms of malabsorption may become evident within a matter of days, indicating little residual carryover effect of the original lipase. Furthermore, the 3-week duration of treatment with either study agent is well established as sufficient to show the degree of lipase effectiveness.

Dosages will typically be fractionated as follows: 1/4 of the daily dose at each 3 main meals, and 1/8 at each of the 2 snacks (ie, 2240 mg/day will be fractionated as follows: 4 capsules of 140 mg with the morning, noontime, and evening meals, plus 2 capsules of

140 mg with the morning and evening snacks). Individual variations may occur as long as total daily dose is achieved.

The dose of prestudy porcine PERT will be the same dose that was being administered during the prestudy period.

Randomized patients will be males and females 18 years or older. 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.

A study flow chart is presented in Appendix 13.1, and a schedule of events is presented in Appendix 13.2.

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, subjects will be assigned in a 1:1 ratio to receive either the sequence consisting of MS1819-SD for 3 weeks followed by PERT for another 3 weeks or the opposite sequence of treatments (PERT for 3 weeks followed by MS1819-SD for another 3 weeks).

Subjects will receive 2240 mg/day of MS1819-SD while in the MS1819-SD period of their treatment sequence. 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.

2.5 Treatment Group Assignments or Randomization

Subjects who meet all of the enrollment criteria will be randomized to receive MS1819-SD followed by PERT or PERT followed by MS1819-SD using a 1:1 allocation ratio.

2.6 Sample Size Determination

The primary objectives of the trial are to assess the safety of MS1819 and whether the efficacy of MS1819 is noninferior to porcine PERT. The sample size was primarily selected to be sufficient to address the safety objectives of this trial. Given the sample size, efficacy will be assessed with the understanding that adequate power for assessing efficacy would only be achieved for differences that are more favorable than expected.

With regard to safety assessment, at least 30 patients completing both periods are judged enough to adequately assess safety. Any event not occurring in the study would have a 95% CI on the rate extending from 0% to 10%; thus events not occurring may be assumed to be uncommon in the population (<10%).

With regard to efficacy, the primary objective is to show that the efficacy of MS1819, measured on the primary endpoint (ie, the CFA), is noninferior to porcine PERT.

- The noninferiority is chosen equal to 15% and the rationale for this choice is as follows: the difference in mean change from baseline in CFA between the reference and placebo was found to be approximately 32.6% in Trapnell (2011). According to the guidance on Noninferiority Clinical Trials to establish effectiveness (2016), the noninferiority (NI) margin should preserve a specified fraction of the difference between the reference and placebo. A NI margin of 15% preserves 54% of the estimated difference between the reference and placebo.
- In a recent unpublished trial, the standard deviation of the change in CFA was found to be around 16% among patients with a baseline CFA at or above 80%. As some patients enrolled in this trial might have a CFA under porcine PERT lower than 80%, a higher standard deviation of around 20% is expected.
- Because the patients enrolled in the trial are already stabilized on porcine PERT, it is expected that the difference in CFA means between MS1819 and porcine PERT slightly favors PERT, which is expected to be around -8%.

Out of an abundance of caution, the planned sample size is limited to roughly 30 subjects completing. With regard to safety assessment, 30 patients completing both periods are judged enough to adequately assess safety. However, assuming a standard deviation of 20% for the paired differences in CFA measurements within each patient, a noninferiority margin of 15%, a more favorable than expected difference of -4.0% in CFA means between MS1819 vs porcine PERT that favors PERT, a sample size of 30 patients completing both periods will provide a power of around 80% to show noninferiority of MS1819 to porcine PERT at the 0.05 2-sided nominal 0.05 level of significance (that is, a one-sided alpha of 0.025). Accounting for a 20% dropout rate, 38 patients will be sufficient to achieve a power of at least 80%.

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).

In general, age will be calculated in years using the date of birth and the date of randomization as [(date of randomization – date of birth)]/365.25, rounded down to the next largest integer using the floor function. For any listing that includes screen failures, age will be labeled as age at screening and will be calculated in years using the date of birth and the date of Visit 1 as [(date of Visit 1 – date of birth)]/365.25, rounded down to the next largest integer using the floor function.

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:

4.1 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all randomized subjects who receive at least 1 dose of treatment and have at least 1 sufficient stool sample. A stool sample will be considered sufficient if the date and time associated with the second blue dye marker is recorded, indicating that the stool sample collection is complete. The mITT will be used for efficacy analyses. Subjects will be analyzed according to the treatment group to which they were randomized regardless of the actual treatment received, unless stated otherwise.

4.2 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. Subjects who are found to be <80% compliant with MS1819 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. Subjects will be included in the treatment sequence to which they were randomized regardless of the actual treatment sequence received.

4.3 Safety Population

The safety population, which will be used for all safety analyses 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.

5. STUDY SUBJECTS

5.1 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 by treatment sequence for all subjects randomized in the study:

- 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.

5.2 Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the study team and recorded on the protocol deviation case report form (CRF) page.

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 by treatment sequence.

Protocol deviation type is selected on the CRF from the list noted in Appendix 13.3.

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.

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 by treatment sequence and overall descriptively for the mITT population. 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 will include age, sex, race, and ethnicity. Age (years) will be calculated using the date of birth and the date of randomization, as described in Section 3.

Baseline characteristic data 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.

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

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 for MS1819-SD 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-SD 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)*140 mg]/number of actual study days on MS1819-SD,

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

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

The expected dose for MS1819-SD is 2240 mg/day.

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

As described in Section 4.2, subjects found to be <80% compliant with MS1819-SD will be excluded from the PP population.

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

8. SAFETY EVALUATION

8.1 Overview of Safety Analysis Methods

All safety analyses will be performed using the safety population and summarized by actual treatment (MS1819-SD regardless of period vs. PERT regardless of period) allowing direct intrasubject comparison of the tolerability of MS1819-SD vs. PERT. 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 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. 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 two 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 will have the start date imputed to both the treatment start date of the first study period and the treatment start date of the second 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 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.

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.

8.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 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 in period 1 will be considered to be TEAEs.

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

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

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

TEAEs that occurred after the subject's last study period will be classified as follow-up TEAEs. If a subject entered both the first and second study periods, any event occurring after the end date of the second study period will be considered a follow-up TEAE. If a subject discontinued prior to the start of the second study period, any event occurring after the end date of the first study period will be considered a follow-up TEAE.

TEAEs will be summarized for all subjects in the safety population. TEAEs will be summarized by treatment group. 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 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-SD and prestudy PERT) 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 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. 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 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.

8.5 Clinical Laboratory Evaluation

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, 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

Values at Visit 3 (At Randomization), At First Dose, and at 3 Weeks Post First Dose, as described in Section 3, in 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.

8.6.2 Physical Examinations

A physical examination will be performed at study visits 3, 6, 9, and 10. 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 (WHO Drug) Global Version (September 2018) 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 period or that stopped on or after day of first dose of study treatment in the first 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 study 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.

The number and percentage of subjects using prior and concomitant medications will be tabulated for each study period 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 medications will be summarized overall by planned treatment sequence. Concomitant medications will be presented by actual treatment group and overall 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 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 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:

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

The primary efficacy endpoint analysis will use the mITT population and be analyzed as randomized. For the analysis 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 analysis. The primary method for the analysis of the primary efficacy endpoint will be based on a mixed model. Missing CFA values will not be imputed.

The mixed model will include terms for sequence (MS1819-PERT, PERT-MS1819), random patient nested in sequence, period (1, 2), treatment (MS1819, PERT), and gastric acid suppression use (Y, N). The mixed model will be implemented using SAS® Proc MIXED, as shown in the model code below. The DDFM=KR option denotes the Kenward-Roger method for the denominator degrees of freedom. The variable GASTFL in the code below is the gastric acid suppression use flag (Y, N).

```
PROC MIXED;
        CLASS SUBJECT SEQUENCE PERIOD TREATMENT GASTFL;
        MODEL CFA = SEQUENCE TREATMENT PERIOD GASTFL /
        DDFM=KR;
        RANDOM SUBJECT(SEQUENCE);
        LSMEANS TREATMENT / CL DIFF;
RUN;
```

The 95% CI of the difference in CFA for MS1819-SD minus CFA for porcine PERT will be used to assess the primary objective. Non-inferiority of MS1819-SD to porcine PERT is achieved if the lower bound of the 95% CI of the difference is greater than -15%,

where 15% is the non-inferiority margin. If non-inferiority is achieved, then superiority will be tested.

The carryover effect will be estimated and tested. If there is a notable carryover, the primary endpoint analysis will be reported for each period separately.

The least squares (LS) means, 95% CIs of the LS means, and the SEs by treatment group will also be presented. In addition, CFA at the end of the first period (Visit 6) and CFA at the end of the second period (Visit 9) will also be summarized by treatment group 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.

9.2.1.1 Supportive Analyses of the Primary Efficacy Analysis

A secondary (supportive) analysis to the primary method for the analysis of the primary efficacy measure will be conducted using the per-protocol population, according to randomized treatment group. For this analysis, LS means, 95% CIs of the LS means, SEs of the LS means, LS mean estimate of the treatment difference (MS1819-SD minus porcine PERT), SE of the difference, and 95% CI of the difference will be displayed.

9.2.1.2 Subgroup Analyses

Subgroup analyses comparing MS1819-SD to porcine PERT using CFA at the end of each treatment period as the dependent variable will be performed for:

- CFA level while receiving porcine PERT (<80%, ≥80%)
- Gastric acid suppression use (yes, no)

The primary efficacy endpoint analysis will be repeated for each subgroup using the mITT population, according to randomized treatment group. For the gastric acid suppression use subgroup, gastric acid suppression use will be removed as a covariate from the model. For each analysis, LS means, 95% CIs of the LS means, SEs of the LS means, LS mean estimate of the treatment difference (MS1819-SD minus porcine PERT), SE of the difference, and 95% CI of the difference will be displayed for each subgroup.

In addition, CFA for each subgroup will be summarized by treatment group using descriptive statistics.

9.2.2 Secondary Efficacy Analyses

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 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:

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

The method for the analysis of CNA will be analogous to the method used for the primary efficacy analysis, as described in Section 9.2.1. For the analysis 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 analysis. Missing CNA values will not be imputed.

The 15% non-inferiority margin used for the primary efficacy analysis of CFA will also be applied to test the non-inferiority of MS1819-SD to porcine PERT in CNA at the end of each treatment period.

A secondary (supportive) analysis to the method for the analysis of CNA will be conducted using the per-protocol population, according to randomized treatment group.

In addition, CNA at the end of each treatment period (Visit 6, Visit 9) will be summarized by treatment group using descriptive statistics.

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), 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.

10. DATA MONITORING

10.1 Data Monitoring

An external, independent Data and Safety Monitoring Board (DSMB) consisting of members of the Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) DSMB, will monitor safety throughout the trial. 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. DIFFERENCES BETWEEN THE SAP AND PROTOCOL AND CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

No subjects were enrolled under the original protocol, so only differences between the SAP and protocol and changes to the analyses planned in Version 2.0 of the protocol are described below.

11.1 Differences between the SAP and Protocol and Changes to the Analyses Planned in Protocol Version 2

In section 10.7.2, the protocol states that stool weight and signs and symptoms of malabsorption will be analyzed with the same approach used for the primary endpoint. Instead, stool weight will be summarized using descriptive statistics. Since the signs and symptoms of malabsorption are categorical variables, this SAP specifies that these variables will be summarized by frequency tables in order to preserve the most information and given that it may not be reasonable to treat the differences between categories as uniformly quantifiable.

12. REFERENCES

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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.

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

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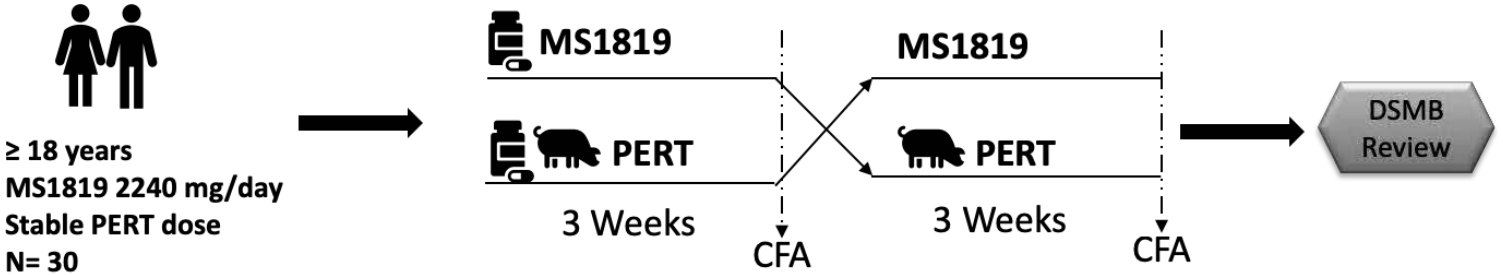
13. APPENDICES

13.1 Study Flow Chart

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



Visit	1	2	3	4	5	6	7	8	9	10

13.2 Schedule of Events

Schedule of Assessments

	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**	**±1**	**±7**	**±2**	**±2**	**±7**	**±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	**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 MS1819-SD			**X**			**X**			**X**	
Verify study drug						**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**	**±1**	**±7**	**±2**	**±2**	**±7**	**±2**
count at the end of confinement										
Return MS1819-SD (only for those on MS1819-SD) 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**
Hematology, clinical chemistry, PT/INR, and aPTT[i]	**X**					**X**			**X**	
Fasting lipids (patient to come in fasting status) and pre-albumin	**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**	**±1**	**±7**	**±2**	**±2**	**±7**	**±2**
Vitamin A, D, E, and K	**X**		**X**			**X**			**X**	**X**
Serum samples for anti-LIP2 lipase antibodies and MS1819-SD concentrations			**X**			**X**			**X**	**X**
Fecal pancreatic elastase[j]	**X**									
Diagnostic Test										
Spirometry	**X**									
Resume Prescribed PERT										
Switch back to prescribed porcine PERT[k]									**X**	

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

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 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 7 day window is permitted around the scheduled confinement for both V6 and V9 to accommodate for scheduling. Patient should bring their prestudy porcine PERT to V3.

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-SD will begin treatment with their prestudy porcine PERT. Patients that were randomized to their prestudy porcine PERT will begin treatment with MS1819-SD.

13.3 Protocol Deviation Types

The CRF includes the following protocol deviation types:

- Consent not obtained
- Re-consent not obtained
- Study assessment(s) administered prior to obtaining consent
- Missing signed consent form
- Incomplete consent form
- Missing documentation of consent process
- Consent form signature error
- Violation of inclusion criteria
- Violation of exclusion criteria
- Accidental unblindingAdministered incorrect study treatment to subject
- Non-compliance with study treatment
- Treatment with prohibited concomitant medications
- Visit missed
- Visit out of window
- Study procedure/assessment missed
- Study procedure/assessment out of window
- Study procedure/assessment performed incorrectly
- Unnecessary study procedure/assessment performed
- Missing source documents for study procedure/assessment
- Incomplete source documents for study procedure/assessment
- Pregnancy reporting out of window
- SAE reporting out of window
- Other

14. ATTACHMENTS

- Table Display Specifications
- Listing Display Specifications