Official Title:

Clinical Study Protocol

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

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Date of Document

October 30, 2018

CLINICAL STUDY PROTOCOL

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Study Name:	**OPTION**: A Phase 2, **Op**en-Label, Mul**ti**center, 2x2 Cr**o**ssover Trial to assess the Safety and Efficacy of MS1819-SD in Patie**n**ts with Exocrine Pancreatic with Insufficiency due to Cystic Fibrosis
Protocol Number:	AZ-CF2001
Investigational Product:	MS1819-SD
Phase:	Phase 2a
Sponsor:	AzurRx BioPharma, Inc. 760 Parkside Avenue Suite 304 Brooklyn, NY 11226 USA
Protocol Date:	October 30, 2018
Protocol Version:	Version 2.0

CONFIDENTIAL

1. PROTOCOL APPROVAL SIGNATURES

Protocol Title: 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

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Protocol Number: AZ-CF2001

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

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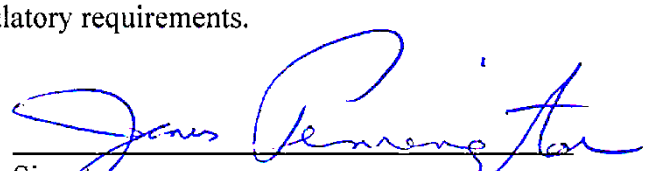

Signature

10-30-18

Date

2. SYNOPSIS

Name of Sponsor/Company: AzurRx BioPharma, Inc.	
Name of Investigational Product: MS1819-SD	
Protocol Number: AZ-CF2001	
Protocol Title: 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	
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Study Site(s): This study will be conducted at approximately 15 sites in North America and European Union.	
Number of Patients: Approximately 30	**Phase of Development:** 2a

Objectives

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).

Study Design

This is a Phase 2, open-label, multicenter, 2x2 crossover study assessing the safety and efficacy of MS1819-SD (2240 mg/day) vs porcine PERT given 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 (ie, 15 for 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).

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.

Inclusion Criteria

To be eligible for study entry, patients must satisfy all of the following inclusion criteria:

1. Signed and dated informed consent form by patient as required by AzurRx or designee and appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Age ≥18 years at the time of screening
3. Male or female
4. Cystic fibrosis, based on 2 clinical features consistent with CF, plus initial diagnostic sweat chloride ≥60 mmol/L by quantitative pilocarpine iontophoresis or genotype

5. Under stable dose of porcine PERT ≥1 month; stable dose is defined as dose of medication not changed during this time period, and the medication must be commercially available and be administered in the recommended dose range.
6. A fair or better nutritional status as defined by:
   - BMI ≥16.0 kg/m^2 for female patients ≥18 years of age, or
   - BMI ≥16.5 kg/m^2 for male patients ≥18 years of age
7. Fecal elastase <100 µg/g of stool at screening
8. Clinically stable with no documented evidence of significant respiratory symptoms that would require administration of intravenous antibiotics, oxygen supplementation, or hospitalization within 30 days of screening or during the screening period.
9. Male and Female patients, if of childbearing potential, must use a reliable method of contraception during the study. A reliable method of birth control is defined as one of the following: oral or injectable contraceptives, intrauterine device, contraceptive implants, tubal ligation, hysterectomy, or a double-barrier method (diaphragm with spermicidal foam or jelly, or a condom), abstinence or vasectomy. Periodic abstinence (calendar, symptothermal, or post-ovulation methods) is not an acceptable method of contraception. The preferred and usual lifestyle of the patient must also be evaluated in determining if sexual abstinence is a reliable method of birth control
10. Be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator

Exclusion Criteria

Patients will be excluded from the study if one or more of the following criteria are applicable:

1. History or diagnosis of fibrosing colonopathy
2. Total or partial gastrectomy
3. A history of solid organ transplant or significant surgical resection of the bowel; significant resection of the bowel is defined as any resection of the terminal ileum or ileocecal valve. Patients who have had qualitative, long-term changes in nutritional status after any other bowel resection (eg, increased or new need for pancreatic enzyme supplementation compared with preoperative status to maintain the same nutritional status) should also be excluded.
4. Any chronic diarrheal illness unrelated to pancreatic insufficiency (eg, infectious gastroenteritis, sprue, inflammatory bowel disease)
5. Known hypersensitivity or other severe reaction to any ingredient of the investigational medicinal product (IMP)
6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥5 ×upper limit of normal (ULN), or total bilirubin level ≥1.5 ×ULN at the Screening visit, unless due to Gilbert's syndrome. Cases of suspected or confirmed Gilbert's syndrome should be discussed with the Medical Monitor
7. Signs and/or symptoms of liver cirrhosis or portal hypertension (eg, splenomegaly, ascites, esophageal varices), or documented liver disease unrelated to CF
8. Patients with a known allergy to the stool marker (FD&C Blue #2)
9. Feeding via an enteral tube during 6 months before screening

10. Routine use of anti-diarrheals, anti-spasmodics, or cathartic laxatives, or a change in chronic osmotic laxatives (eg, polyethylene glycol) regimen in the previous 3 months
11. History of severe constipation with <1 evacuation/week under appropriate laxative therapy within the last 12 months before screening
12. Documentation of distal intestinal pseudo-obstruction syndrome within the last 12 months before screening
13. Forced expiratory volume ≤30% at the Screening visit
14. Lactation or known pregnancy or positive pregnancy test at screening for women of childbearing potential
15. Participation in another clinical study involving an IMP within 30 days before inclusion or concomitantly with this study
16. Patient's with poorly controlled diabetes according to the Investigator's judgment

Concomitant and Prohibited Medication

Standard–of–care medications are allowed (eg, antibiotics, mucolytic agents, aerosols, CFTR modulators). Patients taking CFTR modulators should be on stable doses for at least 3 months. Patients should not start taking CFTR modulators during the duration of the study.

Gastric acid suppressants are allowed but must be on stable dosage for 30 days before screening and must not be altered in dose or stopped during the study.

Prohibited medications during the entire clinical study will be as follows:

- Orlistat lipase inhibitor (eg, Alli®, Xenical®)
- Laxatives consisting of mineral oil and castor oil (chronic use of osmotic laxatives is permitted)
- Symptomatic treatments of diarrhea: loperamide (eg, loperamide generic, Imodium®, Imodium A-D®, Diamode®, Imotil®, Kao-Paverin®); atropine/diphenoxylate (Lonox®); and atropine/diphenoxylate (Lomocot®).

Investigational Product, Dosage, Duration and Mode of Administration

MS1819-SD is supplied as 140-mg capsule to be administered orally and taken with food. Daily doses will be fractionated according to the eating pattern of the patient.

Duration of Study

The estimated study duration will be determined by when all patients complete the study. Each patient will have approximately 21 days for screening, followed by approximately 6 weeks on study. A 2-week End of Study/Early termination period will occur when each patient completes his/her treatment period of study or withdraws from the study. Approximately a 3-week period for data collection and analysis will occur at the end of the study.

Criteria for Evaluation

Safety endpoints:

AEs, SAEs, drop outs, and laboratory values.

Efficacy Endpoints:

Primary Endpoints:

The primary efficacy endpoint is the CFA that will be assessed at the end of each 3-week treatment period.

Secondary Endpoints:

- Stool weights
- Signs and symptoms of malabsorption
- CNA
- Body Weight
- Body mass index
- Serum liposoluble vitamins A, D, E, and K

Statistical Methods

Statistical methods will be further detailed in the Statistical Analysis plan (SAP).

Sample size: The primary objectives of the trial are to assess the safety and investigate the relative efficacy of MS1819 as noninferior to porcine PERT. At least 30 patients completing both periods are judged enough to adequately assess their 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%). 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 to porcine PERT at the 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%.

Analysis Sets:

Safety Set: Patients receiving at least one dose of treatment.

Efficacy Sets

- **Intent-to-Treat Set:** Patients as randomized and receiving at least one dose of treatment. The primary analysis will be performed in the ITT set.
- **Per Protocol Set:** ITT patients completing both periods and without any major protocol deviation. A sensitivity analysis will be performed in the Per Protocol Set.

Handling Missing Data:

Missing data will not be replaced.

Safety Analysis:

Safety (AEs, SAEs, dropouts, and safety laboratory values) will be assessed by descriptive methods.

Efficacy Analysis:

- **Primary Efficacy Endpoint**
    - **Primary Model of Analysis:** The primary endpoint (ie, the CFA assessed at the end of each 3-week treatment period [Visit 6 or Visit 9]), will be analyzed in a mixed model including terms for sequence (MS1819-PERT vs PERT- MS1819); random patient nested in sequence; period (1 vs 2); and treatment (MS1819 vs porcine PERT). The treatment effect, along with the 95% confidence interval (difference in adjusted CFA means, MS1819 minus porcine PERT), will be estimated in this model. Noninferiority will be claimed if the lower bound of the 95% confidence interval is greater than -15%, where 15% is the noninferiority margin. If noninferiority can be claimed, then superiority will be tested.

  Subgroup Analyses: Analyses of CFA considering the same approach used for the primary set will be performed in the following subgroups:

    - by CFA level while receiving porcine PERT (<80% vs ≥80%). Of note, it is expected that about 75% of enrolled patients will have CFAs while receiving porcine PERTs of 80% or greater. An analysis will be done in the subgroup of patients with CFA below 80% while receiving porcine PERT, as well as in the subgroup of patients with CFA of 80% or greater while receiving porcine PERT.
    - By those receiving or not receiving gastric acid suppression
- **Key Secondary Efficacy Endpoints**
    - Stool weights, and signs and symptoms of malabsorption will be analyzed with the same approach used for the primary endpoint, switching non-parametric and semi-parametric methods employed in the case that model assumptions are violated.

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4. LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFFT	Cystic Fibrosis Foundation Therapeutics, Inc.
CFTR	cystic fibrosis transmembrane conductance regulator
cGCP	current Good Clinical Practice
cGMP	current Good Manufacturing practice
CI	confidence interval
CRF	case report form
CRO	contract research organization
DSMB	Data and Safety Monitoring Board
EPI	Exocrine pancreatic insufficiency
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FD	freeze-dried
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	high density lipoprotein
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	Institutional review board
ITT	intent-to-treat
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
PERT	Pancreatic Enzyme Replacement Therapy
PP	per protocol
PPI	proton pump inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SD	spray dried
SOP	standard operating procedures
ULN	upper limit of normal
VLDL	very low density lipoprotein
WHO	World Health Organization

5. INTRODUCTION

5.1 Exocrine Pancreatic Insufficiency

The pancreas is both an endocrine and exocrine organ. As an exocrine gland, it secretes pancreatic juice containing digestive enzymes and a bicarbonate-rich fluid that neutralizes acidic gastric secretions, providing the correct pH for duodenal digestion by the pancreatic enzymes that assist in the absorption of nutrients in the small intestine. Exocrine pancreatic insufficiency (EPI) is defined by a deficiency of exocrine pancreatic enzymes which results in the inability to maintain normal digestion. The symptomatology of EPI is mainly due to pancreatic lipase deficiency, an enzyme that hydrolyzes triglycerides into monoglycerides and free fatty acids.

Lipid maldigestion due to lipase deficiency can lead to weight loss; steatorrhea (characterized by greasy diarrhea); fat-soluble vitamin deficiencies (eg, vitamins A, D, E, and K); and can eventually lead to vitamin B12 deficiency and a potential decrease in quality of life (King et al, 1979). In EPI due to cystic fibrosis (CF) or chronic pancreatitis, there is a decrease in bicarbonate output, causing a lower intestinal pH, which leads to precipitation of bile salt acids and impairment of micelle formation of fats. Fat maldigestion is further exacerbated by lower levels of pancreatic lipase and colipase leading to decreased hydrolysis of intraluminal fat (Struyvenberg et al, 2017).

5.2 Exocrine Pancreatic Insufficiency due to Cystic Fibrosis

Cystic fibrosis is an autosomal recessive chronic progressive disorder with high morbidity and a shortened life expectancy. It affects approximately 70,000 people worldwide (Cystic Fibrosis Foundation). In most Caucasian populations, CF prevalence is 7-8 cases per 100,000 inhabitants but is less frequent in other populations (Farrell, 2008; Banks et al, 2010; Cystic Fibrosis Foundation Patient Registry 2010). In the United States, there are approximately 30,000 affected individuals (Cystic Fibrosis Foundation Patient Registry, 2016). The disease occurs as a consequence of a mutation in the gene encoding for the CF transmembrane conductance regulator (CFTR) protein, a plasma membrane ion channel that mediates transport of chloride, bicarbonate, and other anions. Dysfunction of the CFTR gene leads to a decrease in luminal fluid volume and decreased pH, resulting in protein precipitation within the ductal lumen and loss of normal acinar cell function. Mutation of both alleles of CFTR results in the production of thick mucus, which causes a multisystem disease of the upper and lower respiratory tract, the digestive system, and the reproductive tract.

Cystic fibrosis is frequently associated with EPI and is usually observed at birth because of in utero exocrine pancreatic damage. A neonatal screening study found that 63% of infants with CF were exocrine insufficient, and approximately 30% of the exocrine sufficient group would become insufficient over the next 36 months (Waters et al, 1990). Individuals with

less severe CFTR mutations (Class IV, V, or VI) were more likely to develop EPI later in life (Ledder et al, 2014; Bodewes et al, 2015).

5.3 Standard of Care for the Compensation of Exocrine Pancreatic Insufficiency

Porcine pancreatic enzyme replacement therapy (PERT) is the standard of care to prevent maldigestion, malnutrition, and excessive weight loss (Greenberger and Toskes 2008, Dhanasekaran and Toskes 2010, Greenberger and Toskes 2013). This therapy uses animal pancreatic extracts, which have been marketed since 1938. Porcine pancreatic extracts (porcine PERT) consist of an enzymatic mixture from pig pancreas, namely amylase, protease, and lipase, which digest starch, protein, and lipids, respectively. Therapy with porcine PERTs has demonstrated efficacy on the maldigestion symptoms due to EPI.

Despite their long-term use, major concerns have been raised by the CF Foundation, the CF community, and the Food and Drug Administration (FDA) because of the animal ingredients used for porcine PERTs and the risk of transmission of conventional and nonconventional infectious agents. Furthermore, therapy with porcine PERTs has clear limitations:

- The protease enzymatic constituents of porcine PERTs are suspected to cause fibrosing colonopathy (Kimura et al, 1998; Kimura et al. 1999), a severe adverse event (AE) observed at high doses in young patients with CF.
- To prevent this risk of fibrosing colonopathy, the CF Foundation recommended that dosages should be limited to 500-2500 lipase units/kg/meal, ≤10,000 lipase units/kg/day, or ≤4000 lipase units/g of dietary fat/day (Stallings et al, 2008). Noticeably, porcine PERTs have only mild or null effects on creatorrhea (Van Hoozen et al, 1997, Airinei et al, 2011).
- Incomplete correction of the lipid malabsorption, which can only be reached by high doses of enteric coated enzyme therapy in approximately 50% of patients with EPI caused by chronic pancreatitis and/or pancreatectomy [Dominguez-Munoz et al, 2006; Safdi et al, 2006]. An internal survey based on all publicly available individual data show that only 25% of patients affected by CF with EPI had fully normalized coefficient of fat absorption (CFA) (ie, CFA higher than 93%) on porcine PERT substitution therapy. The incomplete enzymatic activity of porcine PERTs in the physiochemical environment of the upper digestive tract explains their reduced efficacy. A number of factors are involved, including the gastric acid pH in the range of 1 to 4; the intestinal pH ranging from 4 to 6 (porcine PERTs are active at pH > 6.5 in presence of biliary salts); and the protease content of the upper digestive tract (i.e., gastric pepsin).
- The hazard of zoonotic pathogen transmission to humans remains possible with porcine PERTs because of their animal origins. For example, the porcine parvovirus may be present in these extracts, with (minimal) risk that it can cross species and transmit diseases to humans (Cherney, 2008).

- Most pancreatic enzyme products are unstable. To compensate for enzyme degradation over time, most manufacturers currently include overfill in the finished product. Therefore, their composition is poorly standardized and results in large 'lot-to-lot' variation of efficacy and composition. As product instability requires the product to be stored at cool temperatures, efficacy can decrease once the bottle is open (eg, 6 months for Creon®).
- Some additional concerns identified with porcine PERTs include irritation of oral mucosa if chewed/retained and hyperuricemia because of the presence of purines in porcine pancreatic extracts [Package insert Creon, Pancreaze, Zenpep, Pertzye]. In addition, patients with an allergy to proteins of porcine origin may have severe allergic reactions.
- Because all of the currently marketed PERTs are porcine derived, there is a supply risk (both quality and quantity) that is dependent on the availability of pig herds.

Because of the risks and limitations of porcine PERT, new drugs are demanded by pharmaceutical regulatory agencies and patient associations.

A fundamental question is the value and usefulness of a lipase-only enzyme replacement therapy, such as MS1819-SD for patients with EPI. For decades, the only available enzyme supplements to treat EPI have been porcine-derived pancreatic enzymes containing a mixture of lipase, protease, and amylase. While the importance of the individual components in treating maldigestion has not been prospectively assessed, it is widely agreed that the earliest and sometimes only sign of malabsorption is steatorrhea (DiMagno et al, 1993; Ferrone et al, 2007). Extrapancreatic sources of protease and amylase exist (Dominguez-Munoz, 2007; Hammer et al, 2010), whereas little lipase is available other than that secreted by the pancreas. Furthermore, some have suggested that protease deficiency can be treated in part with essential amino-acid mixtures (Engelen et al, 2014). Most agree that amylase is the least important of the 3 supplemental pancreatic enzymes (Ladas et al, 1993) perhaps because of high amylase content in salivary gland secretions. In summary, the future value of a lipase-only supplement, either as a lipase-only replacement therapy in patients with mild to moderate EPI, or as an augmenting lipase for hyporesponsive patients reaching maximal doses of porcine enzyme treatment, remains to be seen. Furthermore, whether other nonporcine enzymes might be added to MS1819-SD should be considered. This Phase 2 study is the first step in development of MS1819-SD for use in CF patients with EPI. If a safe and efficacious dose for treatment of steatorrhea can be established, then appropriate Phase 3 studies can be considered.

5.4 Investigational Product (MS1819-SD)

MS1819-SD is a preparation of a recombinant yeast lipase, designated LIP2, which is a secreted enzyme, isolated from the strictly aerobic *Yarrowia lipolytica* that is found in various foods such as cheese and olive oil. This nonpathogen micro-organism is widely used as a biocatalyst (eg, erythritol production, a polyol used as a food additive) and is generally

recognized as safe by the FDA for several industrial processes. The genetically engineered strain of *Yarrowia lipolytica* contains 5 additional copies of the LIP2 gene integrated into its genome (total of 6 including the endogenous native LIP2 gene). The genetic stability of the strain has been assessed for 100 generations, providing a safety margin as the full fermentation process corresponds to approximately 30 generations. Both current Good Manufacturing Practice (cGMP)-compliant Master Cell Bank and Working Cell Bank have been manufactured.

The LIP2 gene product is a 334 amino-acid precursor that is released extracellularly as a 301 amino-acid protein after cleavage of its peptide signal. The protein is naturally glycosylated which provides efficient protection against the proteolysis by the gastric pepsin (Pignede et al, 2000). At least 4 secreted glycosylated isoforms of LIP2 have been characterized (Aloulou et al, 2007).

Until 2009, the active ingredient for MS1819 (recombinant yeast lipase, designated LIP2) was freeze-dried (FD) to obtain a final drug substance, MS1819-FD. From 2010 onwards, the process was changed for large scale production and the active ingredient for MS1819 was mixed with maltodextrin at a 1:2 ratio (dry weight/weight) and then spray dried (SD) to obtain a final drug substance, MS1819-SD.

In this clinical study AZ-CF2001, MS1819-SD is supplied in capsules of hydroxyl-propylmethyl cellulose containing 140 mg of MS1819-SD.

5.5 Preclinical Studies with MS1819

5.5.1 In Vitro Studies

The enzymatic activity of LIP2 has been extensively investigated *in vitro* and has an appropriate profile to compensate the EPI in patients with severe chronic pancreatic diseases. For example, the optimal activity of LIP2 occurs at pH 4–6, which is usually found in the duodenum of CF patients with decreased pancreas derived bicarbonate. In addition, LIP2 enzymatic activity is not inactivated by bile salts, which are normally present in the duodenum below the Vaters ampulla. Furthermore, LIP2 is active on triglycerides with a wide range of fatty-acid lengths, including long-chain triglycerides, which are the predominant forms of triglycerides in the human diet. Compared with the porcine pancreatic lipase, LIP2 is more active than the porcine pancreatic lipase with all triglycerides tested at pH ranging from 4 to 6.

5.5.2 In Vivo Studies

The efficacy of MS1819-FD has been investigated in minipigs; in which experimental pancreatitis and EPI were induced by pancreatic duct ligation. Daily doses of MS1819-FD 10.5 mg or greater were administered once a day nearly completely corrected the CFA of approximately 20 kg minipigs (Aloulou 2015).

The safety of MS1819-FD has been investigated in 2 nonclinical regulatory trials whereby MS1819-FD was well tolerated at dosages up to 1000 mg/kg in rats and 250 mg/kg in minipigs for up to 13 weeks.

In summary, MS1819-FD was effective in minipigs and was nontoxic in both rodents and nonrodent species up to a maximum feasible dose of over 3 month's administration.

5.6 Clinical Studies with MS1819

5.6.1 FLIP110 First-in-Man Study with MS1819-FD

The efficacy and safety of MS1819-FD have been investigated in a first-in-man study, FLIP110. This exploratory clinical trial without predefined statistical analysis objectives, was a randomized, double blind, placebo controlled, parallel study.

Patients affected with chronic pancreatitis or pancreatectomy and severe EPI, were randomly assigned to 2 phases with an allocation ratio of 2:1 to receive MS1819-FD 20 mg 3 times a day or a 'dummy' placebo treatment identical in aspect and taste. Each treatment was given for a phase of 1 week after a 1-week washout phase.

Twelve patients were randomly included: 8 in MS1819-FD phase and 4 in the placebo phase. Three patients in the MS1819-FD phase were excluded from the per protocol (PP) analysis because of severe protocol deviations (ie, steatorrhea < 7 g/day in the baseline phase demonstrating the lack of significant EPI in these patients).

The primary endpoint of the study was defined as the relative change in steatorrhea compared with baseline. A nonstatistically significant difference of the primary endpoint was found between the 2 phases both in intent-to-treat (ITT: -14.6 % ± 26.6 in the MS1819-FD phase vs +16.9 % ± 40 in the placebo phase; not significant) and PP analysis (-15.8 % ± 20.6 in the MS1819-FD phase vs +16.9 % ± 40 in the placebo phase; not significant), respectively.

Secondary efficacy endpoints also support the efficacy of MS1819-FD compared with placebo in both ITT and PP populations, including the absolute change in CFA (ITT: +6.1 ± 13.4 vs -6.7% ± 11.0), number of daily evacuations over 7 days (ITT: -19.2% ± 22.8 vs +4.1% ± 11.7; p =.09), the weight of stools (ITT: -10.6% ± 27.4 vs +25.5% ± 48.2; not significant), and Bristol scale, which is a classification of the form of human feces to evaluate the effectiveness of treatments for diseases of the bowel (ITT: -5.13% ± 15.5 vs +2.46% ± 16.6; p<.0001).

MS1819-FD was well tolerated with no serious adverse events (SAEs). Only 2 AEs were observed: constipation (2 patients in the MS1819 group) and hypoglycemia (2 patients in the MS1819 group and 1 patient in the placebo group).

In summary, the FLIP110 study supports the continued clinical investigations of the efficacy of higher doses of MS1819-FD using established surrogate biomarkers for EPI correction.

5.6.2 MS1819/16/01 Phase 2a Study with MS1819-SD

An open-label, dose escalation Phase 2a study (MS1819/16/01) was conducted to investigate the safety of escalating doses of MS1819-SD in 11 patients with EPI caused by chronic pancreatitis or pancreatectomy

The primary objective of this study was to investigate the safety of escalating doses of MS1819-SD (280 mg/day, 560 mg/day, 1120 mg/day, and 2240 mg/day). Safety assessments included immunoallergic side effects, digestive symptoms, and clinical laboratory tests. The secondary objective of this study was to investigate the efficacy of MS1819-SD by assessment of CFA.

Data from the first 8 treated patients are available and demonstrates clinical activity, where the greatest MS1819-SD response showed 14.5% improvement in CFA. The maximal absolute CFA response to treatment was 64.2%, with a trend to an inverse relationship to baseline CFA. Positive trends were observed on endpoints such as fecal nitrogen, Bristol stool scale, number of daily evacuations, and weight of stool, consistent with the CFA results.

No SAEs or notable mild to moderate events have been reported to date (Interim Analysis).

5.7 Rationale

Because of the limitations of porcine PERT therapy (outlined in Section 5.3), new drugs are required for the treatment of EPI due to CF or chronic pancreatitis. MS1819-SD has none of the highlighted drawbacks and the results from the FLIP110 study and preliminary results from the MS1819/16/01 study support the safety and efficacy of MS1819. Therefore, it is considered as an appropriate drug candidate for the treatment of EPI caused by CF.

This study, OPTION, is designed to assess the efficacy and safety of 2240 mg/day of MS1819-SD in patients with CF. This dose, recently studied in patients with chronic pancreatitis, is the highest dose studied to date, and was well tolerated. If this dose is well tolerated in patients with CF and shows evidence of improved digestion, higher doses may be considered for study.

5.8 Dose Justification

While this is the first study of MS1819-SD in patients with CF, previous studies in patients with chronic pancreatitis have included doses of MS1819-SD up to 2240 mg/day (see Section 5.6.2). A total of 11 patients have now received up to 3 weeks daily treatment; the tolerability has been acceptable. To bridge from these studies into patients with CF, we have set the dosage for this study at 2240 mg/day.

The use of mass (mg) for dose expression, rather than USP lipase units is the result of the biochemical difference between porcine pancreatic-derived lipase and the microbial-derived lipase from the yeast *Yarrowia lipolytica* (Aloulou et al, 2015). Porcine lipase is active at pH >7, while peak yeast-derived lipase activity occurs at pH 6. The USP assay for porcine lipase units is conducted using an olive oil substrate at pH 9, while the enzymatic activity for MS1819-SD is assayed using tributyrin as substrate at pH 6. No validated conversion factor is available for conversion of USP lipase units to tributyrin units. It has been suggested by the FDA for microbial-derived lipase products that mass rather than units be used for dose expression (Heubi et al, 2016).

6. STUDY OBJECTIVES

6.1 Primary Objectives

The primary objectives of this study are to assess the safety and efficacy of MS1819-SD vs porcine PERT in patients with EPI due to 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. Efficacy will be evaluated by comparing treatment with MS1819-SD to treatment with porcine PERT.

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

The OPTION study is a Phase 2, open-label, multicenter, 2x2 crossover trial to assess the safety and efficacy of MS1819-SD in patients with EPI due to CF in male and female patients aged 18 years or older. Efficacy will be evaluated by comparing treatment with MS1819-SD to treatment with porcine PERT. Refer to Figure 1 for a flow chart of the study design.

During the treatment period, patients will be randomized to either MS1819-SD (2240 mg/day) or to their prestudy porcine PERT.

A Data and Safety Monitoring Board (DSMB), consisting of members external to AzurRx BioPharma, Inc., and including 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.

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.

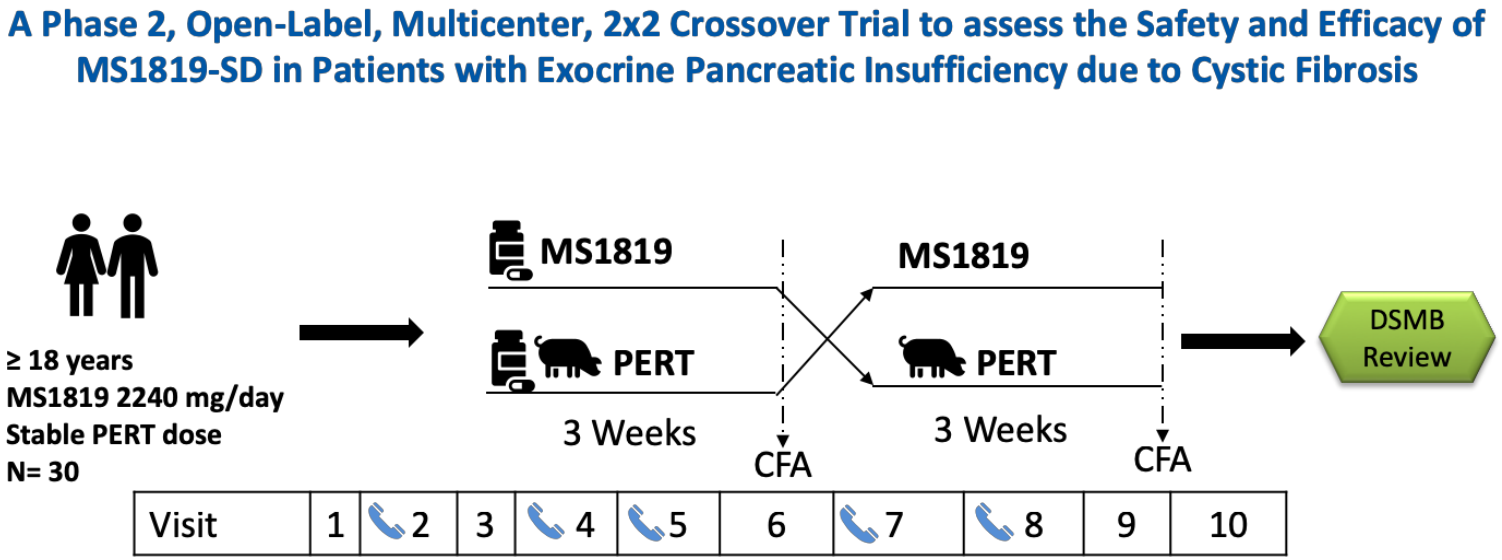
The study will not employ a washout period between the first treatment period and the second treatment period. Recent experience with crossover lipase enzyme treatment from commercial PERTs to investigational lipase has demonstrated that symptoms of malabsorption may become evident within a matter of days, indicating little residual carryover effect of the original lipase (clintrials.gov NCT 02279498; clintrials.gov NCT0305140). Furthermore, the 3-week duration of treatment with either study agent is well established as sufficient to show the degree of lipase effectiveness (FDA Package Insert, CREON; FDA Package insert, PANCREAZE).

This study is divided into 4 main periods.

- Screening Period (up to 21 days)
- First Treatment Period (approximately 3 weeks) of the crossover design
- Second Treatment Period (approximately 3 weeks) of the crossover design
- End-of-Study/Early Withdrawal (approximately 2 weeks)

Refer to Section 7.1.1 (Table 1) for the Schedule of Assessments.

Figure 1: OPTION Study Design Flow Chart



7.1.1 Schedule of Assessments

Table 1: 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**

	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**
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 count at the end of confinement						**X**			**X**	
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**	

	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**
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	**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**
fasting status) and pre-albumin										
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.

[G] The stool samples and weight will be sent and analysed at the central laboratory.

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

[K] 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.

7.2 Study Endpoints

7.2.1 Primary Efficacy Endpoints

Safety and efficacy will be primary endpoints. Safety will be evaluated by descriptive methods. Efficacy will be assessed by noninferiority of CFA, between the MS1819-SD treatment vs the porcine PERT treatment.

7.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study include:

- A comparison of 72-hour stool weights, MS1819-SD vs porcine PERT
- Signs and symptoms of malabsorption
    - 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, 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)
    - Incidence of visible oil/grease in stool (Yes/No)
    - Increased stool quantity (graded as 0=none, 1=mild, 2=moderate, or 3=severe)
    - Worsening of overall bowel habit (graded as 0=none, 1=mild, 2=moderate, or 3=severe)
- CNA
- Body weight
- Body mass index
- Serum liposoluble vitamins A, D, E and K

7.2.3 Safety Endpoints

AEs, SAEs and drop outs.

In addition, laboratory test results will be summarized (Section 15.2):

- Hematology
- Biochemistry
- Fasting lipid profile
- Urinalysis
- Serum MS1819 concentrations
- Antibodies against LIP2 lipase

7.3 Discussion of Study Design

7.3.1 Number of Planned Patients

Approximately 30 patients are planned to complete the study pending a safety assessment after each group completes their clinical treatments and evaluations. To account for a possible 20% dropout rate, approximately 38 patients are planned to be enrolled.

The statistical considerations on which the planned number of patients is based are described in Section 10.

7.3.2 Inclusion Criteria

To be eligible for study entry, patients must satisfy all of the following inclusion criteria:

1. Signed and dated informed consent form by patient as required by AzurRx or designee and appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Age ≥18 years at the time of screening
3. Male or female
4. Cystic fibrosis, based on 2 clinical features consistent with CF, plus initial diagnostic sweat chloride ≥60 mmol/L by quantitative pilocarpine iontophoresis or genotype
5. Under stable dose of porcine PERT ≥1 month; stable dose is defined as dose of medication not changed during this time period, and the medication must be commercially available and be administered in the recommended dose range.
6. A fair or better nutritional status as defined by:
    - BMI ≥16.0 kg/m^2 for female patients ≥18 years of age, or
    - BMI ≥16.5 kg/m^2 for male patients ≥18 years of age

7. Fecal elastase <100 µg/g of stool at screening
8. Clinically stable with no documented evidence of significant respiratory symptoms that would require administration of intravenous antibiotics, oxygen supplementation, or hospitalization within 30 days of screening or during the screening period.
9. Male and Female patients, if of childbearing potential, must use a reliable method of contraception during the study. A reliable method of birth control is defined as one of the following: oral or injectable contraceptives, intrauterine device, contraceptive implants, tubal ligation, hysterectomy, or a double-barrier method (diaphragm with spermicidal foam or jelly, or a condom), abstinence or vasectomy. Periodic abstinence (calendar, symptothermal, or post-ovulation methods) is not an acceptable method of contraception. The preferred and usual lifestyle of the patient must also be evaluated in determining if sexual abstinence is a reliable method of birth control
10. Be considered reliable and capable of adhering to the protocol, according to the judgment of the Investigator

7.3.3 Exclusion Criteria

Patients will be excluded from the study if one or more of the following criteria are applicable:

1. Established or suspected fibrosing colonopathy
2. Total or partial gastrectomy
3. A history of solid organ transplant, or significant surgical resection of the bowel; significant resection of the bowel is defined as any resection of the terminal ileum or ileocecal valve. Patients who have had qualitative, long-term changes in nutritional status after any other bowel resection (eg, increased or new need for pancreatic enzyme supplementation compared with preoperative status to maintain the same nutritional status) should also be excluded.
4. Any chronic diarrheal illness unrelated to pancreatic insufficiency (eg, infectious gastroenteritis, sprue, inflammatory bowel disease)
5. Known hypersensitivity or other severe reaction to any ingredient of the investigational medicinal product (IMP)
6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥5 ×upper limit of normal (ULN) or total bilirubin level ≥1.5 ×ULN at the Screening visit, unless due to Gilbert's syndrome. Cases of suspected or confirmed Gilbert's syndrome should be discussed with the Medical Monitor.

7. Signs and/or symptoms of liver cirrhosis or portal hypertension (eg, splenomegaly, ascites, esophageal varices), or documented liver disease unrelated to CF
8. Patients with a known allergy to the stool marker (FD&C Blue #2)
9. Feeding via an enteral tube during 6 months before screening
10. Routine use of anti-diarrheals, anti-spasmodics, or cathartic laxatives, or a change in chronic osmotic laxatives (eg, polyethylene glycol) regimen in the previous 3 months
11. History of severe constipation with <1 evacuation/week under appropriate laxative therapy within the last 12 months before screening
12. Documentation of distal intestinal pseudo-obstruction syndrome within the last 12 months before screening
13. Forced expiratory volume ≤30% at the Screening visit
14. Lactation or known pregnancy or positive pregnancy test at screening for women of childbearing potential
15. Participation in another clinical study involving an IMP within 30 days before inclusion or concomitantly with this study
16. Patient's with poorly controlled diabetes according to the Investigator's judgment

7.3.4 Removal of Patients from the Study

A patient may be withdrawn from the study at any time for any of the following reasons:

- Loss to follow-up
- Withdrawal of consent, for any reason, at any time
- Major protocol deviations that could compromise the interpretation of the results
- Occurrence of an immunoallergic reaction
- Occurrence of an adverse reaction (ie, an SAE related to IMP) that justifies the discontinuation of the IMP
- Pregnancy

The date of withdrawal and the reason for withdrawal must be fully documented in the case report form (CRF) and a short narrative description should be added in the patient's medical records.

If at the time of withdrawal, the patient has received the investigational study product (partially or totally), study staff should encourage the patient to attend the Early Withdrawal

Visit for follow-up safety investigations. These patients will be included in the ITT efficacy analysis and safety analysis.

If the reason for discontinuation is an AE, then the Investigator will seek to obtain follow-up information and to document the event until its resolution or stabilization. In any case, the Investigator will take all necessary measures to ensure the patient's safety and ensure the patient is treated in accordance with local standard of care.

If a patient is lost to follow-up, then the Investigator should make every effort to obtain maximum information on the reasons for the nonattendance to the visit and on the patient's state of health. All attempts will be documented in the patient's medical records.

Pregnancy

Patients will be instructed that known or suspected pregnancy occurring during the study, in patients or female partners of male patients, should be confirmed and reported to the Investigator. Any patient who becomes pregnant during the study must be promptly withdrawn from the study. Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Full details will be recorded in the CRF, or an SAE report will be completed if the patient has completed the study.

7.4 Investigational Products Administered

7.4.1 MS1819-SD Administration

At the time of prescribing, the Investigator or delegated site staff will fill in a source document with the appropriate dosing instructions.

MS1819-SD doses will typically be fractionated as follows: 1/4 of the daily dosage at each 3 main meals, and 1/8 at each of the 2 snacks (eg, for 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).

Please refer to Table 2 for dosing guidance.

Table 2: MS1819-SD Typical Dosing Schedule

	Dose: 2240 mg/day
Breakfast	4 x 140 mg capsules
Snack 1	2 x 140 mg capsules
Lunch	4 x 140 mg capsules
Snack 2	2 x 140 mg capsules
Dinner	4 x 140 mg capsules
Total	**16 (140 mg) capsules/day**

Note: Individual variations may occur as long as correct total daily dose is achieved.

7.4.2 Porcine PERT

Patients will take their porcine PERT at the same dose that was being administered during the prestudy period, during the appropriate treatment period.

7.4.3 Method of Assigning Patients to Treatment Groups

Patients will be randomized 1:1.

7.5 Previous and Concomitant Therapy

Standard-of-care medications are allowed (eg, antibiotics, mucolytic agents, aerosols, CFTR modulators). Patients taking CFTR modulators should be on stable doses for at least 3 months. Patients should not start taking CFTR modulators during the duration of the study.

Gastric acid suppressants are allowed but must be on stable dosage for 30 days before screening and must not be altered in dose or stopped during the study.

Prohibited medications during the entire clinical study will be as follows:

- Orlistat lipase inhibitor (eg, Alli®, Xenical®)
- Laxatives consisting of mineral oil and castor oil; chronic use of osmotic laxatives is permitted

- Symptomatic treatments of diarrhea: loperamide (eg, loperamide generic, Imodium®, Imodium A-D®, Diamode®, Imotil®, Kao-Paverin®); atropine/diphenoxylate (Lonox®); and atropine/diphenoxylate (Lomocot®).

7.6 Study Drug Materials and Management

7.6.1 MS1819-SD

Study drug MS1819 will be supplied by the Sponsor for use in the protocol and is limited to investigational use only. Please refer to current Investigator's Brochure for additional information.

MS1819-SD is 70% pure preparation of LIP2 protein. The concentrated ultra-filtration product obtained from fermentation is mixed with maltodextrin (1:2 ratio, based on the lipase dry weight) and subjected to spray drying (i.e., the drug substance). The drug product is formulated with inactive excipients and formulated in nonanimal origin capsules of hydroxypropylmethyl cellulose (also named HPMC or hypromellose). MS1819-SD capsules will be used in the study with 140 mg active pharmaceutical ingredient in each capsule.

MS1819-SD will be supplied as per following dosage form and will be provided in blister packs (wallets) in boxes:

- A white hard HPMC capsule filled with an off-white to light grey powder containing approximately140 mg of MS1819-SD.

7.6.1.1 MS1819-SD Shipment, Receipt, and Storage

MS1819-SD will be supplied in blister packs to the sites by the Sponsor, in accordance with local requirements. The IMP will be shipped at room temperature. The site is responsible for the appropriate storage of the IMP. The IMP must be stored in a secured limited-access area and maintained at room temperature ≤ 25°C.

7.6.1.2 MS1819-SD Misuse/Overdose

Any IMP misuse or overdose associated or not associated with any AE should be reported to the Sponsor or designee as an SAE. Overdose is considered as dose taken above the prescribed daily dose for the current dosing phase.

7.6.1.3 MS1819-SD and porcine PERT Compliance

The Investigator is responsible for ensuring compliance. Compliance with MS1819-SD and porcine PERT will be cross-checked with IMP accountability (number of capsules and blisters)

7.6.1.4 MS1819-SD Supply, Resupply, and Accountability

On receipt, the pharmacist or delegated site staff will record the date, details of the bottle, and quantity of capsules.

The investigational sites will be re-supplied with IMPs according to their respective recruitment rates.

The pharmacist or delegated site staff will be provided with specific forms for accountability of the IMP (including the returned blisters). Records will be kept up-to-date throughout the study and must be complete and accurate.

Used and unused IMPs must be made available to the Monitor or Sponsor designee who will verify the IMP accountability and cross-check pharmacy and Investigator records for compliance to the protocol requirements. Any discrepancy must be accounted for and documented.

7.6.1.5 MS1819-SD Return, Destruction, and Recall

Return of IMP:

- Unused, partially used, or empty blisters will be returned by the patient to the site at the end of each cycle.
- At the end of the study, the Sponsor will conduct a final reconciliation between delivered, dispensed, and used/unused IMPs.

Destruction of IMP:

- Unused, partially used, or empty blisters must not be destroyed at the Investigative Sites without written authorization from the Sponsor.
- Unused, partially used, or empty blisters returned to the pharmacy will be destroyed at the Hospital Pharmacy or Sponsor's Drug Distributor only after IMP accountability forms have been fully and accurately completed and verified by the Monitor.

- If an on-site destruction is required, then the site must obtain written authorization for destruction from the Sponsor, which will be filed along with the certificate of destruction in the IMP section of the pharmacy site file.

Recall:

- If an IMP batch is suspected to be defective, then the Sponsor will immediately inform the Investigator and the hospital pharmacist.
- The Monitor will coordinate with the investigative site staff for the return of the concerned batches as per the return procedure. Depending on the study status, new batches may be sent to the investigational site.

7.6.2 Nonabsorbable Dye Marker

The dye marker FD&C Blue #2, also named Indigo carmine or Indigotin, will be supplied in accordance with current Good Manufacturing Practices (cGMP).

7.6.2.1 Shipment, Receipt, and Storage and Dispensing

The dye marker will be supplied. The dye makers should remain between 15–25°C (room temperature) and will not require temperature monitoring during shipment and storage. The bottle must be placed in secure location at site.

8. TIMING OF STUDY PROCEDURES

Patients will provide written informed consent before any study-related procedures are performed.

The study Schedule of Assessments is included in Section 7.1.1 (Table 1).

8.1 Screening Period

Throughout the screening period, Patients are to remain on their prestudy porcine PERT.

8.1.1 Visit 1, D-21 to D1: Screening Visit

The following procedures will be performed at the Screening Visit (which may take place over more than one day):

- Obtain signed informed consent from the patient before any study-related assessments are made
- Collect relevant medical history, including concomitant illnesses/diseases, previous/concomitant medications, and record AEs
- Complete physical
- Specific CF assessment including a pulmonary function test by spirometry to determine FEV1 >30% of predicted normal for age, sex, and height at screening and a sweat chloride test
- Record body height and weight
- Record vital signs while sitting (blood pressure, pulse rate, breathing rate, and temperature)
- Assess for eligibility (against the inclusion and exclusion criteria)
- Record demographic data such as ethnic origin, date of birth, and sex
- Collect urine sample for urinalysis
- Perform a serum pregnancy test, if applicable
- Collect samples for hematology, clinical chemistry, PT/INR, activated partial thromboplastin time (aPTT)
- Collect blood samples for vitamin determination (A, D, E, and K)

- Patients will be required to fast before the collection of screening laboratory tests.
- Collect samples for fasting lipids and prealbumin
- Obtain a stool sample for fecal pancreatic elastase concentration in the selected central laboratory

8.1.2 Visit 2 Telephone (T)

Once patient eligibility is confirmed, patients will be contacted by telephone and instructed to:

- Refrain from alcohol consumption for 24 hours before the visit
- Bring their prestudy porcine PERT with them to the clinic in the event they are randomized to their prestudy PERT

8.2 First Treatment Period (Visits 3, 4 (T), 5 (T), and 6)

8.2.1 Visit 3 (Day 1): Randomization Visit - Must Occur Within 21 Days of Visit 1

During the first treatment period, patients will be randomized to either a fixed dose of MS1819-SD or to their prestudy porcine PERT. Visit 3 will take place if the patient is eligible to continue on the basis of data obtained at the Screening visit. The following procedures will be performed:

- Review Inclusion /Exclusion Criteria
- Focused physical exam to evaluate gastrointestinal tract, heart, and lungs
- Record body height and weight
- Record vital signs while sitting (blood pressure, pulse rate, breathing rate, and temperature)
- Record any changes in AEs and concomitant medication
- Randomization to either a fixed dose of MS1819-SD or to continue their prestudy porcine PERT
- Instruct patients on use and dosing
- Instruct/dispense study drug to patient (if randomized to MS1819-SD), otherwise patients are to continue on their prestudy porcine PERT

- Assess and record malabsorption signs and symptoms
- Collect urine sample for urinalysis
- Perform a urine pregnancy test (urine dip stick), if applicable
- Collect blood samples for vitamin determination (A, D, E, and K)
- Collect a serum sample for circulating anti-LIP2 lipase antibodies and MS1819-SD concentrations

8.2.2 V4 (T) (Day 8 ± 2) and V5 (T) (Day 15 ± 2)

The following procedures will be performed:

- Record any changes in AEs and concomitant medication review.
- Assess and record malabsorption signs and symptoms
- Confirm patient scheduled date for V6 (first stool collection in supervised controlled setting) and remind patients to come in fasted status.

8.2.3 Visit 6: Stool Collection in Controlled Supervised Facility (Day 17 ± 7)

Patients will be admitted for a maximum of 7 days to a facility providing supervised confinement for collection of stool for determination of CFA, CNA, and stool weight. The timing of the previous visits (Visit 1 and Visit 2) should be made with the aim of accommodating the patients' schedules for the supervised confinement. To accommodate patients' schedules for the supervised confinement, a ±7 day visit window is permitted.

- During the third week (Visit 3) (±1 week), patients will undergo admission to a controlled supervised facility for stool collection to support the CFA and CNA assessment and weight. A ±7 day visit window is allowed to accommodate investigative site staff and patients schedules for the supervised confinement.
- After appearance of fecal stool dye markers has been measured, patients CFA and CNA will be measured under their dose of MS1819-SD or prestudy dose of porcine PERT using standardized high-fat meals during the 3-day standardized diet.
- The CFA calculation will be based on the measured fecal fat content in relation to ingested fat quantities during the 3-day stool collection period.

After completion of the initial treatment period during the completion of V3, patients will be instructed to switch their study medication to either a fixed dose of MS1819-SD or their

prestudy porcine PERT. The stool collection and dietary procedures will be conducted as described in Section 8.3.3.1. (Instructions for Supervised Confinement)

The following procedures will be performed at Visit 6:

- Focused physical exam to evaluate gastrointestinal tract, heart, and lungs
- Record body height and weight
- Record vital signs while sitting (blood pressure, pulse rate, breathing rate, and temperature)
- Record any changes in AEs and concomitant medication
- Instruct/dispense study drug
- Verify study drug count on the last day of confinement
- Return MS1819-SD (only for patients randomized to MS-1819SD) on the last day of confinement
- Assess and record malabsorption signs and symptoms
- Begin 72-hour controlled diet
- Marker-to-marker stool collection and stool weight (central laboratory will weigh the stool that is collected)
- Collect urine sample for urinalysis
- Perform a urine pregnancy test (urine dip stick), if applicable
- Collect samples for hematology, clinical chemistry, PT/INR, and aPTT
- Collect samples for fasting lipids and prealbumin
- Collect blood samples for vitamin determination (A, D, E, and K)
- Collect a serum sample for circulating anti-LIP2 lipase antibodies and MS1819-SD concentrations
- Record all fat, protein, and dose of study drug taken with every meal and snack during the confinement period

At the end of the supervised confinement (once the second blue dye marker sample has been collected), patients will crossover to their new treatment). Patients randomized to MS1819-SD will begin treatment on their prestudy porcine PERT. Patients randomized to their prestudy porcine PERT will begin treatment on MS1819-SD.

8.3 Second Treatment Period (Visits 7 [T], 8 [T] and 9)

The second treatment period will begin once patients have passed their second blue dye marker at the end of V6, and the stool sample collection is complete. As soon as this has occurred, patients will crossover to their new treatment (either MS1819-SD or patient's prestudy porcine PERT).

8.3.1 V7 (T) (Day 29 ± 2) and V8 (T) (Day 36 ± 2)

The following procedures will be performed:

- Record any changes in AEs and concomitant medication review.
- Assess and record malabsorption signs and symptoms
- Confirm patient scheduled date for V9 (second stool collection in supervised controlled setting) and remind patients to come in fasted status.

8.3.2 Visit 9: Stool Collection in Controlled Supervised Facility (Day 38 ± 7)

Patients will be admitted for a maximum of 7 days to a facility providing supervised confinement for collection of stools for determination of CFA, CNA and stool weight. The stool collection and dietary procedures will be conducted as described in Section 8.3.3.1 (Instructions for Supervised Confinement). The following procedures will be performed at Visit 9:

- Focused physical exam to evaluate gastrointestinal tract, heart, and lungs
- Record body height and weight
- Record vital signs while sitting (blood pressure, pulse rate, breathing rate, and temperature)
- Record any changes in AEs and concomitant medication
- Instruct/dispense study drug
- Verify study drug count on the last day of confinement
- Return MS1819-SD (only for patients that crossed over to MS-1819SD) on the last day of confinement
- Assess and record malabsorption signs and symptoms
- Begin 72-hour controlled diet

- Marker-to-marker stool collection and stool weight (central laboratory will weigh the stool that is collected)
- Collect urine sample for urinalysis
- Perform a urine pregnancy test (urine dip stick), if applicable
- Collect samples for hematology, clinical chemistry, PT/INR, and aPTT
- Collect samples for fasting lipids and prealbumin
- Collect blood samples for vitamin determination (A, D, E, and K)
- Collect a serum sample for circulating anti-LIP2 lipase antibodies and MS1819-SD concentrations
- At the end of the supervised confinement (once the second blue dye marker sample has been collected):
    - All patients are to resume therapy on their prestudy porcine PERT. Patients who crossed over to MS1819-SD will resume treatment on their prestudy porcine PERT; Patients who crossed over to their prestudy PERT will continue with their prescribed therapy.
    - Patients on MS1819-SD will return all study drug.
- Remind patients of their scheduled Visit 10 date

8.3.3 Visit 10: End-of-Study /Early Withdrawal Visit (Day 56 ± 2)

Patients will return to the clinic for their End of Study visit approximately 2 weeks after their last dose of study drug (either MS1819-SD or the patient's prestudy porcine PERT). In the event that patients do not complete V9, an Early Withdrawal visit will be held approximately 2 weeks after the last dose of study drug (either MS1819-SD or the patient's prestudy porcine PERT). The procedures scheduled for the End-of-Study visit are the same as those that should be conducted for the Early Withdrawal visit. The following procedures will be performed at the End-of-Study/Early Withdrawal Visit:

- Focused physical exam to evaluate gastrointestinal tract, heart, and lungs
- Record any changes in AEs and concomitant medication
- Assess and record malabsorption signs and symptoms
- Collect a serum sample for circulating anti-LIP2 lipase antibodies and MS1819-SD concentrations
- Collect blood samples for vitamin determination (A, D, E, and K)

- Perform a urine pregnancy test (urine dip stick), if applicable

8.3.3.1 Instructions for Supervised Confinement for V6 and V9

Beginning at breakfast (the first meal) on Day 1 of the supervised confinement, patients will be placed on a 72-hour controlled diet, with 100 g fat/day (3 meals and 2 snacks per day) and a minimum of 1.5 to 2 g of protein per kg of body weight. Although it is preferred to have the patient consume exactly 100 g of fat per day, the fat excretion assay remains valid with a fat intake range within 15% of the goal (ie, 85 to 115 g of fat per day). The nutritional planning and calculation of dietary fat and nitrogen (protein) intake will be conducted by a qualified dietician at each site. The actual fat and nitrogen (protein) intake will be calculated from the recorded type and amount of food consumed. A central laboratory will calculate CFA, CNA, and stool weight values on the basis of dietary intake and the fat and nitrogen excreted in stool.

An indicator marker (500 mg of Food, Drug, and Cosmetics [FD&C] Blue #2) will be provided as two 250-mg capsules. The first marker (consisting of two 250-mg capsules) will be given at the beginning of breakfast or first meal on Day 1 of the supervised confinement to mark the start of the controlled diet. The second marker (two 250-mg capsules) will be given at the beginning of breakfast or first meal on Day 4 to mark the end of the controlled diet. Stool collection for fecal fat and nitrogen assessments must begin after the first marker has passed (the first stool containing the first marker is discarded) and is completed when the second marker has passed (the first stool containing the second marker is collected). Patients must continue the supervised confinement until the second stool marker is passed. The controlled diet will be maintained until the patient takes the second marker. Although it is not part of the controlled diet, the breakfast or first meal consumed on Day 4 of the supervised confinement should mimic (as closely as possible) the breakfast or first meal consumed on Day 1 of the supervised confinement.

If the patient has not passed the first blue dye marker within 4 days after ingesting the first dye marker capsules, or within 2 days after ingesting the second dye marker capsules, then 5-10 mg of oral bisacodyl may be given. Bisacodyl is the only laxative that may be given during the marker-to-marker stool collection period. Note: Patients on a stable chronic osmotic laxative may continue this therapy during the marker-to-marker stool collection.

The supervised confinement may take place within an inpatient facility or within an alternative confinement setting. This will be discussed and approved on an individual case basis by the sponsor. The alternative confinement setting will require the supervision of trained study site staff to oversee the study procedures.

9. SAFETY ASSESSMENTS

The planned Schedule of Assessments is included in Section 7.1.1 (Table 1).

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence experienced by a patient in a clinical investigation; it does not necessarily have a causal relationship with this study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Active or worsening of EPI is not considered an AE for the purposes of this study. Worsening of EPI disease should not be recorded as an AE, but should be recorded in the appropriate EPI CRF.

Adverse events may also include postdose complications that occur as a result of protocol-mandated procedures (eg, invasive procedures such as venipuncture, biopsy, etc.). Preexisting events that increase in severity or change in nature during, or as a consequence of, use of a medicinal product in a human clinical study will also be considered AEs. Any preexisting medical condition or diagnosis associated with a clinically significant laboratory abnormality should be documented on the CRF or eCRF. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the unifying diagnosis should be documented as the AE, rather than the individual signs and symptoms (eg, runny nose, scratch throat, cough, and low grade fever should be recorded as a upper respiratory infection and not each of the individual symptoms).

An AE does NOT include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that necessitates the procedure is an AE
- Any preexisting disease or condition or laboratory abnormality present or detected before the start of administration of study medication that does not worsen
- Laboratory abnormalities without clinical manifestations, which do not require medical intervention, or that do not result in termination or delay of study medication

- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, or convenience admissions)
- Overdose of any study drug or concomitant medication without any signs or symptoms, unless the patient is hospitalized for observation
- Worsening and/or flares of EPI disease activity. This should be recorded in the appropriate EPI CRF. However, if disease worsening meets any of the criteria for an SAE, it must be recorded on the SAE form and reported to the Sponsor or designee within 24 hours of becoming aware of the event.

9.1.2 Serious Adverse Event

An SAE is defined as any adverse experience occurring at any dose of study medication that occurs between the time the patient signs the informed consent form through the end-of-study that results in any of the following outcomes:

- Death
- Life-threatening situation (patient is at immediate risk of death)
- In-patient hospitalization or prolongation of existing hospitalization for a clinically relevant reason (note that this excludes "social" hospitalization for nonmedical causes such as lack of transportation to home)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received study drug
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples may include, but are not limited to:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias that do not result in hospitalization
    - Seizures that do not result in hospitalization

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a health care facility.

Worsening and/or flares of EPI disease activity should be recorded in the appropriate EPI CRF. However, if disease worsening meets any of the criteria for an SAE, then it must be recorded on the SAE form and reported to the Sponsor or designee within 24 hours of becoming aware of the event.

9.1.3 "Serious" vs "Severe" Adverse Event

To avoid confusion or misunderstanding over the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided (excerpted from International Council for Harmonisation [ICH] E2A):

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.1.4 SAE Definition Clarifications

- Death is an outcome of an AE, and not an AE in itself.
- All deaths during study through the end-of-study, regardless of cause or relationship, must be reported.
- "Occurring at any dose" does not imply that the patient is actively receiving study drug at the time of the event.
- "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is an SAE.
- "In-patient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time, excepting situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, or convenience admissions). Hospitalization may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered an SAE).

- If any AE worsens during the study and eventually meets the criteria for an SAE the AE should be recorded as a new SAE.

9.2 Reporting Procedures for All Adverse Events

AEs will be recorded in the CRF for all patients from the time the patient signs the informed consent form through the end of the study or patient withdrawal.

The Investigator is responsible for ensuring that all AEs (as defined in Section 9.1 and as further specified below) observed by the Investigator or reported by patients are collected and recorded in the patients' medical records, in the CRF, and as an SAE in the electronic data capture system. These AEs will include the following:

1. All SAEs (as defined in Section 9.1.2) that occur.
2. All nonserious AEs (as defined in Section 9.1.1) that occur.

The following AE attributes must be assigned by the Investigator:

- AE diagnosis or syndrome(s) (if known, signs or symptoms if not known);
- event description (with detail appropriate to the event);
- dates of onset and resolution; severity; assessment of relatedness to study drug; and
- action taken with study medication.

The Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRFs.

It will be left to the Investigator's clinical judgment to determine whether the relatedness of an AE, and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment because of what he or she perceives as an intolerable AE. If either of these situations arises, the patient should be strongly encouraged to complete the End-of-Therapy assessments and be under medical supervision until symptoms cease or the condition becomes stable.

9.3 Grading of Adverse Events,

The Investigator will be asked to provide an assessment of the severity of the AE using the categories noted below. This assessment is subjective, and the Investigator should use medical judgment to compare the reported AE to similar events observed in clinical practice. It is important to recognize that severity is not equivalent to event seriousness.

Grade 1 (Mild): usually transient; requires no special treatment and does not generally interfere with the patient's daily activities.

Grade 2 (Moderate): produces a mild to moderate level of inconvenience to the patient and may interfere with daily activities. These events are usually ameliorated by simple therapeutic measures.

Grade 3 (Severe): significantly interrupts daily activity and requires systemic drug therapy or other medical treatment.

9.4 Relationship to Study Drug

For each reported AE, the Investigator must make an assessment of the relationship of the event to the study drug using the following scale:

Unrelated: The event is definitely not or unlikely associated with study drug administration and is judged because of causes other than the study drug.

Related: Events considered to be related are those that follow a reasonable temporal sequence from administration of the study drug, that are not easily explained by another cause such as known characteristics of the patient's clinical state or other treatment or confirmed by improvement on stopping or slowing administration of the study agent (de-challenge), if applicable.

9.5 Serious Adverse Event Reporting Procedures

Serious adverse events will be recorded from the time the patient signs the informed consent form through the end of study. AEs will be followed until the event resolves or stabilizes, or until the end of study for that patient.

If the AE is an SAE and is assessed as "related to study drug", it must be followed until either the event is considered stable or resolved.

Any SAE assessed as "unrelated to study drug" will be followed as clinically indicated until its resolution or, if not resolving, until considered stable or until the final study visit for that patient whichever comes first.

All SAEs that occur must be reported within 24 hours of discovery or notification of the event. Initial SAE information and all amendments or additions must be recorded as an SAE in the electronic data capture system and sent to the Sponsor or designee.

If a patient is permanently withdrawn from the study because of an SAE, then this information must be captured as an SAE in the initial or follow-up electronic data capture record as well as the End-of-Therapy CRF.

The Investigator should notify the appropriate IEC/IRB of SAEs occurring at the site and other SAE reports received from AzurRx, in accordance with local procedures and statutes.

AzurRx will ensure that applicable regulatory authorities receive all relevant information on an SAE, in accordance with regulatory requirements. Results of AzurRx's investigation of other safety information shall be submitted, as required.

9.6 Pregnancy Reporting Procedures

Patients must be instructed to inform the Investigator immediately if they or their partners become pregnant after the patient has received their first dose of investigational product during the study. The following actions should be taken in the event of a confirmed pregnancy:

1. For female patients, study drug should be discontinued immediately.
2. The pregnancy should be reported to the Safety Group within 24 hours of notification using the applicable Pregnancy Report Form.
3. The Investigator should counsel the patient regarding the possible effects of previous study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.
4. The patient or the patient's pregnant partner must be monitored until the immediate postnatal period or until termination of the pregnancy. The outcome should be reported to the Medical Monitor using the Pregnancy Outcome Form.

Pregnancy is not an AE in and of itself. However, any pregnancy complications or elective terminations of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections (Section 9.2 and Section 9.5). Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Medical Monitor.

9.7 Hepatic Monitoring

The following guidelines are provided for the management of serum transaminase elevations in patients with new, clinically-meaningful increases in liver function tests occurring during the study. All cases of new (ie, since screening) elevations in ALT or AST ≥ 3 times ULN or any questions concerning the management of a patient with elevated serum transaminases should be discussed with the study Medical Monitor.

Patients who experience a new (ie, since screening) elevation in ALT or AST level to ≥3 × ULN OR total bilirubin ≥1.5 × ULN will have hepatic monitoring until one of the following occurs:

- Withdrawal from study if elevation in ALT or AST level to ≥3 × ULN is associated with a rise in total serum bilirubin to ≥2 × ULN (without laboratory findings of cholestasis [elevated serum alkaline phosphatase ≥2 × ULN])
- Withdrawal from study if elevation in ALT or AST level to ≥5 × ULN is associated with new or exacerbated gastrointestinal (GI) symptoms (ie, nausea, vomiting, right upper quadrant pain, and/or jaundice) and other causes are not evident
- Withdrawal from the study if elevation in ALT or AST is ≥10 × ULN regardless of serum bilirubin level

Causes of acute elevation of transaminases should be considered and ruled out (e.g., viral hepatitis, concomitant medications).

Patients discontinued from study drug administration should resume porcine PERT therapy according to physician prescription.

9.8 Data Safety Monitoring Board

An external, independent data monitoring committee (DMC) 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 DMC will consist of suitably qualified individuals, including CF experts.

9.9 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the assessment of biological products administered to patients with CF.

10. STATISTICAL METHODS

10.1 General Considerations

The statistical methods will be further detailed in the Statistical Analysis Plan (SAP).

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the description for making the change, will be described in the SAP and in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Statistical methodology and analyses will be in accordance with the principles outlined by the International Council for Harmonisation (ICH) E9 guidelines.

Tables, listings, and figures will be produced in accordance with the principles outlined by the ICH E3 guidelines.

Summaries will consist of descriptive statistics including the nonmissing counts, mean, standard deviation, median, Interquartiles (IQ), minimum and maximum values for continuous variables, and number and percentage of patients in each defined category for categorical variables.

Statistical tests will be performed at a one-sided 2.5% alpha. However, for the purposes of simplicity and clarity, displays will utilize the equivalent two-sided 5% nominal significance level along with 95% two-sided confidence intervals (CI). The primary goal of the study is to establish the safety of the chosen dose level; with the sample size, it is not anticipated that inferential statistics will achieve significance.

There will be no adjustment for multiplicity arising from secondary efficacy analyses of the primary endpoint and/or secondary endpoint testing. The primary efficacy analysis of the primary endpoint aims to compare the efficacy of MS1819 vs porcine PERT.

As a general rule, missing data will not be replaced.

10.2 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.

With regard to safety assessment, at least 30 patients completing both periods are judged enough to adequately assess their 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. 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%.

10.3 Analysis Sets

- Randomized set: patients as randomized. Unless specified otherwise, this set will be used for all patient listings and summaries of patient disposition.
- Safety Set: patients receiving at least one dose of treatment. Patients will be analyzed according to the treatment actually received. The Safety Set will be

used for all analyses of safety endpoints unless specified otherwise and for the presentation of patients in listings related to dosing of study drug.

- Efficacy sets:
    - ITT Set: Patients as randomized and receiving at least one dose of treatment. The ITT set is considered as the primary set for the efficacy analysis. The ITT set will be used for all analyses of efficacy endpoints.
    - Per Protocol Set: Subset of the ITT set comprising all patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the study clinician. Protocol deviations will be captured throughout the study and classified as minor or major and reviewed at a data review meeting before database lock. Attendees will include appropriate individuals from the Sponsor and contract research organization. Each major deviation will be categorized as either important or not important with respect to the effect on the primary endpoint analysis. A sensitivity analysis will be performed in the Per Protocol Set.

10.4 Handling Missing Data

Missing data will not be replaced.

10.5 Demographic, Other Baseline Characteristics and Medication

Demographics, other baseline characteristics, and medications will be summarized for the Safety Set unless specified otherwise.

10.5.1 Patient Disposition and Withdrawals

The following will be summarized:

- Number of screen failures
- Number of patients included in the Randomized Set, ITT, and PP sets
- Number of patients who completed the study (both treatment periods)
- Number of patients who discontinued the study early with reasons

The patient disposition, inclusion and exclusion criteria not met, eligibility for each analysis set, and protocol deviations will be listed.

10.5.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Set:

- for each sequence of each crossover
- for each crossover
- for all patients

10.6 Safety Analysis

Safety (AEs, SAEs, drop outs, and safety laboratory values) will be assessed by descriptive methods. A DSMB will be in charge to assess the safety of MS1819. The DSMB Chairperson will receive SAE reports in real time during the study. In addition, the DSMB will do a full data review at the end of the study to assess overall safety.

10.7 Efficacy Analysis

10.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the CFA assessed at the end of each 3-week treatment period (Visit 6 or Visit 9). CFA will be calculated as follows:

$$\text{CFA (\%)} = 100 ((\text{fat intake (g)} - \text{fat excretion (g)})/ \text{fat intake (g)})$$

Primary Analysis:

The primary analysis of the primary endpoint, i.e. the CFA assessed at the end of each treatment period (Visit 6 or Visit 9), will be performed in the ITT set.

The primary endpoint will be analyzed in a mixed model including terms for sequence (MS1819-PERT vs PERT- MS1819); random patient nested in sequence; period (1 vs 2); and treatment (MS1819 vs porcine PERT). The treatment effect, along with the 95% confidence interval (difference in adjusted CFA means, MS1819 minus porcine PERT), will be estimated in this model. Noninferiority will be claimed if the lower bound of the 95% confidence interval is greater than -15%, where 15% is the noninferiority margin. If noninferiority can be claimed, then superiority will be tested.

The possible carryover effect, which is entirely confounded with the sequence effect in a 2x2 crossover design, will be estimated. If there is a notable carryover, the analysis will be reported for each period separately.

Residuals of the model will be checked, and plotted vs predicted values.

Secondary Analysis:

The same analysis as described above will be performed in the PP set.

Subgroup analyses: Analyses of CFA considering the same approach used for the primary set will be performed in the following subgroups:

- by CFA level while receiving porcine PERT (<80% vs ≥80%). Of note, it is expected that about 75% of enrolled Patients will have CFAs while receiving porcine PERTs of 80% or greater. An analysis will be done in the subgroup of Patients with CFA below 80% while receiving porcine PERT, as well as in the subgroup of patients with CFA of 80% or greater while receiving porcine PERT.
- By those receiving versus not receiving gastric acid suppression.

10.7.2 Secondary Efficacy Endpoints

Coefficient of nitrogen absorption will be calculated and analyzed in the same manner as CFA.

Stool weights, and signs and symptoms for malabsorption will first be analyzed with the same approach used for the primary endpoint. Models for analyzing the secondary endpoints will be further detailed in the SAP. If these analyses reveal gross departures from model assumptions, a nonparametric or a (Hodges-Lehmann) semiparametric approach will be proposed to analyze non-normally distributed endpoints.

11. QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

An audit/inspection may be carried out by qualified Sponsor staff, by subcontracted auditors or by representatives of national or foreign Health Authorities to ensure that the study is conducted as per protocol and in accordance with regulatory requirements, and to ensure the validity of the data. Participation in this study implies acceptance to cooperate in any potential audit/inspection.

The audit/inspection may consist of an inspection of the premises and equipment together with verification of the study documents and data. The investigational team must be available for inspection or audit. When the Sponsor or the Investigator is informed that an inspection is to be performed, the other party must be informed immediately.

Audits/inspection may take place after the end of the study.

11.2 Monitoring

Data for each patient will be recorded on a CRF. Data collection must be completed for each patient who signs an informed consent form (ICF).

In accordance with cGCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The Investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities, direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

11.2.1 Responsibilities of the Monitor

Instructions for monitoring will be documented in a monitoring plan.

The responsibilities of the study monitor are defined in ICH-E6, Chapter 5. The Monitor, who is mandated by the Sponsor, must ensure that the study is conducted in accordance with GCP guidelines and all applicable local laws, and that the rights, the security and the well-being of the patients are respected.

During the conduct of the study, the monitor reports any deviations or persistent poor compliance with the study requirements and the Sponsor makes decisions about appropriate corrective actions.

Compliance:

- The monitor has the responsibility of assessing the progress of the study, of checking that the informed consent forms have been signed by the patient ensuring adhesion to and compliance with the study protocol and other study-related documents, and of ensuring the accuracy and completeness of the CRFs. Inconsistencies in the study records are to be resolved.

Source Data Verification:

- The monitor will perform source document verification and validation and request clarification to ensure the accuracy, completeness, and reliability of data.

Investigational Medicinal Product:

- The monitor must ensure that IMP handling is properly carried out and documented.

He/she must ensure that the Investigator site file is up-to-date with regard to essential documents.

11.3 Data Management and Coding

The assigned contract research organization will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries.

Study centers will enter data directly into an electronic data capture system by completing the CRF. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

12. ETHICS

12.1 Ethics and Regulatory Considerations

The current study is to be conducted in accordance with globally accepted standards of GCP (ICH-E6), the Clinical Trial Directive 2001/20/EC, the GCP Directive 2005/28/EC, the revised version of the Declaration of Helsinki set out in the European Directive, and with applicable local requirements.

The protocol will be submitted to the Health Authorities and a properly constituted IEC or IRB for formal approval of the study conduct in accordance with local regulations.

The study may not begin until the protocol has received appropriate approval from the Health Authorities in accordance with local requirements.

In accordance with specific local requirements, the Investigator may be responsible for submitting the protocol and any amendments to the local IEC/IRB. A copy of the decision letter, a list and versions of documents submitted, and a list of IEC/IRB members and their affiliation should be provided by the Investigator to the Sponsor.

During the study, the Sponsor should promptly notify the Investigators and Health Authorities of any relevant information that could affect the safety of patients or effect on the conduct of the study. The regulatory authorities will be notified that the study has ended on completion of the study.

12.2 Ethical Conduct of the Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and applicable national laws, local laws, and regulatory requirements.

12.3 Informed Consent

Before a patient's participation in this clinical study, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study. The Investigator is also responsible for asking the patient if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the Investigator

shall inform the patient's primary care physician of the patient's participation in the clinical study.

The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician should be documented in the patient's medical records, and the informed consent form should be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, then the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.4 Patient Confidentiality

Patient data will be kept strictly confidential. Patient anonymity will be protected by using number codes and /or initials.

13. REPORTING AND PUBLICATION, INCLUDING ARCHIVING

The Investigator shall not divulge unpublished data or information related to the study provided by the Sponsor, including but not limited to the study product characteristics, the Investigator's Brochure, the study protocol, case report forms, assay methods, or scientific data, to any third party without written approval from the Sponsor. In addition, any new information that may become available during the course of the study shall be considered as confidential and shall not be used for any purpose other than the performance of the clinical study.

The study data are the property of the Sponsor. The Investigator and any of the research staff shall obtain written approval from the Sponsor before the publication/communication of the results of any work carried out during or in relation to the study. Publication and/or communication of the results of the clinical study will be of a cooperative nature involving authors representing the Sponsor, the Investigators, and the scientific committee, if any.

The Sponsor reserves the right to request modification of the content and/or timing of any publication or presentation if a patent application, an existing patent, or other proprietary rights may be jeopardized.

Authorship of any publication related to the study and the order of presentation of the authors' names shall be approved by the Sponsor. The Sponsor shall not use an Investigator's name in any publication without his/her written permission and vice versa.

The Sponsor should retain all essential study-related documents, i.e., documents which permit evaluation of the conduct of a study and the quality of the data produced, in accordance with the applicable regulatory requirements of his/her country. These essential documents include, but are not limited to, signed protocol, Investigator's Brochure, printed CRFs, medical records, laboratory reports, informed consent forms, drug disposition records, safety reports, information regarding participants who discontinued, and other relevant documents and data.

Study-related documents should be kept together in the Investigator site file provided to the Investigator by the Sponsor. Sufficient information about the identity of all study patients (eg, name, medical records number, patient number, and study number) should be retained by the Investigator so that any Sponsor representatives, auditors, or inspectors may access this information when required. The Investigator must retain all records for 15 years or longer if required by specific local requirements. The Investigator will contact the Sponsor for authorization before the destruction of any study records or in the event of accidental loss or destruction of any of them. All records should be kept in a secure area; however, in the cases of audit or inspection, they should be rapidly made available.

14. REFERENCES

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15. APPENDICES

15.1 Investigator Signature Page

Protocol Title: 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

Study Name: **OPTION**: A Phase 2, **Op**en-Label, Mul**ti**center, 2x2 Cr**o**ssover Trial to assess the Safety and Efficacy of MS1819-SD in Patie**n**ts with Exocrine Pancreatic with Insufficiency due to Cystic Fibrosis

Protocol Number: AZ-CF2001

Confidentiality and cGCP Compliance Statement

I have read and understand the protocol (Study No. AZ-CF2001) and the Investigator's Brochure and I agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will conduct this protocol as outlined herein and will make every effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by AzurRx BioPharma, Inc. to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

I understand that the study may be terminated or enrollment suspended at any time by AzurRx BioPharma, Inc., with or without cause, or by me if it becomes necessary to protect the best interest of the study patients.

_____
Investigator Name (print)

_____
Signature Date

15.2 Clinical Laboratory Tests

Clinical Chemistry:	**Hematology:**
Serum Concentrations of:	**Hematocrit**
Sodium	**Hemoglobin**
Potassium	**Erythrocyte count (RBC)**
Chloride	**Leukocytes (WBC)**
Bicarbonate	**Absolute counts of:**
Blood urea nitrogen (BUN)	**Neutrophils, segmented**
Total Calcium	**Neutrophils, juvenile (bands)**
Phosphorus	**Lymphocytes**
Magnesium	**Monocytes**
Glucose	**Eosinophils**
Creatinine	**Basophils**
Albumin	**Platelets**
Prealbumin	
Total protein	**Other:**
Alkaline phosphatase	**Serum pregnancy test[a]**
Alanine aminotransferase (ALT)	**Urine pregnancy test[a]**
Aspartate aminotransferase (AST)	**Activated partial thromboplastin time (aPTT)**
Lactate dehydrogenase (LDH)	**Prothrombin time/International normalized ratio (PT/INR)**
Total bilirubin	**Vitamin A (retinol)**
Direct bilirubin	**Vitamin D (25-OH-D)**
Uric Acid	**Vitamin E (α-tocopherol)**
	Vitamin K (K1)
Fasting Lipid Profile:	**Stool:**
Total cholesterol	**Marker-to-marker stool collection**
Triglycerides	**Fecal Elastase**
Low Density Lipoprotein (LDL)	
High Density Lipoprotein (HDL)	
Very Low Density Lipoprotein (VLDL)	

Note: All labs will be assayed by AzurRx designated central laboratory unless otherwise noted.

a. **Only for females of child bearing potential**