CLINICAL STUDY PROTOCOL

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

Study Name:	OPTION 2: A Phase 2, Open-Label, Multicenter, 2x2 Crossover Trial to assess the Safety and Efficacy of MS1819 in Enteric Capsules in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis; with an Extension Phase Evaluation of Immediate Release MS1819 Capsules
Protocol Number:	AZ-CF2002
Investigational Product:	MS1819
Phase:	Phase 2b
Sponsor:	AzurRx BioPharma, Inc. 760 Parkside Avenue Suite 304 Brooklyn, NY 11226 USA
Protocol Date:	03 November 2020
Protocol Version:	3.0

1. PROTOCOL APPROVAL SIGNATURES

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

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Protocol Number: AZ-CF2002

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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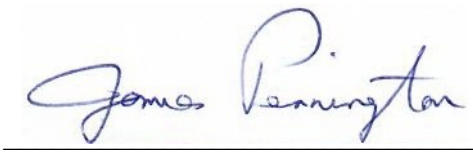

Signature

November 03, 2020

Date

2. SYNOPSIS

Name of Sponsor/Company: AzurRx BioPharma, Inc.	
Name of Investigational Product: MS1819	
Protocol Number: AZ-CF2002	
Protocol Title: A Phase 2, Open-Label, Multicenter, 2x2 Crossover Trial to assess the Safety and Efficacy of MS1819 in Enteric Capsules in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis; with an Extension Phase Evaluation of Immediate Release MS1819 Capsules	
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Study Site(s): This study will be conducted at approximately 15 sites in North America and the European Union.	
Number of Patients: Approximately **30**	**Phase of Development:** 2b
Objectives The primary objectives of this study are to assess the safety and efficacy of MS1819 in enteric capsules vs porcine pancreatic enzyme replacement therapy (PERT) in patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). The exploratory objective of the extension phase (EP) is to find a dose of MS1819 in immediate release capsules that is safe and results in CFA values in a therapeutic range.	
Study Design This is a Phase 2, open-label, multicenter, 2x2 crossover study assessing the safety and efficacy of MS1819, 2240 mg/day vs porcine PERT, and 4480 mg/day vs porcine PERT given at the same dose and dosing regimen that was being administered during the pre-study period. MS1819 will be administered in enteric capsules. MS1819 will be first assessed in a 2x2 crossover including approximately 30 patients completing both periods. Fifteen patients will be randomized to the MS1819 2240 mg/day vs PERT arm, and 15 patients will be randomized to the MS1819 4480 mg/day vs PERT arm. Patients in each arm will further be randomized to receive either the sequence consisting of MS1819 for 3 weeks followed by PERT for another 3 weeks or the opposite sequence of treatments, PERT for 3 weeks followed by MS1819 for another 3 weeks. Randomized patients will be males or females,18 years or older. Safety (adverse events [AEs], serious adverse events [SAEs], discontinuations due to adverse events, and safety laboratory values) will be assessed by descriptive methods. The primary efficacy endpoint is the coefficient of fat absorption (CFA) that will be assessed at the end of the 3-week period of treatment for each 2x2 crossover. Patients enrolled into the extension phase (EP) will be composed of patients who have completed the crossover phase of OPTION 2. These patients must continue to comply with the same inclusion and exclusion criteria as used in the crossover phase of the OPTION 2 trial (some screening tests may need to be repeated and all subjects must have completed an End of Study visit in the crossover phase).	

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

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

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

Inclusion Criteria

To be eligible for study entry in the crossover crossover phase and extension phase, 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 either a new/historic sweat chloride ≥60 mmol/L by quantitative pilocarpine iontophoresis (measured while not on a CFTR modulator) or genotype.
5. On stable dose of porcine PERT ≥1 month (30 days) prior to screening; 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 (need not be repeated for EP)
8. Clinically stable with no documented evidence of acute respiratory symptoms that would require administration of new oral or 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 crossover phase or extension phase of 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 (e.g., 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 (e.g., 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 (need not be repeated for EP)
7. Signs and/or symptoms of liver cirrhosis or portal hypertension (e.g., 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 (e.g., polyethylene glycol) regimen in the previous 3 months prior to screening
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 (repeat at initial visit of EP)
14. Lactation or known pregnancy or positive pregnancy test at screening for women of childbearing potential (repeat at initial visit of EP)
15. Participation in another clinical study involving an investigational product within 30 days prior to screening for this trial.
16. Patient's with poorly controlled diabetes according to the Investigator's judgment

17. Changes in CFTR modulator therapy during the 3 months prior to screening for the crossover trial or participating in the extension phase (for patients already on CFTR modulator therapy)
18. Any condition that the Investigator believes would interfere with the intent of this study or would make participation not in the best interests of the patient.
19. Did not complete end-of-study visit in crossover phase (for participation in extension phase)

Concomitant and Prohibited Medication

Standard–of–care medications are allowed (e.g., antibiotics, mucolytic agents, aerosols, CFTR modulators). Patients taking CFTR modulators must be on stable doses of the same modulator(s) for at least 3 months prior to screening. Patients should not start taking, or modify dose of, CFTR modulators for the duration of the study.

Gastric acid suppressants are allowed but must be on stable dosage of the same suppressant 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 (e.g., Alli®, Xenical®)
- Laxatives consisting of mineral oil and castor oil (chronic use of osmotic laxatives is permitted)
- Symptomatic treatments of diarrhea: loperamide (e.g., 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 is supplied as 280 mg, size zero enteric capsules (Capsugel, Morristown, NJ, USA) to be administered orally and taken with food.

For the EP, MS1819 is supplied as 140 mg, size 2, immediate release capsules 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 in the crossover phase will have approximately 21 days for screening, followed by approximately 6 weeks on study.

Patients who participate in the EP will be dosed with the immediate release MS1819 capsules (4.4 grams/day) for approximately 2 weeks. A second treatment period of approximately 2 weeks may be offered at a higher dose (6.7 grams/day). A 2-week End of Study/Early termination period and visit will occur when each patient completes their treatment period of study or withdraws from the study.

Criteria for Evaluation

Safety endpoints:

AEs, SAEs, discontinuations due to adverse events, 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
- Coefficient of nitrogen absorption (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: Based upon CFA data obtained in the recently completed Phase 2a trial (OPTION), 15 patients per MS1819 dose should provide sufficient point estimates of CFA in each group in the crossover phase. Given the acceptable safety profile obtained in the OPTION trial, a sample of 15 patients should be adequate for observation of safety per dose of MS1819. This study will use descriptive analyses for both safety and primary efficacy.

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

Analysis Sets:

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

Efficacy Sets

- **Modified Intent-to-Treat Se**t (mITT): All randomized patients receiving at least one dose of treatment and have at least one valid stool collection and CFA post baseline while receiving their assigned study drug. The primary analysis will be performed in the mITT set.
- **Per Protocol Set**: mITT 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, discontinuations due to adverse events, and safety laboratory values) will be assessed by descriptive methods.

Efficacy Analysis:

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 will be a comparison of the mean CFAs from the MS1819 treatment vs the porcine PERT treatment, using descriptive statistics. This analysis will be conducted for each of the two MS1819 doses.

An exploratory analysis of non-inferiority between the MS1819 and PERT groups will be conducted. The treatment effect, along with the 95% confidence interval of the difference in CFA (MS1819 minus porcine PERT), will be estimated Non-inferiority will be claimed if the lower bound of the 95% confidence interval is greater than -15%, where 15% is the non-inferiority margin.

Subgroup analyses:

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

- by CFA level while receiving porcine PERT (<80% vs ≥80%). 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.

Secondary Efficacy Endpoints:

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

Stool weights, signs and symptoms for malabsorption, body weight, BMI and lipid soluble vitamins (A, D, E, and K), will be analyzed using descriptive methods.

Exploratory Endpoints in Extension Phase:

Efficacy: CFA, CNA, stool weight, signs and symptoms of malabsorption, body weight, and body mass index, will be analyzed based upon descriptive methods.

Safety: AEs, SAEs, discontinuations due to adverse events, and safety laboratory values will be assessed by descriptive methods.

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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
CNA	coefficient of nitrogen absorption
CP	Crossover Phase
CRF	case report form
CRO	contract research organization
DSMB	Data and Safety Monitoring Board
EP	Extension Phase
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
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
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 for absorption of nutrients in the small intestine. Exocrine pancreatic insufficiency (EPI) is defined as 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. Pancreatic lipase is an enzyme that hydrolyzes triglycerides into monoglycerides and free fatty acids, deficiency.

Lipid maldigestion due to lipase deficiency can lead to weight loss, steatorrhea (excess fat in the feces), fat-soluble vitamin deficiencies (e.g., 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 also 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. CF affects more than 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 mutations 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 progressively become insufficient over the next 36 months (Waters et al, 1990). Even

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 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) (i.e., 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 may explain 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). Due to the acid lability of pig pancreatic lipase, commercial enzymes are formulated as enterically coated beads.
- 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).

- 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.
- As 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 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.

5.4 Investigational Product (MS1819)

MS1819 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 (e.g., 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. MS1819-SD will be referred to as MS1819 as this is the only form of drug substance currently in clinical development.

In is this clinical trial, MS1819 is supplied in ~280 mg (420,000 TBU), size zero enteric capsules (Capsugel, Morristown, NJ, USA).

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 6, and works well in a range from pH 4 to 7 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. 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 administered once a day nearly completely corrected the CFA of approximately 20 kg minipigs (Aloulou 2015).

The safety of MS1819 has been investigated in 2 nonclinical regulatory trials whereby MS1819 was well tolerated at dosages up to 4700 mg/kg in rats and 1175 mg/kg in minipigs for up to 13 weeks, equivalent to 1000mg/kg and 250mg/kg of lipase respectively.

In summary, MS1819 was effective in minipigs and was nontoxic in both rodents and nonrodent species up to a maximum feasible dose 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 (i.e., 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 supported the continued clinical investigations of the efficacy of higher doses of MS1819 using established surrogate biomarkers for EPI correction.

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

An open-label, dose escalation Phase 2a study (MS1819/16/01) was conducted to investigate the safety of escalating doses of MS1819 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 (280 mg/day, 560 mg/day, 1120 mg/day, and 2240 mg/day). Each dose was given over a two-week period. A CFA was obtained at baseline after washout, and after each escalating dose period. 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 by assessment of CFA.

Eleven patients were enrolled into the study, and ten completed all doses. One patient withdrew during the 1120 mg/day dose level due to severe diarrhea. This was not assessed as related to study drug.

In the Intent-to-Treat population, mean CFA rose from a baseline of 46.1% to 62.4% at the highest dose ($p = 0.001$). A number of symptoms improved comparing the highest dose to baseline, including stool consistency ($p < 0.001$), number of bowel movements ($p = 0.006$), steatorrhea ($p = 0.008$), and abdominal pain ($p = 0.148$). The treatment was well tolerated, with only two SAEs reported. Only one SAE was considered by the investigator to be possibly related to study drug, which was a patient with mild, transient elevations of liver enzymes. The elevations were between 2 and 3 X upper limit of normal (ULN), and lasted for about two weeks, a period of time that the patient was no longer receiving study drug. The patient had no symptoms of liver disease.

5.6.3 AZ-CF2001, 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

This trial, referred to as the OPTION trial, was the first experience with MS1819 in patients with cystic fibrosis. The trial began in February of 2019, and all patients completed the trial by July 2019. The trial was conducted in 14 sites, with 11 in the U.S. and 3 in Poland. All sites participated in enrollment. The primary objectives of the trial were to ascertain safety of 2240 mg/day dose of MS1819 in patients with cystic fibrosis and to compare the efficacy of MS1819 to commercial PERT in digestion of fat. The study was not powered for inferential statistics. A total of at least 30 patients were planned to complete the study.

Inclusion criteria were cystic fibrosis patients aged 18 or older, who had been clinically well-controlled while on a stable dose of PERT for at least 30 days. The dose of MS1819 employed was 2240 mg/day. This dose, used previously in a Phase 2 study of chronic pancreatitis, was the highest dose used in man prior to the OPTION study. In discussions

with FDA, it was agreed that the safety profile in the prior study in chronic pancreatitis patients was sufficient to allow this as the dose for a first-time study in cystic fibrosis.

Patients were randomized to begin the study in a treatment arm of MS1819, or a treatment arm using the same PERT, and same dose, they had been receiving prior to enrollment. After three weeks on treatment, a CFA was measured, and the patient was crossed over to the opposite treatment. After three more weeks of treatment, a CFA was measured, and the patient was returned to their pre-study PERT. An end of study visit was done two weeks after completing the treatments or upon early withdrawal of patients.

A total of 46 patients were screened, 41 were enrolled and 32 completed the study. Of the 9 withdrawals, one patient discontinued after completing both study treatment periods, three patients discontinued during treatment with PERT and five patients discontinued during treatment with MS1819. The withdrawals of patients who discontinued during treatment with MS1819 were primarily attributed to increased symptoms of exocrine pancreatic insufficiency.

The mean CFA for the MS1819 group was 56% (range 7% to 92%), and the mean CFA for the PERT group was 86% (range 57% to 97%). This mean CFA of 56% on a dose of 2240 mg/day MS1819 was similar to the mean CFA of 62% in the chronic pancreatitis study at the same dose. The mean coefficient of nitrogen absorption (CNA) for the MS1819 group was 93% and the mean CNA for the PERT group was 97%. Symptoms of exocrine pancreatic insufficiency were more prominent in the MS1819 group.

MS1819 was well-tolerated, with no remarkable adverse events. Three SAEs occurred during the screening period, but none during the trial itself. Each of these SAEs was due to pulmonary exacerbations of cystic fibrosis. Laboratory values were unremarkable during the trial.

5.7 Rationale and Dose Justification

Past *in vitro* studies have shown MS1819 to be relatively acid stable when compared to porcine derived lipases (see Investigator Brochure). However, it is also evident that below pH 4.0, there is increasing inactivation of MS1819 as the pH drops. Work by Gelfond, et al (2013), has shown that in CF patients, the pH in the upper duodenum may be as low as 3.5 for a short period, and the pH in the stomach could be even lower. The gastric emptying time of liquid or solid food may range from 1h-4h or longer and without any gastroprotection MS1819 is likely to have been exposed to low pH in patients with or without gastric acid suppression. Given that in the OPTION study, mean CFA with a dose of 2240 mg/day was 56%, a level below our target of 80%, it may be important to provide more protection of MS1819 against acid inactivation in the stomach and upper duodenum to provide adequate MS1819 dose and optimal lipolytic activity in the duodenum. Accordingly, for this study, enteric capsules will be employed for our MS1819 delivery. Intrinsically enteric capsules

provide API protection against degradation in the gastric environment. The capsule dissolution characteristics of enteric capsules filled with MS1819 show lipase availability at pH 5.5 and above, and no lipase release below pH 5 i.e. adequate gastroprotection. This matches nicely with our peak enzyme activity at pH 6 and allows release in the duodenum where digestion is taking place.

Also, given that our goal is to reach CFA values of 80% or greater, it is reasonable to employ a higher dose than that used in the OPTION study. While it is possible that simply adding the protection of an enteric capsule will provide adequate MS1819 delivery at the 2240 mg/day dose, it is also possible that a higher dose will still be necessary. To explore each of these possibilities, we will use both the 2240 mg/day as well as the 4480 mg/day dose in this study.

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 and has no activity at pH 9. The USP assay for porcine lipase units is conducted using an olive oil substrate at pH 9, while the enzymatic activity for MS1819 is assayed using tributyrin as substrate at pH 6. At pH 6 it is difficult to assess the true lipolytic activity of MS1819 using olive oil as a substrate given the high pKa of oleic acid (the main fatty acid component of olive oil), it is not possible to monitor the lipolysis directly as fatty acid will remain in a protonated form and the assay requires the acid form. 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 in enteric capsules vs porcine PERT in patients with EPI due to CF.

The primary safety objective of this study is to assess the safety and tolerability of doses of 2240 mg/day and 4480 mg/day of MS1819 provided in enteric capsules. Efficacy will be evaluated by comparing CFA values during treatment with MS1819 at doses of 2240 mg/day and 4480 mg/day versus treatment with porcine PERT.

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

This study is a Phase 2, open-label, multicenter, 2, 2x2 crossover trial to assess the safety and efficacy of MS1819 in enteric capsules 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 to treatment with porcine PERT. Refer to Figure 1 for a flow chart of the study design.

Two doses of MS1819 will be studied in parallel groups. These doses will be 2240 mg/day and 4480 mg/day. During the treatment period, patients will be first randomized to the two groups and then to either MS1819 or to their pre-study porcine PERT. After three weeks, a CFA will be collected and the patients will be crossed over to the alternative treatment for three more weeks of treatment, followed by another CFA.

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 of 3 main meals, and 1/8 at each of the 2 snacks. The 2240 mg/day dose will be fractionated as follows: 2 capsules of 280 mg with the morning, noontime, and evening meals, plus 1 capsule of 280 mg with the morning and evening snacks. The 4480 mg/day dose will be fractionated as follows: 4 capsules with each of the three main meals, and 2 capsules with each of the two snacks. Individual variations may occur as long as total daily dose is achieved.

The dose of porcine PERT will be the same dose and dosing regimen that was being administered during the pre-study 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 NCT02279498; clintrials.gov NCT03051490). The recently completed OPTION trial showed no carryover for CFA values after crossover. 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).

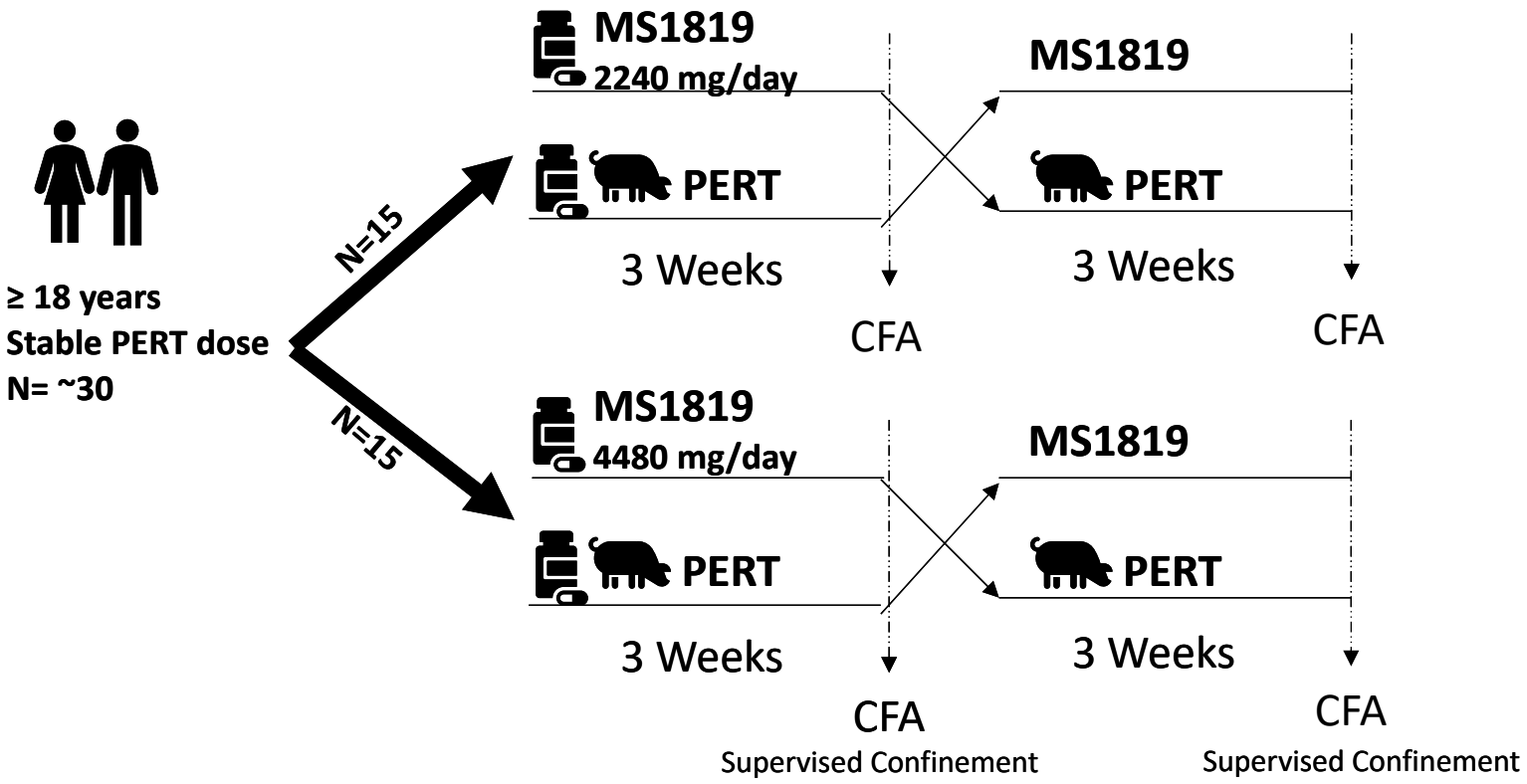
This study is divided into 4 main periods.

- 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 0 (Table 1) for the Schedule of Assessments.

Figure 1: Study Design Flow Chart

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



Visit	1	2	3	4	5	6	7	8	9	10

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**	**±2**	**+5**	**±2**	**±2**	**+5**	**±2**
Pre-Visit Instructions		**X**								
Supervised confinement						**X**			**X**	
Clinical Assessments										
Obtain informed consent	**X**									
Demographics	**X**									
Complete history and physical	**X**									
Focused physical exam[e]			**X**			**X**			**X**	**X**
Confirm CF diagnosis (Inclusion Criteria 4)	**X**									
Height/weight, vital signs (sitting)	**X**		**X**			**X**			**X**	
Inclusion/exclusion criteria review	**X**		**X**							
Concomitant medications	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Confirm scheduled date for next supervised confinement visit				**X**	**X**		**X**	**X**		
Study Treatment										
Randomization			**X**							
Instruct regarding prestudy PERT/Dispense study drug MS1819 (either 2240 or 4480 mg/day)			**X**			**X**			**X**	
Verify study drug count at the end of confinement						**X**			**X**	

	SCREENING		INITIAL TREATMENT PERIOD				SECOND TREATMENT PERIOD			END OF STUDY/EARLY TERMINATION
Visit Number	**1**[a]	**2 (T)**[b]	**3**	**4 (T)**[c]	**5 (T)**[c]	**6**[d]	**7 (T)**[c]	**8 (T)**[c]	**9**[d]	**10**
Study Week	**-3**		**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Study Days	**-21**		**1**	**8**	**15**	**17**	**29**	**36**	**38**	**56**
Visit Window (days)	**V1 to V2 interval ≤21 days**			**±2**	**±2**	**+5**	**±2**	**±2**	**+5**	**±2**
Return MS1819 (only for those on MS1819) at the end of confinement						**X**			**X**	
Record fat and protein intake and study drug taken at all meals and snacks						**X**			**X**	
Cross over to alternative treatment[f]						**X**				
Efficacy Measures										
Malabsorption signs & symptoms			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
72-hour controlled diet record						**X**			**X**	
Marker-to-marker stool collection and stool weight[g]						**X**			**X**	
Laboratory Tests										
Urinalysis	**X**		**X**			**X**			**X**	
Pregnancy test (serum for V1 screening and urine dipstick for other visits)[h]	**X**		**X**			**X**			**X**	**X**
Hematology, clinical chemistry, PT/INR, and aPTT[i]	**X**					**X**			**X**	
Fasting[j] lipids (patient to come in fasting status) and pre-albumin	**X**					**X**			**X**	
Vitamin A, D, E, and K	**X**		**X**			**X**			**X**	**X**
Serum samples for anti-LIP2 lipase antibodies and MS1819 concentrations			**X**			**X**			**X**	**X**

	SCREENING		INITIAL TREATMENT PERIOD				SECOND TREATMENT PERIOD			END OF STUDY/EARLY TERMINATION
Visit Number	**1[a]**	**2 (T)[b]**	**3**	**4 (T)[c]**	**5 (T)[c]**	**6[d]**	**7 (T)[c]**	**8 (T)[c]**	**9[d]**	**10**
Study Week	**-3**		**1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**
Study Days	**-21**		**1**	**8**	**15**	**17**	**29**	**36**	**38**	**56**
Visit Window (days)	**V1 to V2 interval ≤21 days**			**±2**	**±2**	**+5**	**±2**	**±2**	**+5**	**±2**
Fecal pancreatic elastase[k]	**X**									
Diagnostic Test										
Spirometry	**X**									
Resume Prescribed PERT										
Switch back to prescribed porcine PERT[l]									**X**	

[A] Screening procedures can occur up to 21 days before V1 through the first day of dosing (V3). As some lab assessments require fasting status, site may utilize a pre-screening telephone consent process to obtain agreement in advance for patients to adhere fasting for at least 8 hours. Patients will also be asked to bring a stool sample to the screening visit.

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

[C] Visits 4, 5, 7, and 8 are telephone visits to assess any changes to AEs and concomitant medications in addition to confirming the visit date for the next scheduled supervised confinement.

[D] Visit 6 and Visit 9 are the first and second scheduled confinement visits and can take up to 7 days. A 5-day window is permitted around the scheduled confinement for both V6 and V9 to accommodate for scheduling. Dosing must have occurred for at least 16 days prior to the start of the scheduled confinement.

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

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

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

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

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

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

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

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

7.2 Study Endpoints

7.2.1 Primary Efficacy Endpoints

Efficacy will be assessed by comparison of CFA between MS1819 treatment groups vs PERT treatment groups, using descriptive methods.

7.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study include:

- A comparison of 72-hour stool weights, MS1819 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, safety lab values, and discontinuations due to adverse events.

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 trial. To account for a possible 20% withdrawal rate, approximately 36 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 either a new/historic sweat chloride ≥60 mmol/L by quantitative pilocarpine iontophoresis (measured while not on a CFTR modulator) or genotype
5. Under stable dose of porcine PERT ≥1 month (30 days) prior to screening; 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 acute respiratory symptoms that would require administration of new oral or 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 (e.g., 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 (e.g., 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 ×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 (e.g., 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 (e.g., polyethylene glycol) regimen in the previous 3 months prior to screening
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 investigational product within 30 days prior to screening.
16. Patient's with poorly controlled diabetes according to the Investigator's judgment
17. Changes in CFTR modulator therapy during the 3 months prior to screening for the trial (for patients already on CFTR modulator therapy)
18. Any condition that the Investigator believes would interfere with the intent of this study or would make participation not in the best interests of the patient.

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:

- Lost 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 (i.e., 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 mITT 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

MS1819 Administration

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

MS1819 doses will typically be fractionated as follows: 1/4 of the daily dosage at each of the 3 main meals, and 1/8 at each of the 2 snacks. For the 2240 mg/day dose, 2 capsules of

280 mg will be given with the morning, noontime, and evening meals, and 1 capsule of 280 mg will be given with the morning and evening snacks. For the 4480 mg/day dose, 4 capsules will be given with the three main meals, and 2 capsules given for the two snacks.

Please refer to Table 2 for dosing guidance.

Table 2: MS1819 Typical Dosing Schedule

	Dose: 2240 mg/day	Dose: 4480 mg/day
Breakfast	2 x 280 mg capsules	4 x 280 mg capsules
Snack 1	1 x 280 mg capsule	2 x 280 mg capsule
Lunch	2 x 280 mg capsules	4 x 280 mg capsules
Snack 2	1 x 280 mg capsule	2 x 280 mg capsule
Dinner	2 x 280 mg capsules	4 x 280 mg capsules
Total	**8 (280 mg) capsules/day**	**16 (280 mg) capsules/day**

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

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 (MS1819 2240 or 4480 mg)

Patients will be randomized 1:1.

7.5 Previous and Concomitant Therapy

Standard-of-care medications are allowed (e.g., antibiotics, mucolytic agents, aerosols, CFTR modulators). Patients taking CFTR modulators should be on stable doses of the same modulator(s) for at least 3 months prior to screening. Patients should not start taking, or modify dose of, CFTR modulators for the duration of the study.

Gastric acid suppressants are allowed but must be on stable dosage of the same suppressant 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 (e.g., Alli®, Xenical®)
- Laxatives consisting of mineral oil and castor oil; chronic use of osmotic laxatives is permitted
- Symptomatic treatments of diarrhea: loperamide (e.g., 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

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 is a 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 non-animal origin enteric capsules (Capsugel, Morristown, NJ, USA). MS1819 will be supplied as 280 mg, size zero capsules.

MS1819 will be provided in blister packs (wallets) in boxes and/or HDPE bottles

7.6.1.1 MS1819 Shipment, Receipt, and Storage

MS1819 will be supplied in blister packs and/or bottles 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 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 only if it meets the criteria of an SAE. Overdose is considered as dose taken above the prescribed daily dose for the current dosing phase.

7.6.1.3 MS1819 and porcine PERT Compliance

The Investigator is responsible for ensuring compliance. Compliance with MS1819-SD will be cross-checked with study drug accountability and compliance with pre-study porcine PERT will be evaluated by subject self-report.

7.6.1.4 MS1819 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 and/bottles). 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 Return, Destruction, and Recall

Return of IMP:

- Unused, partially used, empty blisters or bottles 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, empty blisters or bottles must not be destroyed at the Investigative Sites without written authorization from the Sponsor.
- Unused, partially used, or empty blisters or bottles 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 must be stored in a secured limited-access area and maintained at room temperature ≤ 25°C and will not require temperature monitoring during shipment.

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.

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
- 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 for at least 8 hours before the collection of screening laboratory tests (insulin dependent diabetics may be excluded from fasting).
- Collect samples for fasting lipids
- Obtain a stool sample for fecal pancreatic elastase concentration in the selected central laboratory

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)

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 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)
- Collect urine sample for urinalysis
- Perform a urine pregnancy test (urine dip stick), if applicable
- Assess and record malabsorption signs and symptoms
- Record any changes in AEs and concomitant medication

- Randomization to either a fixed dose of MS1819 or to continue their prestudy porcine PERT
- Instruct patients on use and dosing
- Instruct/dispense study drug to patient (if randomized to MS1819), otherwise patients are to continue on their prestudy porcine PERT. For patients randomized to MS1819, instructions will vary depending on the dose to which the subject is randomized (either 2240 or 4480 mg/day)

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.

Visit 6: Stool Collection in Controlled Supervised Facility (Day 17 + 5)

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 +5 day visit window is permitted.

- During the third week (Visit 6) (+5 days), patients will undergo admission to a controlled supervised facility for stool collection to support the CFA and CNA assessment and weight. A +5 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 or prestudy dose of porcine PERT using standardized high-fat meals during the 3-day standardized diet. Additional detailed information provided in the study operations manual should be followed.
- 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 V6, patients will be instructed to switch their study medication to either a fixed dose of MS1819 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:

- Begin 72-hour controlled diet
- 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
- Assess and record malabsorption signs and symptoms
- 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 after patients have been in a fasting status for at least 8 hours (insulin dependent diabetics may be excluded from fasting).
- Collect blood samples for vitamin determination (A, D, E, and K)
- Collect a serum sample for circulating anti-LIP2 lipase antibodies and MS1819 concentrations
- Record all fat, protein, and dose of study drug taken with every meal and snack during the confinement period
- Verify study drug count on the last day of confinement
- Return MS1819 (only for patients originally randomized to MS1819) on the last day of confinement

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 originally randomized to MS1819 will begin treatment on their prestudy porcine PERT. Patients originally randomized to their prestudy porcine PERT will begin treatment on MS1819 (at either a dose of 2240 or 4480 mg/day).

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 or patient's prestudy porcine PERT).

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.

Visit 9: Stool Collection in Controlled Supervised Facility (Day 38 +5)

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. Dosing must have occurred for at least 16 days prior to the start of the scheduled confinement. 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:

- Begin 72-hour controlled diet
- 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

- Assess and record malabsorption signs and symptoms
- 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 after patients have been in a fasting status for at least 8 hours (insulin dependent diabetics may be excluded from fasting).
- Collect blood samples for vitamin determination (A, D, E, and K)
- Collect a serum sample for circulating anti-LIP2 lipase antibodies and MS1819 concentrations
- Verify study drug count on the last day of confinement
- Return MS1819 (only for patients that crossed over to MS1819) on the last day of confinement

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 will resume treatment on their prestudy porcine PERT; patients who crossed over to their prestudy PERT will continue with their prescribed therapy. 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 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. 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 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

Dosing must have occurred for at least 16 days prior to the supervised confinements. 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 (i.e., 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 (e.g., 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 (e.g., runny nose, scratch throat, cough, and low grade fever should be recorded as an upper respiratory infection and not each of the individual symptoms).

An AE does NOT include the following:

- Medical or surgical procedures (e.g., 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 (e.g., 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 (e.g., 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 (i.e., 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 (i.e., since screening) elevation in ALT or AST level to ≥3 × ULN OR total bilirubin ≥1.5 × ULN will have hepatic monitoring (ALT, AST, Bilirubin) 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 (i.e., 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 safety monitoring board (DSMB) will monitor and protect the safety and risk/benefit of the study patients throughout the study duration and evaluate the risk/benefit of study drug. The DSMB will consist of suitably qualified individuals, including CF experts.

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.

The primary efficacy endpoint analysis aims to compare the mean CFA after receiving MS1819 vs porcine PERT. With the sample size to be employed, primary efficacy analysis will be descriptive rather than inferential.

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

10.2 Sample Size Determination

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

10.3 Analysis Sets

- 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 summaries of patients in listings related to dosing of study drug.
- Efficacy sets:
    - mITT Set: All randomized patients receiving at least one dose of treatment and have at least one valid stool collection and CFA post baseline while receiving their assigned study drug. The mITT set is considered as the primary set for the efficacy analysis. The mITT set will be used for all analyses of efficacy endpoints.
    - Per Protocol Set: Subset of the mITT 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 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 treatment arm (i.e., 2240 mg/day and 4480 mg/day)
- for each sequence of each crossover
- for each crossover
- for all patients

10.6 Safety Analysis

Safety (AEs, SAEs, discontinuations due to adverse events, 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 will be a comparison of the mean CFAs from the MS1819 treatment vs the PERT treatment, using descriptive statistics. This analysis will be conducted for each of the two MS1819 doses.

An exploratory analysis of non-inferiority between the MS1819 and PERT groups will be conducted. The treatment effect, along with the 95% confidence interval of the difference in CFA (MS1819 minus porcine PERT), will be estimated. Non-inferiority will be claimed if

the lower bound of the 95% confidence interval is greater than -15%, where 15% is the non-inferiority margin.

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

- by CFA level while receiving porcine PERT (<80% vs ≥80%). 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 (CNA) will be calculated and analyzed in the same manner as CFA.

Stool weights, signs and symptoms for malabsorption, body weight, BMI and lipid soluble vitamins (A, D, E, and K), will be analyzed using descriptive methods.

11. EXTENSION PHASE

11.1 Exploratory Objective

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

11.2 Rationale and Dose Justification

The objective of the OPTION 2 study was to utilize an enteric capsule for MS1819 enzyme delivery in order to provide gastric protection against acid deactivation. Based upon in vitro studies, an expected 50% or more of inactivation of MS1819 might occur in the gastric phase if unprotected. The primary clinical endpoint for the study was to achieve consistent CFAs in the range considered by regulatory authorities and clinical experts to indicate an adequate nutritional supplement for fat digestion.

The results of OPTION 2 may not achieve the stated objective. As in the previous OPTION study, (see section 5.6.3 of this protocol), no safety issues have occurred in the OPTION 2 study. An expert in gastric physiology and gastric emptying has been consulted to understand possible mechanisms that may cause less than expected efficacy with the enteric capsules. In summary, it appears that asynchronous gastric emptying between the meal and the capsules is most likely the problem. Thus, upon eventual dissolution in the duodenum, the MS1819 lipase may not be exposed to much of the meal contents which have already passed beyond the duodenum.

It is clear, that while rational, the enteric capsule may not be performing to expectations. The Extension Phase of our clinical trial, described in this amended protocol, is intended to explore a different approach to solve the problem of delivering an adequate enzyme dose for meal digestion. The use of immediate release capsules, as was the case in the original OPTION trial, provides for immediate dissolution and mixing with the meal in the stomach. In this Extension Phase, we propose to overcome the partial loss of enzyme activity from stomach acid exposure by increasing the dosage of the immediate release formulation. Having the previous experience with the 2.2 grams/day dose in the original OPTION trial, we now propose to increase the dose to 4.4 grams/day, and if safe but not resulting in adequate CFAs, proceed to 6.7 grams/day dosing. Past experience showing a dose response in chronic pancreatitis patients (MS1819/16/01 Phase 2a Study with MS1819) offers encouragement that a higher dose accompanied by satisfactory mixing with meal contents will result in meeting our objective of achieving CFAs in a therapeutic range. The Data Monitoring Committee for the original OPTION study has reviewed the safety profile for the 2.2 grams/day dose in immediate release capsules and approved increasing the dose to 4.4 grams/day.

11.3 Extension Phase Study Design

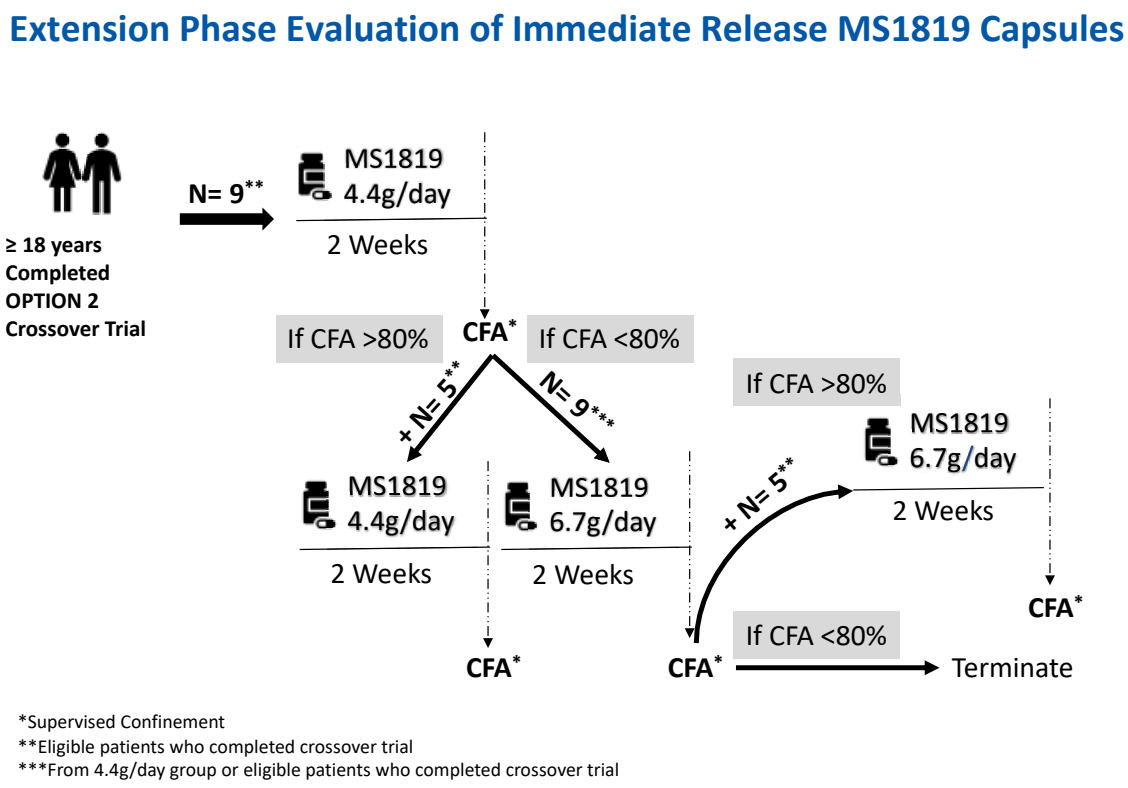
This will be an open label, dose ranging study using an adaptive design. One and potentially two doses of immediate release MS1819 capsules will be studied. Given that we now have a large cohort of patients studied while using a stable dose of PERTs in OPTION and OPTION 2 we will not enroll further PERT control patients.

Patients enrolled into the extension phase (EP) will be composed of patients who have completed the crossover phase of OPTION 2. These patients must continue to comply with the same inclusion and exclusion criteria as used in the crossover phase of the OPTION 2 trial (some screening tests may need to be repeated and all subjects must have completed an End of Study visit in the crossover phase). Concomitant medications will be allowed as in the crossover phase. The Drug Product, immediate release capsules each containing 140 mg of MS1819, will be the same as used in a previous OPTION trial (AZ-CF2001) of MS1819 in patients with EPI due to CF.

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

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

Figure 2: Design Flow Chart: Extension Phase



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

Table 3: Schedule of Assessments: Extension Phase

	4.4 g/day TREATMENT PERIOD			6.7 g/day TREATMENT PERIOD			END OF EXTENSION STUDY/EARLY WITHDRAWAL TERMINATION
Visit Number	**11[A]**	**12(T)[B]**	**13[C]**	**14[A]**	**15 (T)[B]**	**16[C]**	**17**
Study Week	**1**	**1**	**3**	**1**	**1**	**3**	**2 weeks after last dose of study drug**
Study Days	**E1**	**E5**	**E11**	**E1**	**E5**	**E11**	
Visit Window (days)		**±2**	**+4**		**±2**	**+4**	**±2**
Pre-Visit Instructions		**X**			**X**		
Supervised confinement			**X**			**X**	
Clinical Assessments							
Obtain informed consent	**X**			**X[D]**			
Focused physical exam[E]	**X**		**X**	**X**		**X**	**X**
Height/weight, vital signs (sitting)	**X**		**X**	**X**		**X**	
Inclusion/exclusion criteria review	**X**			**X[D]**			
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Confirm scheduled date for next supervised confinement visit	**X**	**X**		**X**	**X**		
Study Treatment							

Dispense study drug MS1819 (either 4.4 or 6.7g/day)	**X**			**X**			
Verify study drug count at the end of confinement			**X**			**X**	
Return MS1819 at the end of confinement			**X**			**X**	
Record fat and protein intake and study drug taken at all meals and snacks			**X**			**X**	
Efficacy Measures							
Malabsorption signs & symptoms	**X**	**X**	**X**	**X**	**X**	**X**	**X**
72-hour controlled diet record			**X**			**X**	
Marker-to-marker stool collection and stool weight[F]			**X**[G]			**X**[G]	
Laboratory Tests							
Pregnancy test (urine dipstick)[H]	**X**		**X**	**X**		**X**	**X**
Urinalysis			**X**			**X**	
Hematology, clinical chemistry, PT/INR, and aPTT[I]			**X**			**X**	
Fasting[J] lipids (patient to come in fasting status) and pre-albumin			**X**			**X**	
Serum samples for anti-LIP2 lipase antibodies and MS1819 concentrations	**X**		**X**	**X**		**X**	**X**
Diagnostic Tests							

Spirometry	**X**			**X[D]**			
Resume Prescribed PERT							
Switch back to prescribed porcine PERT[F]			**X**			**X**	

[A] Subjects do not need to go through full screening again.
[B] Visits 12, and 15 are telephone visits to assess any changes to AEs and concomitant medications in addition to confirming the visit date for the next scheduled supervised confinement.
[C] Visits 13 and 16 are scheduled confinement visits and can take up to 7 days. A +4-day window is permitted around the scheduled confinement for both V13 and V16 to accommodate for scheduling. Dosing must have occurred for at least 10 days prior to the start of the scheduled confinement.
[D] Only for patients that did not participate in first part of extension phase study
[E] The Focused Physical Exam will evaluate gastrointestinal tract, heart, and lungs.
[F] At the end of V13 and/or V16 (after the last stool sample has been collected), Patients will begin treatment with their prestudy porcine PERT.
[G] The stool samples will be sent to the central laboratory and CFA, CNA, and stool weight will be measured.
[H] Pregnancy status will be evaluated via urine pregnancy test
[I] On the basis of laboratory safety values, unscheduled hepatic monitoring testing may be performed in patients with new, clinically meaningful increases in liver function tests occurring during the study, in consultation with study designated Medical Monitor. These tests are to be done through the central labs.
[J] Fasting labs should be taken after patients have been in a fasting status for at least 8 hours.

11.4 EP Study Procedures

11.4.1 Inclusion and Exclusion Criteria

See Section 7.3.2 and 7.3.3 above. These criteria will be identical to those for the original OPTION 2 study except for Inclusion #7 and Exclusion #6 and #19.

Inclusion Criteria

To be eligible for study entry in the crossover phase and extension phase, 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 either a new/historic sweat chloride ≥60 mmol/L by quantitative pilocarpine iontophoresis (measured while not on a CFTR modulator) or genotype.
5. On stable dose of porcine PERT ≥1 month (30 days) prior to screening; 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 (need not be repeated for EP)
8. Clinically stable with no documented evidence of acute respiratory symptoms that would require administration of new oral or 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 crossover phase or extension phase of 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 (e.g., 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 (e.g., 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 (need not be repeated for EP)
7. Signs and/or symptoms of liver cirrhosis or portal hypertension (e.g., 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 (e.g., polyethylene glycol) regimen in the previous 3 months prior to screening
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 (repeat at initial visit of EP)
14. Lactation or known pregnancy or positive pregnancy test at screening for women of childbearing potential (repeat at initial visit of EP)
15. Participation in another clinical study involving an investigational product within 30 days prior to screening for this trial.
16. Patient's with poorly controlled diabetes according to the Investigator's judgment
17. Changes in CFTR modulator therapy during the 3 months prior to screening for the crossover trial or participating in the extension phase (for patients already on CFTR modulator therapy)

18. Any condition that the Investigator believes would interfere with the intent of this study or would make participation not in the best interests of the patient.
19. Did not complete end-of-study visit in crossover phase (for participation in extension phase)

11.4.2 Removal from the Study

See Section 7.3.4 above or at Sponsor discretion.

11.4.3 Previous and Concomitant Therapy

See Section 7.5 above.

11.4.4 Investigational Products

11.4.4.1 MS1819 Administration

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

Table 4: MS1819 Typical Dosing Schedule (Extension Phase)

	Dose: 4.4 grams/day	Dose: 6.7 grams/day
Breakfast	8 x 140 mg capsules	12 x 140 mg capsules
Snack 1	4 x 140 mg capsule	6 x 140 mg capsule
Lunch	8 x 140 mg capsules	12 x 140 mg capsules
Snack 2	4 x 140 mg capsule	6 x 140 mg capsule
Dinner	8 x 140 mg capsules	12 x 140 mg capsules
Total	**32 (140 mg) capsules/day**	**48 (140 mg) capsules/day**

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

11.4.4.2 Study Drug and Materials and Management

The drug product for the extension phase is formulated with inactive excipients and formulated in non-animal origin immediate release HPMC capsules (Capsugel, Morristown, NJ, USA). MS1819 for the extension phase will be supplied as 140 mg, size 2 capsules.

MS1819 will be provided in blister strips in boxes.

Please see Section 7.6. above for additional information about MS1819 management during the study.

11.4.5 Timing of Study Procedures

See Table 3: Schedule of Assessments: Extension Phase.

11.5 Safety Assessments

See Section 9

11.6 Statistical Methods

11.6.1 Sample Size

Sample sizes are estimates based upon prior studies of similar design with CFA and safety endpoints. The extension phase is exploratory in nature, dose-finding, and not intended to be powered for efficacy.

11.6.2 Missing Data

Missing data will not be replaced.

11.6.3 Exploratory Endpoints

Efficacy: CFA, CNA, stool weight, signs and symptoms of malabsorption, body weight, and body mass index, will be analyzed based upon descriptive methods.

Safety: AEs, SAEs, discontinuations due to adverse events, and safety laboratory values will be assessed by descriptive methods.

11.7 Quality Assurance And Quality Control

See Section 12

11.8 Ethics

See Section 13

11.9 Reporting and Publication, Including Archiving

See Section 14

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 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.

12.2 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.

12.2.1 Responsibilities of the Monitor

Instructions for monitoring will be documented in a monitoring plan. The clinical monitoring plan will include options for off-site data verification.

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.

12.3 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.

13. ETHICS

13.1 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.

13.2 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.

13.3 Informed Consent

An IRB/EC approved telephone consent to ensure that subjects come into clinic only if interested in proceeding with screening procedures is encouraged.

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.

13.4 Patient Confidentiality

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

14. 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 (e.g., 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.

15. REFERENCES

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16. APPENDICES

16.1 Investigator Signature Page

Protocol Title	A Phase 2, Open-Label, Multicenter, 2x2 Crossover Trial to assess the Safety and Efficacy of MS1819 in Enteric Capsules in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis; with an Extension Phase Evaluation of Immediate Release MS1819 Capsules
Study Name	OPTION 2: A Phase 2, Open-Label, Multicenter, 2x2 Crossover Trial to assess the Safety and Efficacy of MS1819 in Enteric Capsules in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis; with an Extension Phase Evaluation of Immediate Release MS1819 Capsules
Protocol Number	AZ-CF2002
Protocol Date	November 03, 2020
Protocol Version	3.0

Confidentiality and cGCP Compliance Statement

I have read and understand the protocol (Study No. AZ-CF2002) 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.

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Investigator Name (print)

_____

Signature Date

16.2 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**