Protocol Number: ANG003-22-101

A PHASE 1 OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY AND EFFICACY OF ANG003 IN PATIENTS WITH EXOCRINE PANCREATIC INSUFFICIENCY DUE TO CYSTIC FIBROSIS

Investigational Medicinal Product	ANG003 Pancreatic Enzyme Replacement Therapy
Phase of Development	Phase 1
Indication	Exocrine Pancreatic Insufficiency due to Cystic Fibrosis
Sponsor	Anagram Therapeutics, Inc. 10 Speen Street, Suite 302 Framingham, MA 01701 Telephone: (617) 466-3111
Protocol Date	22 MAR 2024 (Amendment 4 v006) 18 JUL 2023 (Amendment 3 v005) 01 MAY 2023 (Amendment 2 v004) 14 APR 2023 (Amendment 1 v003) 28 DEC 2022 (Initial v002) 07 SEP 2022 (Draft v001)
Protocol Version	006
IND No.	159827

SPONSOR PROTOCOL SIGNATURE PAGE

Protocol Number: ANG003-22-101

Protocol Version: 006

Protocol Date: 22 Mar 2024

Protocol Title: A Phase 1 Open-Label, Multicenter Study to Assess the Safety and Efficacy of ANG003 in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted]

[redacted]

[redacted]

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Number: ANG003-22-101

Protocol Version: 006

Protocol Date: 22 MAR 2024

Protocol Title: A Phase 1 Open-Label, Multicenter Study to Assess the Safety and Efficacy of ANG003 in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis

I confirm that I have read and understood this protocol and agree that it contains all the necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make all reasonable efforts to complete the study within the designated time. I will ensure that all sub-investigators and study staff members have read and understood all aspects of this protocol and are fully informed of the applicable study-related materials.

I agree to conduct this trial in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH), Guideline for Good Clinical Practice (GCP), and all applicable requirements of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and/or local and national regulatory requirements. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB/IEC. I acknowledge the confidentiality statement of this study.

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

I understand that the study may be terminated, or enrollment suspended at any time by Anagram Therapeutics, Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study subjects.

Clinical Institution: _____

Address: _____

Principal Investigator

Name and title (printed): _____

Signature: _____Date(*ddmmmyy*): _____

PROTOCOL SYNOPSIS

Sponsor: Anagram Therapeutics, Inc.

Study Title: A Phase 1 Open-Label, Multicenter Study to Assess the Safety and Efficacy of ANG003 in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis

Study Number: ANG003-22-101

Phase of Development: Phase 1

Name of Investigational Product: ANG003

Name of Active Ingredient(s): The active component of ANG003 is purified microbial lipase, protease, and amylase

Planned Number of Study Sites: Approximately 21 sites in the United States will participate

Objectives:

Primary

- To evaluate safety and tolerability of a single orally delivered ANG003 dose in adult subjects with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF)
- To evaluate four dose levels of ANG003 (4 lipase doses, 3 protease doses and 3 amylase doses) and select a dose(s) for Phase 2

Exploratory

- To evaluate the effect of ANG003 on fat absorption as determined by serial measurements of plasma docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), long chain polyunsaturated fatty acids (LCPUFAs) and total fatty acids (C14:C24)
- To evaluate the effect of ANG003 on protein and carbohydrate absorption as measured by changes in peptides, amino acids, and glucose
- To evaluate erythrocyte composition (DHA, EPA, LCPUFAs, total FA) in subjects with CF.

Study Design:

This study is a multicenter, randomized, parallel, active-treatment Phase 1 study of a single dose of orally administered ANG003 with a test meal in adult subjects with CF-related EPI. The study's overall objectives are to evaluate the safety, tolerability, and the effect of four dose levels of ANG003. Each subject will serve as their own control.

Each subject will be randomized to a single dose level of four possible combinations of lipase, protease, and amylase as shown in Table 1. During the 24-hour Baseline Substrate Absorption Challenge Test (SACT) period, fasting baseline blood samples will be collected prior to the high-fat SACT morning meal (SMM). Subjects will receive omega-3 fish oil triglyceride capsules and two other substrates (whey and potato starch) in the SMM. A small volume of blood will be collected six times in-clinic with two additional samples (10-12 h, 24 h ±2h) collected at home, neutral location or study site.

During the 24-hour ANG003 SACT, subjects will receive a single dose of ANG003 with the SMM. Subjects will receive omega-3 fish oil triglycerides and two other substrates (whey and potato starch) in the SMM. The short-term lipolysis of DHA and EPA triglycerides and the absorption of DHA and EPA fatty acids will be assessed by providing a fixed amount of fish oil softgel capsules (DHA and EPA triglycerides) and measuring levels of DHA and EPA fatty acids in plasma. The postprandial changes in plasma DHA and EPA levels with and without ANG003 will be compared during the two SACT periods.

Within-treatment changes in the Baseline and ANG003 SACT periods provides increased statistical power to detect differences as each subject serves as their own control. The parallel study design allows for mean estimation of within and between treatment changes in exploratory endpoints. Approximately 48 to 60 total eligible subjects, or 12 to 15 subjects per dose level are expected to be enrolled in the study.

Table 1. Dosage Compositions

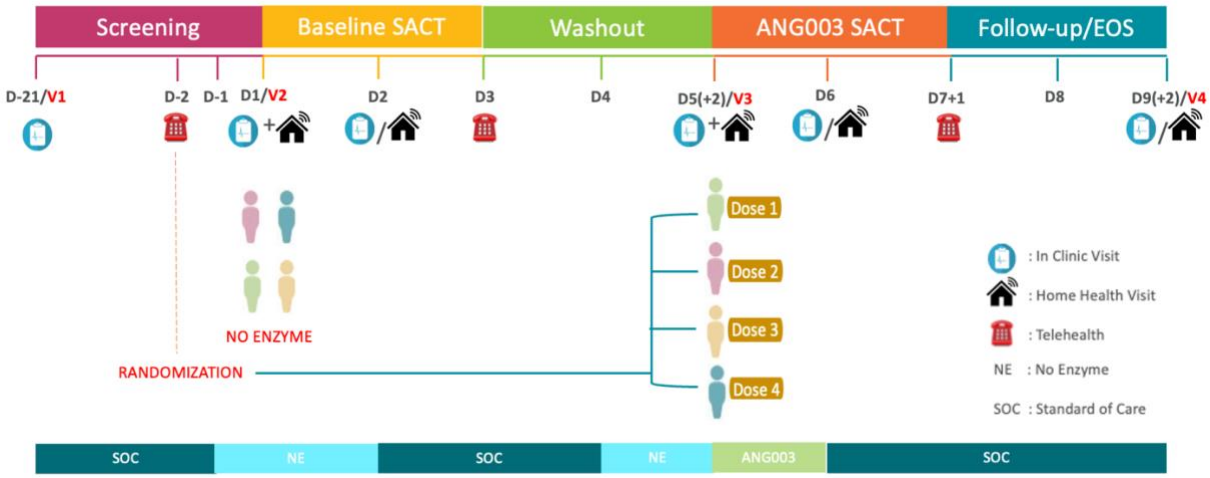
DOSE LEVEL	ANG003 DOSE (LIPASE / PROTEASE / AMYLASE)	[redacted]
1	20 mg / 25 mg / 40 mg	[redacted]
2	40 mg / 50 mg / 80 mg	[redacted]
3	80 mg / 50 mg / 80 mg	[redacted]
4	120 mg / 75 mg / 120 mg	[redacted]

The duration of the study will be approximately 30 days and the overall study design is displayed in Figure 1. The study consists of five distinct study periods as follows: 1) Screening; 2) Baseline SACT; 3) Washout; 4) ANG003 SACT; and 5) Safety Follow-up/End of Study (EOS). Subjects will report into the clinic for up to six study visits as follows: Visit 1 (Screening / V1 may occur up to -21 days before Visit 2), Visit 2 (Day 1), Day 2, Visit 3 (Day 5 (+2d)), Day 6, and Visit 4 (Day 9 (+2d)). For sites using the home healthcare nursing option, visits on Days 2, 6 and 9 may be conducted at home or neutral location. The two SACT Periods consist of a minimum 8 h fast before the baseline (t_0) blood draw prior to the SMM. Seven post-test meal blood samples will be drawn up to 24 h ±2h to measure fat absorption of DHA and EPA, fatty acids, peptides, and amino acids.

To evaluate absorption of key macronutrients, subjects will receive 12 standard meals (6 unique meals provided twice) and 4 snacks (2 unique snacks provided twice) to consume for a total of 4 days (Day -1, Day 1, Day 4, Day 5). The Sponsor has contracted with a meal delivery vendor and specific nutritional guidelines will be setup in advance by Registered Dieticians. Prepared meals have been nutritionally customized to mimic a standard CF diet.

The SMM is standardized, relatively high in fat, and contains fixed doses of substrates (i.e., 10 g of intact whey protein isolate and 20 g of potato starch). A fixed dose of an omega-3 fish oil supplement (~4 g DHA and EPA) will be consumed 2 - 3 bites into the breakfast test meal. On Day 1 and Day 5, the SMM will contain the same substrates. On Day 5, subjects will receive one dose of ANG003 with the SMM. Except for the two SMMs, no other meals during the SACT Periods will contain substrates.

Figure 1. Study Schematic



Abbreviations: EOS=End of Study; NE=No enzyme; SACT=Substrate Absorption Challenge Test; SOC=Standard of Care.

SCREENING PERIOD: Day -21 to -1

The Screening period may be up to 21 days long (Screening / V1 may occur up to -21 days before Visit 2). Day 1 / Visit 2 may occur as soon as 3 days after Screening / V1 as long as all eligibility requirements are met, in order to account for the dietary restrictions that begin on Day -3. During or prior to Visit 1, subjects will review and provide informed consent before completing any study conduct procedures. During screening, assessments will be performed, and clinical study staff will determine if the subject meets all inclusion criteria and does not meet any exclusion criterion for study entry. Waivers for any eligibility criteria are not allowed. If no existing confirmation of EPI by a fecal elastase test, fecal fat, or pancreatic function test(s), the subject will be provided with a home test kit for measuring stool elastase.

Screening assessments will include demographics, medical and PERT history, Patient Assessment Gastrointestinal Symptoms (PAGI-SYM), height, weight, vital signs, oximetry, full physical examination, fatty acid dried blood spot (DBS), safety laboratory testing (hematology, clinical chemistry, urinalysis, blood lipids, serum proteins), follicle stimulating hormone (FSH) test (if applicable), pregnancy test for childbearing females, blood samples for analysis endpoints, serum vitamin tests (A, D, E and K), vitamin DBS tests (A, D and E) and concomitant medication review. Procedures performed are specified in the Schedule of Assessments (Table 4) and sample collection will be detailed in a study-specific Laboratory Manual. At Visit 1, study staff will distribute one continuous glucose monitor (CGM) and train subjects on the proper application and use to measure interstitial glucose levels for future visits.

From Screening to Day -3, all subjects will continue their normal standard of care (SOC) treatment for CF including typical diet and enzyme replacement therapies. Nutritional supplements may also continue with the exception of omega-3 consumption; omega 3 > 500 mg DHA+EPA/day should be discontinued or reduced to <500 mg DHA+EPA/day from Screening / V1 to Day 9/EOS). SOC may also include the administration of CF transmembrane regulators (CFTR) modulator therapies and inhaled bronchodilators. Starting on Day -1 thru the 24 h blood draw on Day 2, H2-receptor antagonists (H2-blockers) and proton pump inhibitors (PPI), and SOC porcine pancreatic enzyme supplements are prohibited.

Prior to Day -3

Prior to Day -3, study staff will contact eligible subjects by phone to schedule an in-clinic Day 1 study visit. Detailed verbal instructions will be given on dietary and nutritional supplement restrictions, prohibited medications, fasting requirements, and blood sample collection to ensure a commitment to protocol compliance. On Day -3, dietary restrictions begin so subjects will be instructed to stop eating fish/shellfish through Day 9.

Day -2

On Day -2, study staff will contact subjects by phone as a reminder to apply the CGM sensor and transmitter to their skin on Day -1, consume only foods from the controlled meal plan, and stop use of PERTs after breakfast or 24 h before SACT. If study eligible, study staff will randomize the subject to one of four dose groups within the Electronic Data Capture (EDC) system. Subjects will be stratified initially by use of CFTR therapy or non-CFTR therapy. Randomization in EDC will trigger the release of investigational product (IP) directly to the site. The random allocation sequence will be generated by an independent Sponsor Statistician.

Day -1

Eligible subjects will receive a 2-day controlled meal plan via a meal delivery service vendor in advance of Day -1 or the 24 h prior to the Baseline SACT Period. Freezer-friendly meals and snacks will be provided in a single shipment to the subject's home to consume on Day -1 and Day 4. Each meal and snack will be labeled with ingredients, and freezing/ reheating instructions will be provided. Meals and snacks for Day 1 and Day 5 will be shipped directly to the clinical site.

On Day -1, subjects will apply the CGM sensor and transmitter to their skin, to begin the 24 h warmup period prior to Day 1 to ensure glucose reading accuracy. Subjects will follow their regular PERT regimen thru breakfast on Day -1 before stopping their PERT with the remainder of meals and snacks to allow a 24-hour PERT-free period before the test meal on Day 1. On Day 2 after the 24-hour blood draw, subjects may resume their PERT regimen at breakfast.

No protein powders, shakes, bars, or any other protein supplements are allowed on Day -1 for the 24-hour period before Day 1. No meals or snacks will be consumed by subjects on Day -1 outside of the standardized meals and snacks provided. Only calorie-free beverages (e.g., water, zero-calorie waters with fruit essence, zero-calorie waters enhanced with vitamins, zero-calorie sparkling water, black coffee, black tea, zero-calorie soda, or zero-calorie iced teas) are allowed during waking hours on Day -1. H2-receptor antagonists and PPIs will also be discontinued 24 h prior to Day 1. Subjects will complete a minimum 8 h overnight fast and refrain from drinking water for 1-hour prior to arrival at the study site on Day 1.

BASELINE SACT PERIOD: Days 1 and 2

On Day 1, a baseline (t_0) blood sample will be collected prior to the SMM. Over the 8-hour study visit on Day 1, subjects will consume the SMM, lunch, and one snack all supplied by the meal delivery vendor. Subjects will consume only calorie-free beverages (e.g., water, zero-calorie waters with fruit essence, zero-calorie waters enhanced with vitamins, zero-calorie sparkling water, black coffee, black tea, zero-calorie soda, or zero-calorie iced teas) for the day. The total daily calorie target is 2,800 kcal consistent with a standard CF diet. The macronutrient distribution will be approximately 36 - 40% kcal from fat, 15 - 20% kcal from protein, and 40 - 49% kcal from carbohydrates (Table 2).

First, a baseline blood sample will be collected at t0 then each subject will be asked to consume 100% of a small nutritional bar containing intact whey (10 g) and potato starch (20 g) to ensure full consumption of these two substrates. Second, a fixed dose of an omega-3 supplement (~4 g DHA+EPA) will be taken with a calorie-free beverage. Third, subjects will be provided with the breakfast test meal to consume in its entirety. The nutritional bar and breakfast test meal will each be individually weighed with a food scale at two timepoints: 1) before providing to the subject and, 2) if

the subject is unable to consume 100% of the nutritional bar and/or test meal. A digital picture will also be taken of the leftovers.

Four blood samples will be drawn post SMM at 1, 2, 4 and 6 h before a standard lunch is consumed. The exact time of each blood draw will be recorded. Timepoints for scheduled blood draws (±5 mins) are based on the start time of the t0 sample. The standard snack may be consumed any time after lunch.

Glucose readings will be collected via CGM. The CGM will be in blinded mode so readings will not be visible to study staff or subjects. Data will be recorded prior to the SMM (t_0) and at 15 min intervals i.e., 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, and 240 min post-test meal. After 4h of glucose readings, the CGM sensor will be removed and the data from transmitter will be extracted via the reader within 5-days of the visit. The transmitter will be retained at the site until the end of the study. The subject is given a second CGM to bring home for placement on Day 4, 24 h prior to arriving at the clinic on Day 5.

Subjects will depart the study site after an 8 h blood draw with their standardized dinner meal provided in a cooler bag. No meals or snacks will be consumed by subjects on Day 1 outside of the standardized meals and snack provided. The subsequent 10 to 12 h blood sample will be collected outpatient (home or neutral location) or the subject may prefer to return to the study site. The exact time of the draw will be recorded. Depending on the subject's preference, arrangements will be scheduled in advance for a home healthcare nurse to collect and process bloodwork obtained on subjects after they leave the study site, and ship samples to the associated central laboratory. Experienced, qualified (i.e., Registered Nurse, Nurse Practitioner and/or Physician Assistant) and protocol trained nurses will perform home or neutral location visits. To mitigate health risks and have subjects comfortable with a nurse visiting their home, infection control protocols (Appendix 1) and state COVID-19 guidelines will be followed.

On Day 2, subjects will be given the PAGI-SYM to answer questions on the frequency and severity of GI symptoms. A home healthcare nurse or study staff will collect vital signs, capture adverse events, review concomitant medications, perform a symptom-directed PE, and collect a 24 h (±2 h) pre-breakfast blood sample. The Bristol Stool Scale will be collected to categorize stool type. After the 24-hour study conduct procedures are performed, subjects will resume their normal PERT regimen with daily meals, snacks, beverages and restart H2-receptor antagonists or PPIs if previously discontinued.

Table 2. Dietary Intake of Caloric Distribution

FOOD* INTAKE	~% Total kcal	~Total kcal
Breakfast	30	840
Lunch	30	840
Snack	10	280
Dinner	30	840
DAILY TOTAL	100	~2,800

* Each meal will have similar macronutrient distributions
(Fat 36 - 40%, Protein 15 - 20%, and Carbohydrate 40 - 49%)

WASHOUT PERIOD: Days 3 and 4

Study staff will contact subjects by telephone on Day 3 to assess subject status, including AEs, concomitant medications, adherence to dietary and nutritional supplement restrictions, and protocol compliance with prohibited medications. Subjects will also be reminded to insert the CGM subcutaneous sensor and attach transmitter on Day 4. On Day 4, subjects will consume the same three

standard meals and one snack as on Day -1 of the Screening Period provided by the meal delivery service.

On Day 4, subjects will apply the CGM sensor and transmitter to their skin, to begin the 24h warmup period prior to Day 5 to ensure glucose reading accuracy. Subjects will follow their regular PERT regimen thru breakfast on Day 4 before stopping their PERT with the remainder of meals and snacks to allow a 24-hour PERT-free period before the test meal on Day 5. Subjects may resume their PERT regimen at breakfast on Day 6 after the 24-hour blood draw. Protein powders, shakes, bars and/or supplements are prohibited on Day 4 for the 24 h period before Day 5. No meals or snacks will be consumed by subjects on Day 4 outside of the standardized meals and snacks provided. Only calorie-free beverages (e.g., water, zero-calorie waters with fruit essence, zero-calorie waters enhanced with vitamins, zero-calorie sparkling water, black coffee, black tea, zero-calorie soda, or zero-calorie iced teas) are allowed during waking hours on Day 4. H2-receptor antagonists and PPIs are also discontinued on Day 4 thru the 24 h blood draw on Day 6.

ANG003 SACT PERIOD: Days 5 and 6

On Day 5 (+2d) after a minimum 8 h overnight fast, subjects will refrain from drinking water for 1 h prior to their arrival at the study site. Immediately after the baseline (t_0) blood draw, subjects will be provided the SMM containing three substrates and their assigned dose of ANG003. Authorized site staff will observe each subject self-administer the assigned dose of ANG003 on Day 5.

To ensure the same dietary intake of macronutrients proportioned on Day 1, the same meals and snacks will be repeated on Day 5. First, a baseline blood sample will be collected at t0 then each subject will consume a small nutritional bar containing intact whey (10 g) and potato starch (20 g) to ensure full consumption of these two substrates. Second, a fixed dose of an omega-3 supplement (~4 g DHA+EPA) will be taken with a calorie-free beverage. Third, the assigned dose level will be taken 2 – 3 bites into the breakfast test meal. All mini-tablets in the assigned dose level should be swallowed whole with no chewing or crushing. Fourth, subjects will be instructed to consume the breakfast test meal in its entirety. The nutritional bar and breakfast test meal will each be individually weighed with a food scale at two timepoints: 1) before providing to the subject and, 2) if the subject is unable to consume 100% of the nutritional bar and/or test meal. A digital picture will also be taken of the leftovers.

Only calorie-free beverages are allowed for the day. Serial blood samples will be collected at 1, 2, 4, and 6 h before the standard lunch is consumed. The exact time of each draw will be recorded. Timepoints for scheduled blood draws (±5 mins) are based on the start time of the t0 sample. The standard snack may be consumed any time after lunch.

Glucose readings will be collected via a wearable CGM system. The CGM will be in blinded mode so readings will not be visible to study staff or subjects. Data will be recorded prior to the SMM (t_0) and at 15 min intervals up to 4 h after the SMM. After 4 h of glucose readings, the CGM sensor and transmitter will be removed, and the data from the transmitter will be extracted via the reader within 5-days of the visit. The transmitter will be retained at the site until the end of the study.

Subjects will depart the study site after an 8-hour blood draw with their standardized dinner meal provided in a cooler bag. No meals or snacks should be consumed by the subjects on Day 5 outside of the standardized meals and snack provided. The subsequent 10 to 12 h sample will be collected as an outpatient (home or neutral location) or at the study site. The exact time of the draw will be recorded. Arrangements will be scheduled in advance for a home healthcare nurse to collect and process bloodwork obtained from subjects after they leave the study site, and ship samples to the associated central laboratory. Subjects may return to the study site for blood draws if they prefer.

On Day 6, subjects will be given the PAGI-SYM to answer questions on the frequency and severity of GI symptoms. A home healthcare nurse or study staff will collect vital signs, capture adverse events, review concomitant medications, perform a symptom-directed PE, and collect a 24 h (±2 h) blood sample before breakfast. The Bristol Stool Scale will record stool type and frequency over 48 h. After the 24-hour study conduct procedures are completed, subjects will resume their normal PERT regimen with daily meals, snacks, beverages and restart use of H2-receptor antagonists or PPIs if they were previously discontinued.

SAFETY FOLLOW-UP / EOS: Days 7 to 9

Telephone contact from study staff will occur on Day 7 to assess subject status, AEs, concomitant medications, adherence to dietary, supplement restrictions, and protocol compliance with prohibited medications. Regular use of PERTs will continue thru Day 9. Consumption of fish/shellfish and omega-3 supplements >500 mg DHA+EPA/day is restricted thru Day 9/EOS.

For subjects completing the study, the safety follow-up visit will be performed in-clinic or at home/neutral location, on Day 9 (+2d). Final study assessments are outlined as shown in Table 4. Subjects who discontinue early will return to the study site as soon as possible for an EOS visit. Any subject with an ongoing AE/SAE at the EOS visit will be followed until resolution or the Investigator has determined that the event has stabilized.

Dietary and Nutritional Supplement Restrictions

Except for avoiding fish/shellfish beginning on Day -3, subjects will follow their usual dietary management of EPI based upon individual recommendations from a dietician and/or healthcare professional(s). Daily omega-3 fish oil supplements >500 mg (DHA and EPA per day) is restricted from Screening / V1 thru Day 9/EOS. Beginning on Day -3 until Day 9/EOS, consumption of fish/shellfish is prohibited. Protein powders, shakes, bars, and supplements are restricted on Day -1 (24 h before Day 1) through Day 1 and from Day 4 through Day 5. PERTs are restricted after breakfast on Day -1 thru the 24 h blood sample on Day 2 AND after breakfast on Day 4 thru the 24 h blood sample on Day 6. Immediately after the 24 h (±2 h) blood draw, subjects may resume use of PERTs.

Subjects will be instructed to consume only calorie-free beverages (e.g., water, zero-calorie waters with fruit essence, zero-calorie waters enhanced with vitamins, zero-calorie sparkling water, black coffee, black tea, zero-calorie soda, or zero-calorie iced teas) during waking hours on Days -1 and 4. The same beverages are allowed during in-clinic Days 1 and 5.

Table 3. Protocol Restrictions

RESTRICTED FOOD, NUTRITIONAL SUPPLEMENTS AND MEDICATION	TIMING OF RESTRICTION	
	START	END
Omega-3 supplements >500 mg (DHA and EPA) daily	Screening	Day 9
Fish / shellfish	Day -3	Day 9
Protein powders, shakes, bars, and supplements	Day -1 Day 4	Day 1 Day 5
H2-receptor antagonists and proton pump inhibitors	Day -1 Day 4	Day 1 Day 5

Investigational Product, Dosage, and Mode of Administration: ANG003 consists of three orally administered enzymes (lipase, protease, and amylase) of microbial origin. These digestive enzymes were selected primarily based upon their: (1) activity at physiologically relevant pH levels without the need for enteric coating, (2) ability to digest a full range of fats, including LCPUFAs for lipase, dietary

proteins for protease, complex carbohydrates for amylase, and (3) lipase resistance to acid hydrolysis and proteolysis to assure activity in the stomach and throughout the small intestine (duodenum, jejunum, ileum).

ANG003 is an IP comprised of separate mini-tablets of each formulated enzyme packaged in sachets. Each clinically labeled sealed sachet will contain a combination of three enzyme-specific mini-tablets to achieve the stated enzyme combinations (Table 1). Additional information will be provided in a separate IP Manual.

Number of Subjects: Approximately 48-60 subjects will be enrolled with 12 to 15 subjects in each of four dose levels (*Lipase* 20 mg, 40 mg, 80 mg, and 120 mg; *Protease* 25 mg, 50 mg, and 75 mg; *Amylase* 40 mg, 80 mg, and 120 mg).

Criteria for Eligibility:

Inclusion criteria

Subjects must meet ALL the following criteria to be eligible to participate in the study:

1. Male and female subjects 18 years of age or older.
2. Confirmed diagnosis of CF defined by:
    a. CF signs and symptoms AND
    b. Two CF-causing mutations on genetic testing or sweat chloride >60 mEq/L.
3. Documented history of fecal elastase <100 μg/g stool.
4. EPI clinically controlled for at least 3 months. Controlled EPI is defined as minimal clinical symptoms and on a stable dose of PERT for 90 days before Screening as determined by the Investigator.
5. Adequate nutritional status measured by body mass index (BMI) $\geq$20 kg/m^2 for adult subjects.
6. Females of childbearing potential must either be sexually inactive (abstinent) during Screening until 28 days after the single ANG003 dose or be willing to use acceptable methods of birth control. Acceptable contraception is defined as:
    a. Oral, injected or implanted hormonal methods of contraception (e.g., Depo-Provera®, Implanon®) OR
    b. Placement of an intrauterine device or intrauterine system OR
    c. Barrier methods of contraception: condom or occlusive cap (e.g., diaphragm or cervical /vault caps) with spermicidal foam/gel/film/cream/suppository.
7. Females of non-childbearing potential must be post-menopausal with documented amenorrhea for at least one year prior to Day 1 and FSH serum levels consistent with post-menopausal status OR undergone sterilization procedures at least six months prior to dosing such as:
    a. Hysteroscopic sterilization
    b. Bilateral tubal ligation or salpingectomy
    c. Hysterectomy
    d. Bilateral oophorectomy.
8. All male participants who have not had a vasectomy must use effective contraception from Day 1 to 28 days after the ANG003 dose. Effective contraception is defined as a condom and spermicide for the male or condom and at least one of the following for a female partner:
    a. Intrauterine device
    b. Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive
    c. Be of non-childbearing potential.
9. Subject must be willing and able to adhere to the assessments, visit schedules, prohibitions, and dietary restrictions, as described in this protocol.

Exclusion Criteria

Subjects meeting any of the following criteria will be ineligible to participate in the study:

1. Subjects with diabetes mellitus who are unable to refrain from short-acting and rapid-acting insulin on Days 1 and 5 for a daily total of 6 h (up to 4 h CGM reading). NOTE: Subjects who are utilizing an insulin pump are classified as unable to refrain from short-acting and rapid-acting insulin for two 6 h periods and therefore are excluded.
2. Involuntary loss of 10% or more of usual body weight within last 6 months or involuntary loss of greater than 5% or more of body weight within 1 month.
3. Requires use of naso-gastric, J-tube, G-tube, and/or enteral feeding for the study duration.
4. CF pulmonary exacerbation within 30 days prior to the Baseline SACT Period (Visit 2).
5. Subjects who cannot discontinue omega-3 supplements >500 mg of DHA and EPA daily.
6. Subjects unable to tolerate missing a dose of PERT.
7. Subjects unable or unwilling to stop acid-blocking medicine (such as proton pump inhibitors or H2-receptor antagonists) for two 48-hour periods.
8. Liver cirrhosis and/or known portal hypertension, cholestatic liver disease, history of lung or liver transplant, listing for organ transplant or significant bowel resection.
9. Active cancer disease.
10. Known intestinal inflammatory diseases such as Crohn's Disease or ulcerative colitis, gastroparesis, diarrheal illness unrelated to EPI (e.g., infectious gastroenteritis, sprue, lactose intolerance, inflammatory bowel disease).
11. History of fibrosing colonopathy or recurring distal intestinal obstructive syndrome (DIOS) within six months of Visit 1.
12. Subjects with significant clinical/laboratory/radiological signs within 28 days before Visit 1 or between Visits 1 and 2 indicating unstable disease in the Investigator's opinion. NOTE: Hepatic function tests (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transaminase [GGT], bilirubin) must be ≤ 3 x upper limit of normal (ULN); hemoglobin ≥ 10 g/dL, platelets ≥ 75,000/mm^3, neutrophils ≥ 1.0 x 10^9/L, serum creatinine ≤2.0 mg/dL (177 µmol/L)
13. Known history of hepatitis B surface antigen (HBsAG), anti-hepatitis C virus (HCV) antibodies, or anti-Human Immunodeficiency Virus (HIV) 1 or 2 antibodies, or current positive laboratory-confirmed COVID-19 (SARS-CoV-2) infection.
14. Current alcohol, medication, or substance abuse.
15. Treatment with an investigational drug, biologic, or device within 30 days of Visit 1.
16. Female subjects who are pregnant, have a positive serum pregnancy test at Visit 1, are lactating, or plan to become pregnant during the study and/or < 90 days after receiving investigational product.
17. Allergy to soy or foods containing soy.

Primary and Exploratory Endpoints:

Primary

The safety and tolerability endpoints include the following:

- Frequency of adverse events, serious adverse events, and AEs leading to discontinuation
- Incidence of malabsorption symptoms (e.g., abdominal pain, constipation, diarrhea, distension/bloating, flatulence, indigestion/heartburn, nausea, steatorrhea, and vomiting)

- Clinical laboratory evaluations (hematology included complete blood cell count with differential and platelet count, serum biochemistry including blood urea nitrogen and creatinine, liver function tests, coagulation profile, and urinalysis)
- Vital signs (body temperature, heart rate, respiratory rate, blood pressure)
- Physical examination
- Concomitant medications

Exploratory

The exploratory efficacy endpoints include changes in:

- Plasma DHA and EPA AUC_{8h} and AUC_{24h}
- Time to peak concentration of DHA, EPA
- Peak plasma concentration of total DHA (µg/mL)
- Peak plasma concentration of total EPA (µg/mL)
- Change in plasma concentration of total DHA+EPA (µg/mL) over time
- Change in plasma composition (%) of DHA + EPA over time
- Erythrocyte membrane composition (%) of DHA, EPA (dried blood spot; omega-3 index)
- Erythrocyte membrane composition (%) ratio of omega-6 to omega-3 fatty acids
- Plasma composition (%) ratio of omega-6 to omega-3 fatty acids
- Plasma concentration of dietary peptides and amino acids (µg/mL)
- Serum protein concentrations (total protein, pre-albumin, albumin, transferrin)
- Change in plasma concentration of glucose (mg/dL) as measured by continuous glucose monitoring
- Change in plasma C-peptide over time.

Statistical Methods:

The applicable statistical methods will be described in a separate Statistical Analysis Plan (SAP), developed prior to data lock and data analysis. The SAP will provide complete statistical analytical details for the safety and exploratory efficacy data analysis, including the presentation of results in tables and listings.

Data from all clinical assessments will be listed and, where appropriate, summarized using descriptive statistics within and between treatment groups defined by the four dose levels. Summary statistics (n, mean, standard deviation, median, minimum, maximum) of the actual value, change and percent change will be presented for continuous variables. Frequencies of categorical variables will be presented. Where appropriate, the presentation of results will include shift tables.

Exploratory data analyses will include analysis of variance methods. Summary statistics of within and between treatment changes in efficacy measures will generate P-values and confidence intervals to quantify the magnitude of treatment effect and to inform dose selection in planning for future studies.

SAS software (SAS Institute, Cary, NC) will be the primary software for statistical analysis of safety (Safety Analysis Set [SAF] population) and exploratory efficacy (SAF and Per Protocol Analysis Set population [PPS]).

Sample Size Considerations

The sample size of 48 to 60 subjects is from 4 treatment groups of equal size with at least 12 to 15 subjects per treatment group. The sample size calculations were based on pre-clinical studies however no formal sample size estimation is planned due to the exploratory nature of the trial. Within-treatment changes in the baseline and test SACT periods increases precision as each subject serves as their own control. Between treatment differences in the change from baseline with 12 to

15 subjects per treatment group will provide adequate point estimates and confidence intervals for efficacy variables.

Analysis Datasets

- **Safety Analysis Set (SAF)**: All subjects who received at least one dose of the study product will be included in the Safety population.
- **Per Protocol Analysis Set (PPS)**: PPS is defined as all patients in the Safety population who have completed the study and having had no significant protocol deviations.

Safety and Exploratory Endpoint Evaluation

AEs will be summarized by frequencies and percentages within treatment group and overall. Treatment-emergent adverse events will be tabulated by System Organ Class and Medical Dictionary for Regulatory Activities Preferred Term, with subjects represented once at each level of classification (e.g., preferred term). Frequencies of malabsorption symptoms will be presented.

For safety variables (adverse events, incidence of malabsorption, clinical laboratory tests, vital signs, PE, and concomitant medications) descriptive statistics of measurement values, changes from baseline and percent changes from baseline will be displayed by visit and treatment group, and shift tables will be created where appropriate. Physical examination results will be summarized for each variable.

Summary statistics of continuous exploratory endpoints at baseline SACT and ANG003 SACT challenge, and the change from baseline SACT in exploratory endpoints will be provided by treatment group. Differences in SACT changes among treatment will be summarized. Summary statistics include but are not limited to plasma DHA, EPA and fatty acid efficacy endpoints, erythrocyte membrane composition, amino acids, peptides, and glucose. Changes in serial measurements (e.g., glucose) will use analysis of variance to quantify within and between treatment changes from baseline.

P-values within and between treatment, and 95% confidence intervals for mean values and change and percent change from baseline are generated to quantify the significance of treatment effect.

Exploratory endpoints will be summarized by concentration and by percent of total fatty acids.

Absolute values and changes in safety parameters will be displayed, and shift tables will be created for fatty acid analysis.

Table 4. Schedule of Assessments

STUDY PERIOD	SCREENING		BASELINE CHALLENGE		WASHOUT	ANG003 CHALLENGE		FOLLOW-UP/EOS	
Study Visit (Day)	**Visit 1 (In-clinic)**		**Visit 2 (Day 1 In-clinic)**		**Phone**	**Visit 3 (Day 5 In-clinic)**		**Phone**	**Visit 4 (In-clinic or Home)**
Study Day(s)	Day -21	**Phone** Day -2[a]	Day 1	Day 2 Home or Clinic	Day 3	Day 5 (+2d)	Day 6 Home or Clinic	Day 7 +1 day	Day 9 (+2d) Home or Clinic
Informed Consent	X								
Inclusion / Exclusion	X								
EPI Confirmation [b]	X								
Demographics	X								
Medical History	X								
PAGI-SYM [c]	X			X			X		
Bristol Stool Scale [d]				X			X		
Height and BMI [e]	X								
Weight	X		X			X			
Vital Signs [f]	X		X	X		X	X		X
Pulse Oximetry [g]	X		X	X		X	X		X
Physical Examination [h]	F		SD	SD		SD	SD		SD
Fatty Acid DBS [i]	X								
Chemistry, Hematology, Urinalysis and Serum Proteins [j]	X		X			X			X
Blood Lipids [k]	X		X	X		X	X		X
FSH [l]	X								
Pregnancy Test [m]	S		U						U
C-peptide [n]	X		X			X			X
Fatty Acid Analysis [o]	X		X	X		X	X		X

STUDY PERIOD	SCREENING		BASELINE CHALLENGE		WASHOUT	ANG003 CHALLENGE		FOLLOW-UP/EOS	
Study Visit (Day)	Visit 1 (In-clinic)		Visit 2 (Day 1 In-clinic)		Phone	Visit 3 (Day 5 In-clinic)		Phone	Visit 4 (In-clinic or Home)
Study Day(s)	Day -21	Phone Day -2[a]	Day 1	Day 2 Home or Clinic	Day 3	Day 5 (+2d)	Day 6 Home or Clinic	Day 7 +1 day	Day 9 (+2d) Home or Clinic
AminoAcid and Peptide Analysis [o]	X		X	X		X	X		X
Serum Vitamins A, D, E and K	X		X						
Vitamins A, D and E DBS [p]	X		X						
Randomization		X							
Continuous Glucose Monitor q	X		X			X			
ANG003 Dosing						X			
SMM (Weights and Picture) [r]			X			X			
Concomitant Medications	X		X	X	X	X	X	X	X
AE Reporting	X		X	X	X	X	X	X	X

Abbreviations: AE = adverse event; ß-hCG = beta-Human chorionic gonadotropin; BMI = body mass index; CGM = continuous glucose monitor; DBS = dried blood spot; EOS = end of study; EPI =exocrine pancreatic insufficiency; F = full; FA =f atty acid; GI = gastrointestinal; PAGI-SYM = patient assessment gastrointestinal symptoms; SD = symptom directed; S = serum; SMM = SACT Morning Meal; U = urine

a Prior to Day -3, study staff will need to schedule an in-clinic Day 1 visit and remind patients to stop eating shellfish/fish Day -3 to Day 9. On Day -2, study staff will phone the subject to re-confirm eligibility in order to randomize the subject in EDC. Refer to section 4.1.2

b If no confirmed documentation of EPI by fecal elastase test, fecal fat and/or pancreatic function test, the subject may receive a central laboratory [redacted] home test kit to measure stool elastase or testing may occur through the site's local laboratory facility, whichever is more convenient. Turnaround times for results should be taken into consideration.

c PAGI-SYM will be completed by the subject on an electronic device before other study conduct procedures are performed.

d Subject instructions will be provided to ensure accurate completion of the Bristol Stool Scale.

e Height to be assessed at Screening only and BMI will be calculated.

f Vital signs include body temperature (oral/tympanic/forehead), heart rate, respiratory rate, and blood pressure will be collected after the subject has been at rest (seated or supine) for 5 min.

g Pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 min.

h Full PE at Screening / Visit 1 and SD physicals to review new signs and symptoms at all other visits.

I Instructions and a separate dried blood spot laboratory card ([redacted] will be provided for certified testing of one Visit 1 sample.

j Tests for chemistry, hematology, urinalysis, and serum proteins are outlined in Table 7.

k Blood lipids include total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.

l Only for post-menopausal women with documented amenorrhea for at least one year from Visit 1.

m Serum pregnancy test (ß-hCG) at Visit 1. A negative urine pregnancy must be available immediately prior to or on Day 1.

n C-peptide serial blood draws at t0, 1, 2, 4 and 6 h (±5 min) on Days 1 and 5. Timepoints for serial blood draws are based on the start of the t0 sample. Single sample collection at Screening, and Visit 4 (Day 9).

o Blood samples will be collected prior to the test meal (t_0) then 1, 2, 4, 6 and 8 h (±5 min) post-test meal for fatty acid analysis, amino acid and peptide analysis. Timepoints for serial blood draws are based on the start of the t0 sample. The 10 – 12 h sample can be collected outpatient via home nursing or by study staff in clinic. Single sample collection Screening & Visit 4 (Day 9).

p One DBS card will be for vitamins A and E and a second DBS card for vitamin D. No card for vitamin K will be used.

q Site staff will dispense one CGM to subjects and train on proper usage at Screening / Visit 1. On Day -1 and Day 4, the CGM sensor and transmitter will be applied by the subject, to their skin, 24 h in advance of the in-clinic visits on Day 1 and Day 5. Glucose readings will be collected up to 4 h on Day 1 and Day 5 at the following time points: prior to the test meal (t_0) and at 15 min intervals at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, and 240 min post-test meal.

r SMM: SACT Morning Meal, defined as nutritional bar (containing intact whey protein and potato starch), fish oil supplements and breakfast test meal. The nutritional bar and breakfast test meal will be individually weighed with a food scale 1) before given to the subject and, 2) if the subject is unable to consume 100% and there are leftovers. If the subject is unable to consume 100% of the nutritional bar and/or test meal, a digital picture will also be taken of the leftovers, with the digital camera provided.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse Event
AUC	Area Under the Curve
BMI	Body Mass Index
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CFR	Code of Federal Regulations
CFTR	Cystic Fibrosis Transmembrane Regulators
CGM	Continuous Glucose Monitor
CI	Confidence Interval
C_{max}	Maximum Concentration
CRO	Clinical Research Organization
DBS	Dried Blood Sample
DHA	Docosahexaenoic Acid
DIOS	Distal Intestinal Obstructive Syndrome
DMC	Data Monitoring Committee
EC	Enzyme Commission
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EPA	Eicosapentaenoic acid
EPI	Exocrine Pancreatic Insufficiency
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hour
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
LCPUFA	Long-Chain Polyunsaturated Fatty Acids
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCT	Medium-Chain Triglycerides
MCV	Mean Corpuscular Volume

ABBREVIATION	DEFINITION
min	Minute
NDA	New Drug Application
O3I	Omega-3 Index
PAGI-SYM	Patient Assessment of Gastrointestinal-Symptoms
PE	Physical Examination
PERT	Pancreatic Enzyme Replacement Therapy
pPERT	Porcine-derived Pancreatic Enzyme Replacement Therapy
PPE	Personal Protective Equipment
PPI	Proton Pump Inhibitors
PPS	Per Protocol Analysis Set
RBC	Red Blood Cell
SACT	Substrate Absorption Challenge Test
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMM	SACT Morning Meal
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
T_{max}	Time of Peak Concentration
V	Visit

1.0 INTRODUCTION

1.1 OVERVIEW

Anagram Therapeutics, Inc. (Anagram) is developing a novel digestive enzyme replacement therapy comprised of microbial lipase, protease, and amylase, to be active in the GI tract for digestion and absorption of key macronutrients. This novel orally administered enzyme formulation is in the form of mini-tablets. ANG003 is under development as a treatment for malabsorption syndromes resulting from EPI or other life-threatening conditions (e.g., CF, digestive tract cancers, chronic pancreatitis, pancreatectomy, pancreatic cancer) that affects one or more of the steps in the hydrolysis and dietary absorption of fats, proteins, and carbohydrates. Manifestations of EPI include steatorrhea, malnutrition, abdominal discomfort, bloating, bone disease, GI pain, poor growth, weight loss, trace element and vitamin deficiency, poor glucose control and fatty acid abnormalities.[1]

The goal of ANG003 is to provide microbially-derived and biotechnology-produced orally delivered digestive enzymes to ensure reliable and virus-free enzymes that are active and/or survive in the harsh acidic and proteolytic environment of the stomach and small intestine including in the abnormal CF intestine (acidic pH and viscous secretions) without the need for enteric coating. ANG003 is intended to work within the stomach and small intestine to aid in the digestion of dietary fats, proteins, and carbohydrates in patients with EPI, thereby acting as a replacement for digestive enzymes physiologically secreted by the pancreas.

[redacted]

1.2 BACKGROUND

EPI is characterized by inadequate delivery of pancreatic enzymes to the proximal small intestine (duodenum), resulting in maldigestion and malabsorption of macronutrients and micronutrients. The etiology of EPI and malabsorption is associated with disorders such as CF, chronic pancreatitis, Shwachman-Diamond Syndrome, and pancreatic malignancy. EPI results from the reduction or lack of exocrine secretions by the pancreas. Both pancreatic acinar cells, which are responsible for enzyme synthesis and secretion, and ductal cells, which are responsible for bicarbonate secretion, may be affected. This results in reduced production and secretion of pancreatic digestive enzymes including lipase, protease, and amylase from the pancreas to support the breakdown of dietary food into their

absorbable constituents. The lack of secretion of pancreatic bicarbonate lowers pH in the small intestine and creates a suboptimal milieu for activation of pancreatic enzymes as well as causing bile salt precipitation, which adversely affects micelle formation and subsequently fatty acid absorption in enterocytes located in the small intestine.[2] Manifestations of EPI lead to malnutrition, fatty acid abnormalities including the hardest to absorb and most physiologically relevant LCPUFA such as DHA and EPA, fat-soluble vitamin A, D, E, and K deficiencies, poor growth, changes in lean body mass, weight loss, bone disease, impaired glucose uptake, steatorrhea and profound GI symptoms including abdominal discomfort, bloating, and GI pain. These manifestations ultimately lead to a significant decrease in quality of life and reduced life expectancy.[1]

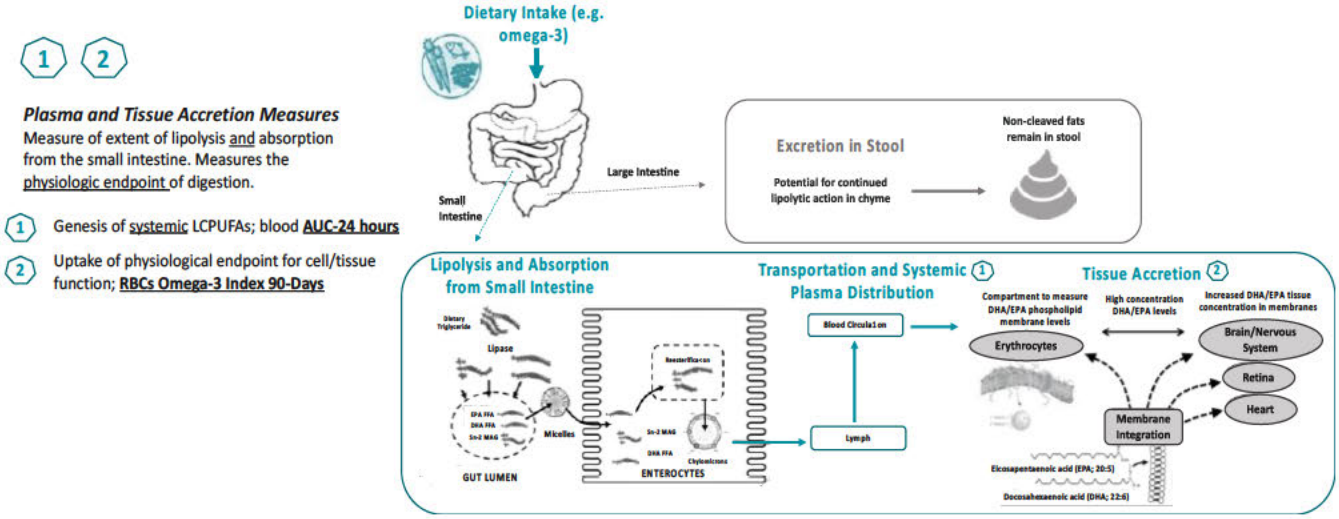
Lipid malabsorption with resulting steatorrhea is typically more problematic and develops earlier in the overall course of EPI than maldigestion and malabsorption of proteins and carbohydrates. This is driven by the complexity of lipid digestion and absorption specificity by the enterocytes of the small intestine. Of the three digestive enzymes, lipase is considered the most critical to maintain caloric intake since 9 kcal of energy is derived per gram of fat versus 4 kcal of energy per gram of protein or carbohydrate.

Fats varying in fatty acid chain lengths are hydrolyzed (digested) and metabolized (absorbed) differently. While all fats provide caloric benefits, they have different impacts on physiological functions.[3] Both long-chain triglycerides (LCTs) and medium-chain triglycerides (MCTs) provide calories, however, only specific essential fats such as LCPUFAs (e.g., omega-3 such as DHA and EPA) are structural components of membranes and precursors of biological mediators involved in the regulation of many physiological functions (growth, immunity, inflammation).[4] Long-chain fats are the most concentrated energy source, having more than twice the caloric density of proteins or carbohydrates.

The process of lipolysis and absorption from the small intestine is illustrated in Figure 2. Since dietary fats are primarily ingested as long-chain triglycerides in solid foods and nutritional formulas they must be hydrolyzed or digested by pancreatic lipase to be absorbed in the small intestine for use as energy and exert their beneficial physiological effects in tissues. After oral intake, fats (lipids) enter the stomach, where they are dispersed as fine droplets, primarily due to the mechanical influence of stomach peristalsis. Dietary lipids are predominantly hydrolyzed by pancreatic lipase and absorbed in the small intestine. Gastric lipases have a role in digesting shorter chain-length triglycerides.

Pancreatic lipase is released from the pancreas upon meal ingestion and is critical for digesting fats in their triglyceride form, including LCPUFAs such as omega-3 and omega-6 fats, into free fatty acids and monoglycerides (sn-2). Pancreatic lipase hydrolyzes triglyceride bonds in the small intestine and functions as the primary mechanism to digest dietary long-chain triglycerides. Pancreatic lipase favors cleaving fatty acids from the sn-1 and sn-3 position to form an sn-2 monoglyceride and two free fatty acids as the byproducts of lipolysis. Lipolysis is generally efficient under the influence of bile acids, as monoglycerides combine with bile acids to form micelles with free fatty acids and fat-soluble vitamins in their interior. The micelles are then taken up by enterocytes and incorporated into chylomicrons and enter the circulation via the lymphatic system via passive diffusion. Once free fatty acids and monoglycerides are absorbed in the bloodstream, they are used as energy and delivered to various tissues in the body for numerous physiological purposes.

Figure 2. Lypolysis and Absorption from the Small Intestine



The importance of adequate nutrition in the successful management of EPI has been well characterized in patients with CF-related EPI. Treatment of EPI in this population is especially difficult to manage due to the multiplicity of factors associated with CF, which adversely affect digestion and subsequent absorption of food. According to the 2020 Cystic Fibrosis Foundation (CFF) Patient Registry[5], 83.8% of people with CF take PERT to prevent severe steatorrhea, GI distress, fatty acid abnormalities, and malnutrition. Lower fatty acid levels (e.g., DHA) are associated with worse pulmonary status, increased antibiotic use, worse bone metabolism, and impaired growth in children with CF.[6] Reduced plasma levels of LCPUFAs have been related to decreased FEV_1 and implicated in the predisposition of CF lung disease.[7] Despite these rather severe outcomes, the clinical evaluation of PERT efficacy is suboptimal due to the lack of physiologically relevant clinical tools to measure the treatment of maldigestion and malabsorption.

1.3 Cystic Fibrosis

CF is a life-threatening genetic disorder that results in the accumulation of thick mucus that clogs sinuses, the pulmonary tract, the digestive tract, and the pancreas.[8] CF is an inherited disease caused by recessive mutations in the CFTR gene which causes altered transport of chloride, bicarbonate, and sodium ions across epithelial cell membranes. The CFTR protein is a single polypeptide chain, that appears to function both as a cyclic adenosine monophosphate regulated chloride channel and as a regulator of other ion channels. The CFTR is expressed in many tissues, reflected in the numerous disease manifestations associated with CFTR deficits.[9]

CF is a systemic disease involving multiple organ systems that largely parallels the distribution of CFTR expression throughout the body. The concept of increased mucus viscosity and inspissation of secretions encompasses many of the manifestations of CFTR dysfunction in end organs, including the sinuses, lung, pancreas, small and large intestines, liver, and vas deferens. While multiple organs are affected by CF, the primary cause of death is from pulmonary disease.[10] The abnormal mucus blocking airways can cause life-threatening lung infections resulting in 71% of the mortality in CF.[8] Despite the significant therapeutic advances, in 2020 the current life expectancy shows a median age of death is 34.4 years and CF is associated with considerable morbidity.[8]

The GI effects of CF are diverse. In the pancreas, the failure of exocrine secretion leads to retention of enzymes and ultimately destruction of pancreatic tissue. The CF intestinal epithelium dysfunctions impact motility, function, and uptake of nutrients in the small and large intestine. In the hepatobiliary system, focal biliary cirrhosis, bile duct proliferation, chronic cholecystitis, and cholelithiasis are common.[11]

People with CF have abnormal fatty acid metabolism with increased release and turnover of arachidonic acid and decreased levels of DHA, EPA and LA.[12] Specific fatty acid alterations present in the plasma and tissues of patients with CF may have an important role in the CF disease process.[13] In addition, due to ion transport abnormalities caused by mutations in the CFTR gene, the intestinal mucosa is lined with thick viscous mucus that forms a barrier at the mucosal surface and essentially decreases the surface area available for fat absorption.

Given that DHA is described as the most consistently decreased LCPUFA in CF, and that together with EPA has clinical and biochemical importance and contribute to disease pathology,[14] determining dietary influences on plasma LCPUFA levels is relevant to clinical care and correcting fatty acid abnormalities.[12] LCPUFA abnormalities correlate with disease severity and play an important role in physiological pathways of known significance in CF including pro-inflammatory eicosanoid metabolites of arachidonic acid (prostaglandins, leukotrienes, lipoxins) and anti-inflammatory metabolites of DHA and EPA (resolvins, protectins, maresins). Indeed, DHA is the precursor of a series of mediators, including resolvins, docosatrienes, and neuroprotectins, that are involved in the resolution phase of inflammation. DHA exerts a cardinal influence on cell functionality, and a decrease of DHA bioavailability in patients with CF may have deleterious effects particularly on pulmonary and pancreatic functions.[15]

1.3.1 Rationale for Development of ANG003

Anagram is developing a highly purified and well-characterized mix of digestive enzymes ([redacted] lipase [redacted], protease and amylase) of microbial origin to improve macronutrient lipolysis and absorption, reduce gastrointestinal symptoms and to reduce the tremendous pill treatment burden on patients that exists currently with porcine derived SOC (pPERT). The primary objectives of the Phase 1 program will be to acquire initial safety and tolerability information and to select the dosage strength(s) of the lipase, protease, and amylase enzymes for Phase 2 studies. In the Phase 1 study, the SACT will evaluate clinical biomarkers of absorption directly related to byproducts of hydrolysis for individual substrates of fat, protein, and starch in a well-controlled standardized testing environment and allow for selecting enzyme doses for future studies. Absorption using four dose levels of lipase, protease and amylase will be assessed.

1.3.2 Risk / Benefit Assessment

In this safety and efficacy study, the amount of time off prescribed enzymes is kept to a minimum. No formal interaction studies have been conducted. Care should be taken to ensure the mini-tablets are not chewed or crushed in the mouth.

1.4 NON-CLINICAL STUDIES

1.4.1 Pharmacology

Three preclinical pharmacology studies have been conducted [redacted] to evaluate the effect of each enzyme in a

well-established porcine model of EPI. The studies were conducted to evaluate macronutrient uptake to provide support for the safety and efficacy of the enzymes in ANG003 for clinical trials. The EPI pig model was chosen since at the functional and developmental level humans and pigs share many similarities with the GI tract, genitourinary structures and development of brain and pancreas.[16]

The EPI pig model is a surgical model of pancreatic insufficiency used to study the uptake of macronutrients and to evaluate different preparations of orally administered pancreatic enzymes.[17, 18, 19, 20, 21, 22] EPI in pigs is achieved by ligation of the accessory exocrine pancreatic duct, which serves as the main pancreatic duct that drains pancreatic juices to the duodenum. Surgical ligation dramatically reduces the levels of digestive enzymes in the duodenum, causing a reduction in fat, protein, and carbohydrate digestion and absorption. In addition, duodenal pH is also reduced, as in humans with EPI, producing another hurdle for enzyme activity in the gut lumen.[4, 17] The increased acidity in the small intestine also can provoke bile acid precipitation, which affects micelle formation and lipid absorption. After duct ligation, young pigs develop steatorrhea, reduced fat, protein, carbohydrate, and nutrient absorption, as well as fatty acid deficiencies resulting in impaired growth and development, all of which are observed also in humans with EPI.[23, 24]

The porcine model of EPI disease has been previously used in short-term and long-term chronic studies.[21] A comparison of the recommended daily allowances of vitamins and minerals in the human diet and the daily nutrient requirement of pigs reveal similarities between the two species. This likely contributes to their comparable mucosal barrier physiology and enteric microbiota.[25] As would be expected, the EPI porcine model has been used to evaluate porcine enzymes (pancreatin) and their role in EPI.[17, 20, 26] The model is well-suited for evaluating the use of porcine enzymes which is physiological for the animal. The EPI porcine model has been adapted for use for evaluating microbially derived enzymes.[21, 27]

The EPI pig model supports the translation of knowledge obtained from *in vitro* studies to animal and eventually human trials. During the *in vivo* studies enzyme activity in chyme was assessed. Evaluating enzyme activity in chyme appears to be a useful and novel method to assess enzyme release characteristics. Results of the current study also support the use of the EPI pig model and the sensitive analytical methods as an indicator for determining enzyme activity and absorption of macronutrients (e.g., fatty acids as byproducts of fat triglyceride digestion). The methods also serve as an important measurement for determining the optimal dose of enzymes and can be used in future studies involving enzyme dose selection. The results will also inform the clinical study design of future Phase 1, Phase 2, and Phase 3 clinical trials.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4.2 PHARMACOKINETICS

Following oral dosing, ANG003 is not expected to be absorbed into the circulation. Within the GI tract the ANG003 enzymes will be metabolized in a manner identical to that of ingested nutritional dietary proteins (i.e., digested into short peptides and single amino acids, which then pass through the mucosal epithelial cells into blood or lymph). Remaining intact enzymes, partially digested protein, and unabsorbed short peptides and single amino acids, will be excreted in the bowel. Standard absorption distribution metabolism excretion studies are not proposed for ANG003 based on its composition (protein with a known enzymatic reaction) and its route of oral administration.

Pharmacokinetic, bioavailability and safety pharmacology studies, definitionally require systemic absorption of intact product. Since there is no systemic absorption of the orally administered proteins, these studies will not be performed with ANG003.

1.4.3 GENOTOXICITY AND CARCINOGENICITY

Since there are no known mutagenic proteins,[29] standard genotoxicity tests are not appropriate for biotechnology-derived pharmaceuticals, such as proteins and peptides (ICH S6). Like other proteins and peptides, ANG003 will not directly induce changes in deoxyribonucleic acid (DNA) (i.e., by intercalation into the double helix or by alkylating DNA bases); nor will ANG003 induce indirect genetic effects (such as an interaction with microtubules to induce aneupoidy).

Genotoxicity studies are not proposed for ANG003 since it is a protein with known enzymatic activity. Similarly, rodent carcinogenicity studies are not proposed for ANG003's nonclinical program. Neither ANG003 nor peptide fragments produced by proteolysis will act as initiating agents by directly altering DNA. There is no potential for ANG003 (or peptide fragments) to act indirectly to induce cell proliferation or clonal expansion of spontaneously transformed cells in mammals. Since ANG003 is a protein with a known enzymatic function it should not be absorbed to any significant level.

1.4.4 TOXICOLOGY

Two 7-day GCP-compliant oral gavage toxicology studies are in progress to support the Phase 1 single-ANG003 administration clinical study. These toxicology studies were conducted in Sprague-Dawley rats and Beagle dogs.

The toxicology program was developed based on the following:

1. ANG003 consists of three orally administered microbial-sourced enzymes given with food. The enzymes, microbially lipase, protease, and amylase, are intended to work within the GI tract to aid in the digestion of dietary fats, proteins, and carbohydrates. ANG003 does not contain enteric coating.
2. The ANG003 enzymes are proteins, as such, like all dietary proteins, will be digested within the GI tract into their constituent amino acids, which are absorbed across the mucosal epithelium to ultimately become part of the body's amino acid pools. There is no expectation that intact enzymes will be absorbed systemically.

[redacted]

1.5 CLINICAL EXPERIENCE

1.5.1 ANG003

The purpose of this initial study with ANG003 is to enhance the understanding of safety and tolerability of four test doses.

[redacted]

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

- To evaluate safety and tolerability of a single orally delivered ANG003 dose in adult subjects with EPI due to CF
- To evaluate four dose levels of ANG003 (4 lipase doses, 3 protease doses, and 3 amylase doses) and select a dose(s) for Phase 2

2.1.2 EXPLORATORY OBJECTIVES

- To evaluate the effect of ANG003 on fat absorption as determined by serial measurements of plasma DHA and EPA, LCPUFAs and total fatty acids (C14:C24)
- To evaluate the effect of ANG003 on protein and carbohydrate absorption as measured by changes in peptides, amino acids, and glucose
- To evaluate erythrocyte composition (DHA, EPA, LCPUFAs, total FA) in subjects with CF

2.2 ENDPOINTS

2.2.1 PRIMARY

The safety and tolerability endpoints include the following:

- Frequency of adverse events, serious adverse events, and AEs leading to discontinuation
- Incidence of malabsorption symptoms (e.g., abdominal pain, constipation, diarrhea, distension/bloating, flatulence, indigestion/heartburn, nausea, steatorrhea, and vomiting)
- Clinical laboratory evaluations (hematology included complete blood cell count with differential and platelet count, serum biochemistry including blood urea nitrogen and creatinine, liver function tests, coagulation profile, and urinalysis)
- Vital signs (body temperature, heart rate, respiratory rate, blood pressure)
- Physical examination
- Concomitant medications

2.2.2 EXPLORATORY

The exploratory efficacy endpoints include changes in:

- Plasma DHA and EPA AUC_{8h} and AUC_{24h}
- Time to peak concentration of DHA, EPA
- Peak plasma concentration of total DHA (µg/mL)
- Peak plasma concentration of total EPA (µg/mL)
- Change in plasma concentration of DHA + EPA (µg/mL) over time
- Change in plasma composition (%) of DHA + EPA over time
- Erythrocyte membrane composition (%) of DHA, EPA (DBS; O3I)
- Erythrocyte membrane composition (%) ratio of omega-6 to omega-3 fatty acids
- Plasma composition (%) ratio of omega-6 to omega-3 fatty acids
- Plasma concentration of dietary peptides and amino acids (µg/mL)
- Serum protein concentrations (total protein, pre-albumin, albumin, transferrin)
- Change in plasma concentration of glucose (mg/dL) as measured by CGM.
- Change in plasma C-peptide concentration over time.

3.0 SUBJECT POPULATION

Subjects with a diagnosis of CF-related EPI who meet all the inclusion and do not meet any exclusion criterion are eligible for study participation.

3.1 SELECTION OF SUBJECTS

3.1.1 INCLUSION CRITERIA

Subjects must meet ALL the following criteria to be eligible to participate in the study:

1. Male and female subjects 18 years of age or older.
2. Confirmed diagnosis of CF defined by:
   a) CF signs and symptoms AND
   b) Two CF-causing mutations on genetic testing or sweat chloride >60 mEq/L.
3. Documented history of fecal elastase <100 µg/g stool.
4. EPI clinically controlled for at least 3 months. Controlled EPI is defined as minimal clinical symptoms and on a stable dose of PERT for 90 days before screening as determined by the Investigator.
5. Adequate nutritional status measured by BMI $\geq$20 kg/m^2 for adult subjects.
6. Females of childbearing potential must either be sexually inactive (abstinent) during Screening until 28 days after the Day 5 dose of ANG003 or be willing to use acceptable methods of birth control. Acceptable contraception is defined as:
   a) Oral, injected or implanted hormonal methods of contraception (e.g., Depo-Provera®, Implanon®) OR
   b) Placement of an intrauterine device or intrauterine system; OR
   c) Barrier methods of contraception: condom or occlusive cap (e.g., diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
7. Females of non-childbearing potential must be post-menopausal with documented amenorrhea for at least one year prior to dosing and FSH serum levels consistent with post-menopausal status OR undergone sterilization procedures at least six months prior to dosing such as:
   a) Hysteroscopic sterilization
   b) Bilateral tubal ligation or salpingectomy
   c) Hysterectomy
   d) Bilateral oophorectomy.
8. All male participants who have not had a vasectomy must use effective contraception from Day 1 to 28 days after the Day 5 ANG003 dose. Effective contraception is defined as a condom and spermicide for the male or condom and at least one of the following for a female partner.
   a) Intrauterine device
   b) Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive
   c) Be of non-childbearing potential.
9. Subject must be willing and able to adhere to the study assessments, visit schedule, dietary and nutritional supplement restrictions, and prohibited medications.

3.1.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be ineligible to participate in the study:

1. Subjects with diabetes mellitus who are unable to refrain from short-acting and rapid-acting insulin on Days 1 and 5 for a daily total of 6 h (up to 4 h CGM reading). NOTE: Subjects who

are utilizing an insulin pump are classified as unable to refrain from short-acting and rapid-acting insulin for two 6 h periods and therefore are excluded.

2. Involuntary loss of 10% or more of usual body weight within last 6 months or involuntary loss of greater than 5% or more of body weight in 1 month.
3. Requires use of naso-gastric, J-tube, G-tube, and/or enteral feeding for the study duration.
4. CF pulmonary exacerbation within 30 days prior to the Baseline SACT Period (Visit 2).
5. Subjects who cannot discontinue taking omega-3 supplements >500 mg of DHA and EPA daily.
6. Subjects unable to tolerate missing a dose of PERT.
7. Subjects unable or unwilling to stop acid-blocking medicine (such as proton pump inhibitors or H2-receptor antagonists) for two 48-hour periods.
8. Liver cirrhosis and/or known portal hypertension, cholestatic liver disease, history of lung or liver transplant, listing for organ transplant or significant bowel resection.
9. Active cancer disease.
10. Known small intestinal inflammatory diseases such as Crohn's Disease or Ulcerative Colitis, gastroparesis, diarrheal illness unrelated to EPI (e.g., infectious gastroenteritis, sprue, lactose intolerance, inflammatory bowel disease).
11. History of fibrosing colonopathy or DIOS within six months of Visit 1.
12. Subjects with significant clinical/laboratory/radiological signs within 28 days before Visit 1 or between Visits 1 and 2 indicate unstable disease in the Investigator's opinion. NOTE: Hepatic function tests (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transaminase [GGT], bilirubin) must be ≤ 3 x upper limit of normal (ULN); hemoglobin ≥ 10 g/dL, platelets ≥ 75,000/mm^3, neutrophils ≥ 1.0 x 10^9/L, serum creatinine ≤2.0 mg/dL (177 μmol/L)
13. Known history of hepatitis B surface antigen (HBsAG), anti-hepatitis C virus (HCV) antibodies, or anti-Human Immunodeficiency Virus (HIV) 1 or 2 antibodies, or current positive laboratory-confirmed COVID-19 (SARS-CoV-2) infection.
14. Current alcohol, medication, or substance abuse.
15. Treatment with an investigational drug, biologic, or device within 30 days of Visit 1.
16. Female subjects who are pregnant, have a positive serum pregnancy test at Visit 1, are lactating, or plan to become pregnant during the study and/or <90 days after receiving investigational product.
17. Allergy to soy or foods containing soy.

3.2 SUBJECT AND STUDY DISCONTINUATION

Subjects who discontinue or withdraw after randomization may be replaced at the discretion of the Sponsor.

3.3 SUBJECT DISCONTINUATION / WITHDRAWAL

Subject discontinuation or withdrawal from the study occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the study. A subject may be discontinued from the study for any of the following reasons:

- Adverse Event
- Investigator's decision (e.g., if in the Investigator's opinion it is not in the best medical interest of the subject to continue study participation)
- Subject noncompliance or unwillingness to comply with the procedures required by the study
- Protocol deviation (e.g., violation of eligibility criteria or receipt of incorrect IP or dose)
- Subject becomes lost to follow-up (the subject stopped coming for visits, and study staff are unable to contact the subject).

Any subject who becomes pregnant during the study must be immediately and permanently discontinued from study treatment. All pregnancies in female subjects that occur during the trial must be reported to the Sponsor, [redacted] Pharmacovigilance team and followed to conclusion. The Investigator must also follow the outcome of mother and infant to 12 months post-delivery.

All subjects will be informed that they have the right to withdraw/discontinue from the study at any time, for any reason, without prejudice, and without having to justify their reasons or decisions. In case of premature discontinuation of study participation, the Investigator will schedule an EOS visit, particularly for acquiring AE follow-up data (if applicable) and to collect samples for laboratory evaluations. This visit should be documented in the appropriate electronic Case Report Form (eCRF). The Investigator will record the reason for the study discontinuation, if available, provide or arrange for appropriate follow-up for such subjects, and document the course of the subject's condition. In addition, the Investigator will report the subject's discontinued/withdrawal to the Sponsor.

For subjects who are lost to follow-up (e.g., subject status is unclear because of failure to appear for the ANG003 SACT Period), the Investigator will document in the source documents any steps taken to contact the subject (e.g., dates of telephone calls). Any subject who withdraws consent will not have further information or data collected from them, except for follow-up information about ongoing SAEs at the time of withdrawal. Every effort will be made to follow-up subjects who are withdrawn from the study for SAEs considered related to the IP.

If study withdrawal is caused by a Suspected Unexpected Serious Adverse Reaction (SUSAR), it will be reported to the IRB/IEC and Sponsor.

3.4 STUDY OR SITE TERMINATION

The Sponsor reserves the right to discontinue the study or to terminate study conduct at a clinical site at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of a significant safety finding
- Medical or ethical reasons affecting the continued performance of the study
- A decision on the part of the Sponsor to suspend, discontinue, or shorten the study
- Failure of the Investigator to enroll eligible subjects
- Failure of the Investigator to comply with ICH GCP guidelines or applicable regulations.

Regulatory Authorities also have the right to terminate the study for any reason. In the event the study is terminated, the IRB/IEC will be notified of the relevant decision.

4.0 STUDY DESIGN

4.1 OVERALL STUDY DESIGN AND PLAN

This is a Phase 1 multicenter, randomized study of orally administered ANG003 with one SMM in adult subjects with CF-related EPI. The overall study objectives are to evaluate the safety, tolerability and effect of four parallel dose levels of ANG003 on the absorption of fatty acids, especially DHA and EPA by plasma measurements. Approximately 48 to 60 eligible subjects with 12 to 15 subjects per dose level are expected to be enrolled in the study.

This parallel study design allows for mean estimation of within and between treatment changes in exploratory variables. Changes in exploratory endpoints within treatment are performed at increased statistical power as the subjects serves as their own control. Serial measurements of efficacy endpoints improve statistical power to compare treatment groups in these changes (e.g., treatment comparison of glucose changes pre and postprandial).

The study is composed of five periods:

1. Screening Period which allows a maximum of 21 days to complete all screening assessments. Subjects deemed Screen Failures may be considered for re-screening on a case by case basis with permission of the Sponsor's Medical Monitor.
2. Baseline SACT Period (24 h) which includes Day 1 in-clinic and Day 2 at home or in-clinic.
3. Washout Period to allow a 2-day washout of substrates on Day 3 and Day 4 prior to the treatment challenge test.
4. ANG003 SACT Period (24 h) which begins the single dose of study drug on Day 5 (+2d) in-clinic and includes Day 6 at home/neutral location or in-clinic.
5. Safety Follow-up Period/EOS which includes telephone contact on Day 7 and the final study visit on Day 9 (+2d) at home/neutral location or in-clinic.

For the two 24-hour SACT Periods, fasting baseline blood samples will be collected prior to the high-fat SMM. The short-term lipolysis of DHA and EPA triglycerides and the absorption of DHA and EPA fatty acids will be assessed by providing a fixed amount of fish oil (DHA and EPA triglycerides) and measuring levels of DHA and EPA fatty acids in plasma and erythrocytes. Subjects will receive omega-3 fish oil triglyceride capsules with the breakfast test meal and other substrates (whey, potato starch) in the nutritional bar. A small volume of blood will be collected six times in-clinic with two additional samples (10-12 h, 24 h ±2 h) collected outside of the clinic, at home, neutral location or study site.

Fat absorption in plasma will be determined by evaluating the AUC, concentration peak (C_{max}) and time of peak concentration (T_{max}) over a 24 h interval. In addition to DHA (22:6n-3) and EPA (20:5n-3), the following 22 fatty acids by class will be measured:

(i) saturated (14:0, 16:0, 18:0, 20:0, 22:0, 24:0)
(ii) monounsaturated (16:1, 18:1, 20:1, 24:1)
(iii) trans unsaturated (16:1tr, 18:1tr, 18:2tr)
(iv) n-6 polyunsaturated (18:2, 18:3, 20:2, 20:3, 20:4, 22:4, 22:5), and
(v) n-3 polyunsaturated (18:3, 22:5).

The sum of the DHA, EPA, and the 22 fatty acids constitute the total fatty acid content of the blood, and each individual fatty acid can be expressed as a percent of the total or as a concentration (e.g., µg/mL).

4.1.1 SCREENING PERIOD (DAY -21 TO DAY -1)

At or before Visit 1, subjects will review and provide written consent before completing any study conduct procedure. After signing the ICF, screening assessments will be performed, and clinical study staff will determine if the subject meets all inclusion criteria and does not meet any exclusion criterion for study entry.

Screening assessments will include a review of eligibility criteria, demographics, medical and PERT history, PAGI-SYM, height, weight, BMI, vital signs, full physical examination, fatty acid dried blood spot sample, standard laboratory testing (hematology, clinical chemistry, urinalysis, blood lipids, serum proteins), FSH test (if applicable), pregnancy test for childbearing females, blood samples for endpoint analysis, vitamin tests, and review of concomitant medications. All screening assessments listed in Table 4 must be completed within a maximum 21-day window. Day 1 / Visit 2 may occur as soon as 3 days after Screening / V1 as long as all eligibility requirements are met, in order to account for the dietary restrictions that begin on Day -3. Subjects will be given a CGM and instructions provided on how to apply the device on Day -1.

Daily omega-3 fish oil supplements >500 mg (DHA and EPA per day) is restricted during Screening period and through EOS / Day 9.

Re-screening a patient who has previously been identified as a Screen Failure will be permitted with permission of the Sponsor's Medical Monitor. The timing of re-screening must be in consultation with the Sponsor Medical Monitor. All screening procedures, including re-signing the ICF, must be performed at the re-screening visit.

4.1.2 DAY -3 TO DAY -1

Prior to Day -3, study staff will contact eligible subjects by phone to schedule an in-clinic Day 1 study visit. On Day -2, study site staff will contact subjects by phone as a reminder to apply the CGM sensor and transmitter to their skin on Day -1, and to answer any questions. After confirmation of eligibility, the subject will be randomized in the EDC system to allow IP to be shipped in time for administration on Day 5.

Eligible subjects will receive a controlled meal plan via a meal delivery service vendor in advance of Day -1 or the 24 h prior to the Baseline SACT Period. No protein powders, shakes, bars, or any other protein supplements are allowed on Day -1 for the 24-hour period before Day 1. Only calorie-free beverages (e.g., water, zero-calorie waters with fruit essence, zero-calorie waters enhanced with vitamins, zero-calorie sparkling water, black coffee, black tea, zero-calorie soda, or zero-calorie iced teas) are allowed during waking hours on Day -1. Subjects will discontinue their regular PERT regimen after breakfast on Day -1 to be PERT-free for 24 h prior to their Day 1 visit. On Day -1, subjects will begin a minimum 8 h fast after dinner and refrain from drinking water for 1 h prior to arrival at the study site.

4.1.3 Baseline SACT Period: Days 1 to 2

After an 8-hour fast, a baseline (t_0) blood sample will be collected before consumption of the SMM. The SMM provides a fixed amount of omega-3 fish oil with triglycerides, intact whey protein isolates and potato starch (Table 6). The nutritional bar and test meal will each be individually weighed with a food scale at two timepoints: 1) before providing to the subject and, 2) if the subject is unable to consume 100% of the nutritional bar and/or test meal. A digital picture will also be taken of the leftovers.

During the 8-hour study visit on Day 1, subjects will consume the SMM, lunch, and one snack. The total daily calorie target is 2,800 kcal. The macronutrient distribution will be approximately 36 - 40% kcal from fat, 15 - 20% kcal from protein, and 40 - 49% kcal from carbohydrates.

Table 6. Macronutrient Substrates

DIET	FAT	PROTEIN	CARBOHYDRATES
Measures	Plasma Fatty Acids (DHA, EPA; LCPUFAs, total C14:24)	Plasma (Dietary peptides, amino acids)	Continuous glucose monitoring (glucose)
Macronutrient Substrate	DHA+EPA oil 4 g	Intact whey protein isolates 10 g	Potato starch 20 g

After breakfast, serial blood samples will be collected at 1, 2, 4 and 6 h before the standard lunch is consumed. After 4 hours, the CGM sensor and transmitter will be removed and the data from the transmitter downloaded through the reader device within 5-days of the visit. The transmitter will be retained at the site until the end of the study. After the 8 h blood draw, subjects will depart the study site and the subsequent 10 to 12 h sample will be collected at home, neutral location or upon return to the study site. Arrangements will be scheduled in advance for sample collection from a home healthcare nurse to collect, process and ship samples to the associated central laboratory.

On Day 2, the 24 h (±2 h) sample will be drawn pre-breakfast by a home healthcare nurse or, at the choosing of the subject, the study site. Vital signs and a SD physical will be performed, and the Bristol Stool Scale collected and PAGI-SYM completed. Subjects will resume their regular PERT regimen with daily meals and snacks. Refer to Table 4 for all required assessments.

4.1.4 Washout Period: Days 3 to 4

Telephone contact from the study staff will occur on Day 3 to assess subject status, including AEs, concomitant medications, adherence to dietary and supplement restrictions, and protocol compliance with prohibited medications. On Day 4, subjects will consume the same three meals and one snack as on Day -1. Only calorie-free beverages (e.g., water, zero-calorie waters with fruit essence, zero-calorie waters enhanced with vitamins, zero-calorie sparkling water, black coffee, black tea, zero-calorie soda, or zero-calorie iced teas) are allowed during waking hours on Day 4. On Day 4, subjects will apply the CGM sensor and transmitter to their skin, 24 hours prior to their Day 5 visit. After dinner, subjects will begin an 8 h overnight fast. Subjects will discontinue their regular PERT regimen 24 h prior to Day 5. Protein powders, shakes, bars and/or protein supplements are not allowed on Day 4 for the 24-hour period before Day 5.

4.1.5 ANG003 SACT PERIOD: DAYS 5 TO 6

At Visit 3 (Day 5 (+2d)), subjects will have completed a minimum 8 h overnight fast and refrain from drinking water for 1 h prior to arrival at the study site. A pre-breakfast baseline (t_0) blood sample will be collected and baseline assessments from Day 1 will be repeated.

During the 8 h in-clinic visit, subjects will consume the same three standard meals and one snack as received during the Baseline SACT Period. Only the SMM will contain intact whey protein isolate, potato starch. After consumption of the nutritional bar, subjects will be administered ~4 g of omega-3 (triglycerides of EPA and DHA) supplement capsules.

The nutritional bar and test meal will each be individually weighed with a food scale 1) before providing to the subject and, 2) if the subject is unable to consume 100% and leftovers remain. If the subject is unable to consume 100% of the nutritional bar and/or test meal, then a digital picture will also be taken of the leftovers.

Post-breakfast, serial blood samples will be collected at 1, 2, 4, and 6 h in-clinic. After 4 hours, the CGM sensor and transmitter will be removed and the data from the transmitter downloaded through the reader device within 5-days of the visit.. The transmitter will be retained at the site until the end of the study. After the 8 h blood draw, subjects will depart the study site and the subsequent 10-12 h sample will be collected at home, neutral location or upon return to the study site.

On Day 6, the 24 h (±2 h) sample will be drawn before breakfast at the location decided by the study subject. A completed Bristol Stool Scale will also be collected and PAGI-SYM completed. Refer to Table 4 for all required assessments.

4.1.6 SAFETY FOLLOW-UP / EOS: DAYS 7 TO 9

Telephone contact from study staff will occur on Day 7 to assess subject status, including AEs, concomitant medications, and adherence to dietary and supplement restrictions. At the final study Visit 4 (Day 9 (+2d)) in-clinic or at home, assessments will include vital signs, SD physical, standard laboratory testing (hematology, clinical chemistry, urinalysis, blood lipids, serum proteins), urine pregnancy test (if applicable), blood samples for endpoint analysis, AE, and concomitant medication review.

5.0 STUDY DRUG AND TREATMENT OF SUBJECTS

5.1 DESCRIPTION OF ANG003

ANG003 consists of three orally administered microbial-sourced digestive enzymes that are in tablet form. Each of the three enzymes are manufactured separately as individual Drug Substances that are collectively termed as ANG003. The lipase is a product of recombinant DNA technology, while the protease and amylase are wild type microbial enzymes.

For the Phase 1 study, the ANG003 IP is comprised of ~~separate mini-tablets for each enzyme packaged into sachets. The mini-tablets are formulated with excipients that provide immediate release and allow for food digestion to begin within the stomach and continue in the small intestine.~~

[redacted]

5.3 STORAGE

All clinical trial materials including CGM systems will be provided to clinical sites and supply logistics will be managed by Anagram or their designee. All IP must be maintained in a secure place at the clinical site under appropriate storage conditions. The Sponsor or representative(s) must be granted access upon a reasonable request to check IP storage, dispensing procedures, and accountability records.

[redacted]

5.4 ACCOUNTABILITY

ANG003 may be dispensed only under the supervision of a qualified Pharmacist or authorized study team designee and only to eligible study subjects. The responsible study staff will maintain adequate documentation on the (1) receipt of IP, and (2) IP dispensed by subject number. The study monitor will review all IP records, reconcile all dispensed IP, and address any inventory discrepancies for full accountability.

5.5 HANDLING AND DISPOSAL

All used and unused IP at site must be retained under adequate storage conditions until the Day 9/EOS visit.

5.6 RANDOMIZATION

Eligible subjects will be randomly assigned to one of four dose levels according to a formal randomization scheme generated by an independent Statistician. Each subject will be randomized to a single treatment group in Table 1 thru the EDC system. Initially subjects will be stratified by use of CFTR modulator therapy or non-modulator therapy and then assigned a dose level. The randomization codes will be maintained by a designated Statistician and a Sponsor QA staff member. Additional information on randomization is described in the IP Manual.

5.7 STUDY DRUG DOSE AND ADMINISTRATION

IP may be dispensed under the supervision of a qualified Pharmacist or an authorized study team designee member as delegated by the Investigator and noted on the delegation of authority log. The designated individual will verbally train the subject to self-administer a single dose of ANG003, according to the assigned randomized schedule, 2 - 3 bites into the breakfast test meal on Day 5. Complete instructions for dispensing and administering IP will be presented in the protocol-specific IP Manual.

5.7.1 DISPENSING OF STUDY DRUG

When ANG003 is dispensed on Day 5, the individually labeled sachet will be contained in an outer box with approved clinical labeling and the assigned randomization number. Documentation of administration includes recording the subject number, randomization number on the sachet label. Used and unused sachets will be retained during the study for the CRA to perform drug accountability. Detailed instructions are available in the IP Manual.

5.8 TREATMENT COMPLIANCE

To ensure the correct subject treatment assignment on Day 5, the kit number dispensed, date and subject number will be recorded in the site's source documents. Details regarding IP administration will be documented on the appropriate pages of the eCRF and on the Study Drug Dispensing and Accountability Log included in the IP Manual.

5.8.1 CONCOMITANT MEDICATIONS

Concomitant medication is considered any medication, including Covid-19 and other vaccines, other than IP that is administered from Screening/Visit 1 through the Day 9 visit. Any change in concomitant medication taken after obtaining consent must be recorded in the eCRF, noting the type of medication, the dose, duration, and indication. If the administration of a non-permitted concomitant medication becomes necessary, participation in the study may be discontinued prematurely.

Concomitant therapy (sucralfate, metoclopramide, bile acids, cholecystokinin antagonists, etc.) that influence duodenal pH, gastric emptying, or bile secretion and bowel management medications (e.g., laxatives, antidiarrheals, antispasmodics) are allowed only if the subject has been taking the prescribed dose > 4 weeks before Screening. Continuation of daily omega-3 supplementation is acceptable if < 500 mg from Visit 1 through Day 9.

5.8.2 RESTRICTED AND PROHIBITED MEDICATIONS

All subjects enrolled in the study must abstain from use of restricted medications for the specific time periods outlined below.

- Routine PERTs are restricted after breakfast on Day -1 thru the 24-hour blood sample on Day 2 AND after breakfast on Day 4 thru the 24-hour blood sample on Day 6. Immediately after the 24 h blood draws, subjects may resume use of PERTs.
- H2-receptor antagonists and PPIs are restricted for 48 h from Day -1 thru the 24 h blood sample on Day 2 AND Day 4 to the 24-hour blood sample on Day 6. Immediately after the 24 h blood draws, subjects may resume use of H2-receptor antagonists and PPIs.
- For subjects with diabetes taking insulin, the use of all short-acting and rapid-acting insulin will be restricted on Days 1 and 5 prior to the SMM and for a total duration of up to 6 hours post t0. After the 6-hour post-t0 blood draw is obtained, subjects may resume short-acting and rapid-acting insulin with the standardized lunch. Long-acting insulin may be continued throughout the study period.
- Subjects are not allowed to consume >500 mg Omega-3 nutritional supplements from Screening through Day 9, other than those supplements provided for the study on Day 1 and Day 5 as part of the SMM.

Use of a new prescription medication is prohibited from Screening through Day 9 unless approved by the Investigator and Sponsor or if required in an emergency. New over-the-counter medications, homeopathic preparations, or herbal supplements are prohibited for the study duration. Prohibited medications include any IP other than ANG003 and herbal remedies with purported immunostimulant properties (e.g., mistletoe extract) or that are known to potentially interfere with major organ function (e.g., hypericin).

5.8.3 DIETARY, OTHER RESTRICTIONS AND PRECAUTIONS

Dietary restrictions include no fish/shellfish starting on Day -3 through Day 9 (Table 3). Other than nutritional supplement restrictions and the prohibited medications outlined above, there are two other protocol restrictions: (1) no major elective surgery (excluding diagnostic biopsy) and (2) subjects must avoid alcohol or drug abuse/misuse during the study.

6.0 STUDY ASSESSMENTS

6.1 SAFETY ASSESSMENTS

6.1.1 DEMOGRAPHICS AND MEDICAL HISTORY

Demographics and baseline characteristics including date of birth, gender, race, ethnicity, and medical history will be obtained from each subject and entered in the eCRF.

6.1.2 HEIGHT, WEIGHT, AND BODY MASS INDEX

Height will be measured using a calibrated, wall-mounted stadiometer at the Day 1 study visit. Body weight will be measured using a calibrated scale. BMI will be calculated at Screening Visit 1 (to assess eligibility) according to the following equation: BMI = weight (kg) / (height [m])^2

6.1.3 VITAL SIGNS

Vital signs will be measured at all visits after the subject has been seated or supine for 5 min. Body temperature (oral/tympanic/forehead), heart rate, respiration rate and blood pressure will be measured. Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure measurements will be repeated at the Investigator's discretion. Any confirmed clinically significant abnormal vital sign measurements occurring after signing of the ICF are to be recorded as AEs.

6.1.4 PULSE OXIMETRY

Blood oxygen saturation by pulse oximetry will be measured at all clinic and home study visits. Oximetry will be assessed following a 5 min rest seated or supine. This is a noninvasive measurement of oxygen delivery to the tissues and has been correlated with clinical status and lung function.

6.1.5 PHYSICAL EXAMINATION

The Investigator or designee will perform a full physical examination, covering major body systems at Screening Visit 1. Results will be recorded in the eCRF as normal, abnormal not clinically significant, or abnormal clinically significant. All subsequent PE on Day 1, Day 2, Day 5, Day 6 and Day 9 will be targeted to new signs and symptoms including specific assessments of any changes from previous status.

[redacted]

6.1.7 CLINICAL LABORATORY TESTING

All laboratory samples for clinical laboratory assessments (Table 7) will be collected at the time points displayed in Table 4. Placement of a peripheral venous catheter may simplify collection procedures for the multiple blood draws. Safety laboratory tests will be analyzed by a centralized laboratory [redacted] and results provided on an ongoing basis to sites. Efficacy tests (i.e., fatty acids, amino acids and peptides) sent to the specialty laboratory [redacted] will be evaluated in the clinical study report and not sent to sites. Samples will be processed according to the study-specific procedures outlined in the Laboratory Manual. The Laboratory Manual will detail for research staff the kit contents, reordering supplies, sample collection, handling, storage, and shipment instructions.

All laboratory reports must be reviewed, signed, and dated by the Investigator or designee and maintained in the source documents. A legible copy of all reports must be filed in a subject medical record (source document) for that visit and the data recorded in eCRF. Any abnormal laboratory test result (occurring after signed consent) considered by the Investigator to be clinically significant will be recorded as an AE.

Laboratory tests may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately evaluate the subject's current condition, follow-up, and/or manage an AE.

6.1.8 SAFETY LABORATORY ASSESSMENTS

Blood and urine samples (Table 7) will be collected according to the Schedule of Assessments (Table 4). Subjects will be instructed to fast overnight at least 8 h prior to Visits 2 and 3.

The serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed only for females of childbearing potential at screening and EOS. FSH will be assessed at Visit 1 in females of non-childbearing potential that are postmenopausal with documented amenorrhea for at least 1 year prior to Visit 1.

6.2 EXPLORATORY ASSESSMENTS

6.2.1 PATIENT ASSESSMENT OF GASTROINTESTINAL DISORDERS – SYMPTOM SEVERITY INDEX (PAGI-SYM)

The PAGI-SYM questionnaire measures specific symptoms of patients with upper GI disorders, specifically gastroesophageal reflux disease, dyspepsia, and gastroparesis. The questionnaire is designed to collect GI related data, so it is also applicable for patients with CF-related EPI. PAGI-SYM contains 20 questions scored on a 6-point Likert response scale ranging from 0 (none) to 5 (very severe). The adult version of the PAGI-SYM questionnaire will be administered prior to any test or study conduct procedure according to Table 4. Subjects will complete the PAGI-SYM at Screening, Day 2 and Day 6 with a mobile device (e.g., smartphone or tablet) or computer. Typically, the PAGI-SYM questionnaire is completed in 5 to 10 minutes.

6.2.2 BRISTOL STOOL SCALE

The Bristol Stool Scale is a diagnostic tool with a validated scale system to classify stool into seven categories from type 1 (hard) to type 7 (loose). It is a practical guide for assessment of how long stool has remained in the intestines and can identify bowel problems. Pictorial identification will help assess stool type based on numeric categories.

6.2.3 GLUCOSE MONITORING

Each Investigator screening potential study subjects will need to determine if a subject with diabetes can manage 4 - 6 h in-clinic stays without short-acting or rapid-acting insulin particularly those subjects with HbA1c >8% (corresponding to an average glucose of >183 mg/dL by CGM). If in the Investigator's judgement there is a potential risk of severe hyperglycemia >400 mg/dL, then the subject would not be considered a good candidate for the study. Note that subjects who utilize an insulin pump to deliver short-acting or rapid-acting insulin will be excluded from study participation.

For each subject, the Sponsor will source a commercially available wearable minimally invasive CGM system to measure interstitial glucose levels. A subcutaneous sensor and transmitter will be applied to the subjects skin and will continuously measure glucose levels in blinded mode prior to and during the test meal up to 4 h post-test meal on Days 1 and 5. A fingerstick test measurement should be obtained if the subject shows signs and symptoms of hyperglycemia. Sites will follow standard clinical practice for management of glucose control.

Detailed instructions for the CGM system are provided within the CGM system box. Sites will provide 1 CGM and instruct subjects during their screening visit on how to apply the sensor and transmitter. Sites will give each subject a second CGM system at the end of Day 1. After 4 hours on Day 1 and Day 5, the sensor and transmitter are removed from the subject. The sensor is thrown away and the transmitter is used to download the data via the reader provided to the site within 5-days of the visit. Separate instructions for how to download the data will be provided. Transmitters will be retained at the site until the end of the study in case there was a problem with the initial download of data.

If the CGM sensor (e.g., sensor error, missing reading, etc.) or transmitter (e.g., transmitter failure, not working, signal loss, etc.) is functioning improperly on Days 1 and 5, the sensor and transmitter should remain on the subject for 4 h and then removed. The transmitter should be retained; however, the sensor may be properly discarded.

7.0 EVALUATIONS AND PROCEDURES BY VISIT

7.1 STUDY VISITS

Details of study assessments at each visit are presented in the Schedule of Assessments (Table 4). Additional details of study procedures are given below. There is little flexibility regarding the timing of the scheduled study visit days in relation to the Visit 2 Day 1 Baseline SACT Period.

7.1.1 COVID-19 TESTING

Sites will be instructed to implement the institutional polices for their site regarding COVID-19.

Table 7. Safety Laboratory Evaluations - Central

CHEMISTRY PANEL
Alanine aminotransferase (ALT/SGPT)
Albumin
Alkaline Phosphatase (ALP)
Amylase
Aspartate Aminotransferase (AST/SGOT)
Bilirubin, Total, Direct, Indirect
Blood Urea Nitrogen
Calcium
Creatine Phosphokinase
Creatinine
Electrolyte Panel (Na^+, K^+, Cl^-, Bicarb.)
Gamma Glutamyl Transferase
Globulin, Total
Glucose
HbA1c
Lactate Dehydrogenase
Lipase
Phosphorus
Protein, Total
Urea
PREGNANCY
Serum Pregnancy Test
Follicle-Stimulating Hormone
LIPID PANEL
High-Density Lipoprotein
Low-Density Lipoprotein
Total Cholesterol
Triglycerides

HEMATOLOGY PANEL
Hemoglobin
Hematocrit
Differential WBC Count: Basophils, Eosinophils, Lymphocytes, Neutrophils
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelets
Red Blood Cell Count
White Blood Cell Count
URINALYSIS
Bilirubin
Blood
Creatinine
Glucose
Ketones
Leukocyte Esterase
Nitrite
pH
Protein
Specific Gravity
Uric Acid
* Microscopic (bacteria, casts, crystals, erythrocytes, and leukocytes)
VITAMINS A, D, E and K
SERUM PROTEINS
Total Protein
Pre-albumin
Albumin
Transferrin

* If urine is positive for blood, leukocyte esterase, nitrite, or protein, then microscopic examination will be performed.

7.2 Screening Period Visit 1 (Day -21 to Day -1)

Prior to performing any study-related procedure, the Investigator/designee will obtain written consent from the subject. After consent is obtained, the subject will be assigned a unique, sequential subject number. Once a number is assigned, it cannot be reassigned even if the original subject is found to be

ineligible or withdraws consent. A Screening log of all consented subjects will be maintained by each clinical site.

Subject screening will be conducted within 21 days prior to Visit 2 (Day 1). Screening evaluations may be completed over several days, if necessary. The following assessments, procedures and data collection will be performed in the sequence listed during Visit 1:

1. Review inclusion and exclusion criteria to assure subject is eligible to participate.
2. Collect and record demographics data.
3. Collect and record medical history to include active medical conditions and all surgeries for the past 5 years, disease history, including date of diagnosis of CF and specific CF mutation(s), if available.
4. Review and record concomitant medications including prescription medications, over the counter medications, and the use of prohibited medications.
5. Administer PAGI-SYM questionnaire.
6. Perform and record vital signs, height, weight, and calculate BMI.
7. Perform pulse oximetry.
8. Perform and record full PE.
9. Collect three dried blood spot cards: (1) Fatty acid (2) Vitamins A and E, and (3) Vitamin D.
10. Collect blood for hematology, chemistry, blood lipids, C-peptide, fatty acids, amino acids, peptides, serum pregnancy test in women of childbearing potential, and urine for chemistry.
11. Collect blood for FSH testing for postmenopausal women, if applicable.
12. Distribute one CGM and train subject on proper insertion and usage.

When eligibility is confirmed, prior to Day -3 study staff will contact the subject to schedule Visit 2. Fasting is required for Visit 2 (Day 1) and subjects must plan to remain at the study site for up to the 8 h blood draw or up to the 10-12 hour blood draw if the subject is not utilizing home healthcare. Any SOC medications and equipment needed by the subject during the day must be brought to the study site for scheduled in-clinic visits.

On Day -2, study staff will phone the subject as a reminder that the CGM subcutaneous sensor and transmitter must be applied on Day -1, re-confirm eligibility, review meal and dietary/PERT instructions for Day -1 and randomize the subject in EDC, in order for IP to arrive at clinic in time for Day 5 administration.

7.3 BASELINE SACT PERIOD ON VISIT 2 (DAY 1 IN-CLINIC)

Subjects will arrive at the study site after a minimum 8 h fast and 24 h discontinuation of PERTs.

1. Perform urine pregnancy test, if applicable.
2. Review and record any AEs.
3. Review and record concomitant medications.
4. Perform and record vital signs, and weight.
5. Perform pulse oximetry.
6. Perform a SD physical.

7. Collect blood for hematology, chemistry, urinalysis, blood lipids, serum proteins, C-peptides, fatty acids, amino acids, and peptides for analysis, and vitamins A, D, E and K testing.
8. Collect three dried blood spot cards: (1) Fatty acid (2) Vitamins A and E, and (3) Vitamin D.
9. Ensure subject inserted subcutaneous sensor and transmitter 24 h in advance.
10. Individually weigh the nutritional bar and breakfast test meal with the food scale before giving it to the subject. Ask subject to consume the entire nutrition bar and meal. If subject is unable to consume 100% of the nutrition bar and/or breakfast test meal, obtain the individual weight and take a digital picture of the leftovers.
11. Provide SMM
12. Collect serial blood draws for C-peptides, fatty acids, amino acids and peptides.

After 4 hours remove CGM sensor and transmitter and extract the data via the reader. Distribute second CGM for subject to bring home for insertion on Day 4.

7.3.1 BASELINE SACT PERIOD (DAY 2 IN-CLINIC OR AT HOME/NEUTRAL LOCATION)

Prior to any food consumption, subjects will be visited by a healthcare nurse at home, neutral location or return to the study site to have the following procedures performed:

1. Administer PAGI-SYM questionnaire.
2. Perform and record vital signs.
3. Assess AEs and perform a SD physical.
4. Collect Bristol Stool Scale.
5. Collect 24 h (±2 h) blood sample for blood lipids, amino acids, fatty acids and peptides for analysis.

7.4 WASHOUT PERIOD (DAYS 3-4)

Study staff will contact the subject via telephone on Day 3 and AEs and concomitant medications will be assessed.

1. Review and record any AEs.
2. Review and record concomitant medications.
3. On Day 4, subjects will insert the CGM subcutaneous sensor.

7.5 ANG003 SACT PERIOD (DAY 5 IN-CLINIC)

Subjects will arrive at the study site after an 8 h overnight fast for the following procedures:

1. Review and record any AEs.
2. Review and record any concomitant medications.
3. Perform and record vital signs, and weight.
4. Perform pulse oximetry.
5. Perform a SD physical.
6. Collect blood for hematology, chemistry, urinalysis, blood lipids, serum proteins, C-peptides, and fatty acids, amino acids, and peptides for analysis.

7. Ensure subject applied the subcutaneous sensor and transmitter 24 h in advance
8. Individually weigh the nutritional bar and breakfast test meal with the food scale before giving it to the subject. Ask subject to consume the entire nutrition bar and meal. If subject is unable to consume 100% of the nutrition bar and/or breakfast test meal, obtain the individual weight and take a digital picture of the leftovers.
9. Provide SMM and administer ANG003 according to the Directions For Use located in IP Manual.
10. Collect serial blood draws for C-peptides, fatty acids, amino acids and peptides.
11. After 4 h remove CGM sensor and transmitter and extract data via the reader.

7.5.1 ANG003 SACT Period (Day 6 In-clinic or at Home/Neutral Location)

Prior to breakfast, subjects will be visited by a healthcare nurse either at home/neutral location or subjects may return to the study site to have the following procedures performed:

1. Administer PAGI-SYM questionnaire.
2. Perform and record vital signs.
3. Perform pulse oximetry.
4. Review and record any AEs.
5. Review and record any concomitant medications.
6. Perform a SD physical.
7. Collect Bristol Stool Scale.
8. Collect 24 h (±2 h) blood sample for blood lipids, fatty acids, amino acids and peptides for analysis.

7.6 Safety Follow-up Period (Days 7 - 9)

7.6.1 Safety Follow-up Phone Call (Day 7)

Study staff will contact the subject on Day 7 via telephone and the following assessments will be performed:

1. Review and record AEs.
2. Review and record concomitant medications.

7.6.2 Safety Follow-up / EOS (Day 9 In-Clinic or at Home/Neutral Location)

Depending upon the subject's preference, the Day 9 visit will be scheduled at home, neutral location or at the study site. The following study procedures will be performed:

1. Perform urine pregnancy test, if applicable.
2. Review and record any AEs.
3. Review and record concomitant medications.
4. Perform and record vital signs.
5. Perform pulse oximetry.
6. Perform a SD physical.

7. Collect blood for hematology, chemistry, urinalysis, blood lipids, C-peptide, serum proteins, fatty acids, amino acids and peptides for analysis.

7.6.3 UNSCHEDULED VISITS

Unscheduled visits are those visits that occur between regularly scheduled visits and are performed to assess a previously noted AE (especially in case AEs are considered by the Investigator to be possibly related to the use of the IP), abnormal laboratory values, and/or clinical findings or to perform an assessment which could not be done during the regular visit. In such cases, the Investigator may arrange at their discretion for a subject to have an unscheduled visit. The subject will be contacted via telephone to arrange an unscheduled visit to assess the noticed abnormalities. The unscheduled visit page(s) in the eCRF must be properly completed.

8.0 SAFETY MONITORING AND REPORTING

8.1 ADVERSE EVENTS

Safety will be assessed by the incidence of AEs, incidence of malabsorption symptoms, clinical laboratory test results, vital signs, PEs and use of concomitant medications.

An AE is defined as any untoward medical occurrence associated with the use of a study product in humans which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of IP, whether or not considered causally related.

All medical conditions present prior to study entry will be documented in the Medical History section of the eCRF. However, medical conditions occurring after the moment of signing ICF are to be recorded as AEs. Screen failure subjects will have AE information noted only in the source document. The Investigator is obliged to interview each subject at every visit and clarify/discuss with him/her any abnormality that may indicate any potential AE.

8.2 SERIOUS ADVERSE EVENTS

An AE is considered “serious” (SAE) if, in the view of either the Investigator or Sponsor, it meets one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to require medical or surgical intervention to prevent one of the serious criteria listed in the definition above. Since SAEs are critically important for the identification of significant safety problems, it is important to consider both the Investigator’s and the Sponsor’s assessment. If either the Sponsor or the

Investigator believes that an event is serious and related to IP, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Information about all SAEs will be collected and recorded on the Serious Adverse Event Report Form and reported to the [redacted] Pharmacovigilance team and Sponsor within 24 h of learning of its occurrence.

Events not to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.

Any SAEs occurring after consent is obtained and up to the end of the study must be reported to the [redacted]Pharmacovigilance team. SAEs occurring after the study termination must be reported only if considered IP related as per Investigator judgment.

8.3 DOCUMENTING AND REPORTING OF AES AND SAES

All medical conditions present prior to study entry will be documented in the Medical History eCRF. However, medical conditions occurring after signed consent are to be recorded as AEs. Screen failure subjects will have AE information noted only in the source document. The Investigator is obliged to interview a subject at every visit and clarify/discuss with him/her any abnormality that may indicate any potential AE.

Subjects will be encouraged to visit the site or to inform the Investigator by telephone to report any AE that occurs between scheduled visits. Reporting of AEs will begin from the moment of signing the ICF and up to the EOS and all AEs occurring after initiation of IP will be considered as TEAEs. AEs related to the IP that are ongoing at EOS will be followed for outcome information until resolution or stabilization.

For each AE, the investigator will evaluate and report the following:

- its duration (start and end dates)
- the severity grades
- its relationship to the IP
- its relationship to a study procedure
- the action(s) taken
- the outcome
- whether the event is serious or nonserious.

If there is an increase in the severity of an AE, it must be recorded as a separate event. Any change in severity should be recorded in the source data and eCRF accordingly until a stop date is provided. If the same AE occurs several times in the same subject, then the AE in question must be documented and assessed as a new one at each time unless the event is a continuation of the previously reported event rather than a reoccurrence of the event.

8.3.1 Classification of Adverse Events Severity

The severity of all AEs, both serious and non-serious, will be assessed using the severity grading scale listed in Table 8.

Table 8. Classification of Adverse Events by Severity

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (AE is transient and easily tolerated by the subject)
Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental daily activities (AE causes the subject discomfort and interrupts the subject's usual activities)
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care daily activities
Grade 4: Sign or symptom resulting in a potential threat to life
Grade 5: Sign or symptom resulting in death

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre-defined outcomes as described in protocol Section 8.2.

8.3.2 Classification of Adverse Events by Relationship

The Investigator will assess the potential relatedness of each AE to ANG003 using the classification system listed in Table 9. An Investigator causality assessment (unrelated to IP or related to IP) must be provided for all AEs (both serious and non-serious).

Investigators will also assess whether the AE is causally related to a protocol required study procedure / intervention.

Causality assessments must be recorded on the eCRF and any additional forms as appropriate.

Table 9. Classification of Adverse Events by Relationship to Investigational Product

Classification	Description
Unrelated to IP	Clinical event with an incompatible time relationship to IP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IP.
Related to IP	Clinical event with a reasonable time relationship to IP administration, and that is unlikely to be attributed to concurrent disease or other drugs or interventions. -OR-

	Clinical event with plausible time relationship to IP administration, and that cannot be explained by concurrent disease or other drugs or interventions.

8.3.3 CLASSIFICATION OF ADVERSE EVENT OUTCOME

Outcome of the AE will be recorded as defined in Table 10.

Table 10. Adverse Event Outcome

1. Recovered/Resolved - One of the possible results of an AE outcome that indicates that the event has improved or recuperated. The subject recovered from the AE. Record AE stop date.
2. Recovering/Resolving - One of the possible results of an AE outcome that indicates that the event is improving. No AE stop date should be recorded.
3. Not recovered/Not resolved/Ongoing - One of the possible results of an AE outcome that indicates that the event has not improved or recuperated. No AE stop date should be recorded.
4. Recovered/Resolved with sequelae - One of the possible results of an AE outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated.
5. Fatal - The AE directly caused death. Record the date of death as the AE stop date.

8.3.4 RAPID NOTIFICATION ON SERIOUS ADVERSE EVENTS

Any SAE occurring after the moment of signed consent and up to Day 9 must be reported to the [redacted] Pharmacovigilance team. SAEs occurring after study termination must be reported only if considered IP related as per Investigator judgment. Any such SAE due to any cause regardless of causality to the IP, must be reported on the SAE reporting form within 24 h of occurrence or when the Investigator becomes aware of the event. Properly completed SAE reporting forms should be sent via email to the Pharmacovigilance team:

- Pharmacovigilance e-mail: [redacted]

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions, including clear and anonymized copies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether the Investigator considers the event to be related to IP.

Appropriate measures should be taken to treat SAEs, and the response should be recorded. Clinical, laboratory and diagnostic measures should be employed as needed to determine the etiology of the problem. The Investigator must report all available additional follow-up information to the Pharmacovigilance team within 24 h. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved. Any SAE that is not resolved by the EOS or upon

discontinuation of the subject's participation in the study is to be followed until its resolution or stabilization.

All SUSARs (i.e., unexpected serious AEs considered drug related as assessed by the Investigator /Sponsor /authorized person) will qualify for expedited reporting and cross reporting to the IRB/IEC, FDA, and participating Investigators.

8.3.5 OVERDOSE

The Investigator must immediately but no later than 24 h notify the Sponsor and CRO of any occurrence of overdose with IP by telephone and by email notification. An overdose is defined as any dose greater than the dose assigned to the individual study subject. Any overdose must be recorded in the concomitant medication section of the eCRF.

Overdose of IP will not be automatically recorded as an AE; however, it will be considered a protocol deviation. Any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate AE eCRF. Since accidental overdoses of the study drugs could have serious clinical consequences and/or represent compliance issue, they should be reported to and evaluated by the Sponsor. The Investigator will record the event in the subject's source document, eCRF and will monitor the subject.

8.4 EXPOSURE DURING PREGNANCY

Potential exposure during pregnancy must be recorded and the subject must be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the subject discontinues IP or discontinues from the study. If a subject within this study or a subject's partner becomes pregnant while treated or exposed to IP, the Investigator must submit a pregnancy form to the Pharmacovigilance team via the same method as SAE reporting. When the outcome of the pregnancy becomes known, the Pregnancy Outcome Form will be completed and returned to the Sponsor or the Sponsor's designee. The Investigator should also follow the outcome of mother and infant to 12 months post-delivery, complete the Follow-up Form, and return to the Sponsor or Sponsor's designee. If additional follow-up is required, the Investigator will be requested to provide the relevant information.

8.4.1 RAPID NOTIFICATION ON PREGNANCIES

Female subjects of childbearing potential must have a negative pregnancy test at Visit 1. After administration of IP, any known cases of pregnancy in female subjects will be reported immediately by telephone and by emailing a completed Pregnancy Report to the CRO's Pharmacovigilance team within 24 h of knowledge of the event. The pregnancy will not be processed as a SAE. However, the Investigator will follow-up with the subject or female partner of the male subjects (after obtaining the ICF, as appropriate) until completion of the pregnancy and must determine the outcome of the pregnancy in the shortest possible time.

The Investigator should notify the Pharmacovigilance team of the pregnancy outcome by submitting a follow-up Pregnancy Report. The Investigator will also notify the Pharmacovigilance team of the outcome of the mother and infant at 12 months post-delivery. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or

congenital anomaly), the Investigator will report the event by telephone and by e-mailing a completed SAE form to the Pharmacovigilance team within 24 h of knowledge of the event.

8.5 DATA SAFETY MONITORING BOARD

Accumulated safety data will be reviewed by the Cystic Fibrosis Foundation Data Safety Monitoring Board during an interim safety analysis when 50% of subjects have received ANG003 or at six months from the first subject enrolled, whichever comes first. A Data Monitoring Committee (DMC) subcommittee will serve on the review board for this trial. The DMC will be headed by a Chair and consist of a physician with expertise in CF, a biostatistician experienced in clinical trial monitoring, and a Patient Representative Board member. The DMC will be governed by an approved Project Charter. Stopping rules will be defined and procedures for data reviews, safety reporting, and decision making will be outlined in the DMC Project Charter.

9.0 SUBJECT SAFETY MANAGEMENT

9.1 STOPPING CRITERIA FOR INDIVIDUAL SUBJECTS

For individual subjects, the criteria below will result in no further dosing at that dose level or higher and this information will be communicated to all study sites. These subjects will continue to be followed for safety through Day 9/EOS visit or resolution of the event, whichever is later.

- Any SAE regardless of causality
- Any grade ≥ 3 AE regardless of causality.

10.0 STATISTICAL METHODS

10.1 STUDY DESIGN

This study is a multicenter, randomized, parallel, active-treatment Phase 1 study of a single dose of orally administered ANG003 with one SMM in adult subjects with CF-related EPI. The study's overall objectives are to evaluate the safety and tolerability and the effect of four dose levels of ANG003. Each subject will be randomized to one of four possible dose combinations of lipase, protease, and amylase as shown in Table 1. Subjects will receive a single dose of ANG003 with one test meal during the 24-hour SACT treatment period. The effects of ANG003 on lipid absorption will be evaluated by giving fish oil containing triglycerides of DHA and EPA with the two test meals and comparing the postprandial changes in plasma DHA and EPA levels with and without the active agent.

10.2 GENERAL CONSIDERATIONS

A formal SAP will be developed prior to database lock and data analysis. The SAP will contain complete details for the safety and exploratory efficacy analysis.

Data from all clinical assessments will be listed and, where appropriate, summarized using descriptive statistics within and between treatment groups defined by the four dose levels. Summary statistics (n, mean, standard deviation, median, minimum, maximum) of the actual value, change and percent change will be presented for continuous variables. Frequencies of categorical variables will be presented.

Summary statistics of within and between treatment changes in exploratory efficacy measures will generate P-values and confidence intervals to quantify the magnitude of treatment effect and to inform dose selection in planning for future studies.

10.3 SAMPLE SIZE CONSIDERATIONS

A sample size of 60 can be supported using the EPI03 results. Study EPI03 was analyzed by a paired ANOVA model with terms representing treatment (4 dose levels and 'no enzyme') and subject (pig). Least-squares means by treatment are: No enzyme (604.7), Dose 1 (740.1), Dose 2 (940.2), Dose 3 (1174.2) and Dose 4 (1032.6), with pooled standard deviation of 320. The F-test from the overall model tests the null hypothesis of no difference in the treatment groups, versus the alternative hypothesis of any difference among treatment. Sample size is estimated using SAS software (PROC GLMPOWER, SAS Institute, Cary, NC) by the same statistical model. A sample size of 60 subjects (15 subjects/treatment group) will have 80% power to detect a difference among treatment groups.

10.4 ANALYSIS POPULATIONS

Analysis Datasets

Safety Analysis Set (SAF):	All subjects who received at least one dose of IP will be included in the SAF. Analysis of this population will be performed on an 'as treated' basis.
Per Protocol Analysis Set (PPS):	PPS is defined as all patients in the SAF with no major protocol deviations. Randomization errors will be classified as major protocol deviations, therefore 'as treated' and 'as randomized' analyses are identical in PPS.

10.5 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS

All subjects screened and enrolled will be accounted for in study summaries. All post-enrollment discontinuations will be summarized by reason for discontinuation. Subjects screened but not enrolled will be listed.

Demographic and other relevant baseline characteristics (including age, gender, race, weight, height, and BMI), medical history and concomitant medications will be summarized using descriptive statistics by treatment group. Subject disposition, including numbers completing the study and prematurely withdrawing from the study, as well as reasons for discontinuation and/or withdrawal, will be summarized.

10.6 SAFETY ANALYSIS

Safety parameters will be analyzed for the SAF and presented by treatment arms. Patients will be grouped according to the actual treatment the patients received (i.e., "as treated"). Safety endpoints will be summarized using descriptive statistics. Summary tables for AEs will include only AEs that started or worsened during or after the Baseline SACT Period, i.e., TEAEs. The number and proportion of subjects with AEs will be tabulated by body system, MedDRA Preferred Term, severity, and relationship to the IP. AE frequencies and percentages will be presented by treatment group and overall. Subjects are represented once at each level of AE classification (e.g., preferred term).

Frequencies of malabsorption-specified AEs of special interest will be summarized by treatment group.

For continuous safety variables clinical laboratory tests and vital signs, summary statistics of measurement values, changes from baseline and percent changes from baseline will be displayed by visit and treatment group. Laboratory abnormalities and PE findings will be described by frequencies within treatment group, and as appropriate, shift tables of category changes from baseline.

Concomitant medications will be listed by subject.

10.7 EXPLORATORY EFFICACY ANALYSIS

Exploratory analysis will be performed in the SAF and PPS populations.

Summary statistics of continuous exploratory endpoints at baseline SACT and ANG003 SACT challenge, and the change from baseline SACT in exploratory endpoints will be provided by treatment group. Differences in SACT changes among treatment will be summarized. Summary statistics include but are not limited to plasma DHA, EPA and fatty acid efficacy endpoints, erythrocyte membrane composition, peptides, amino acids and plasma glucose. Changes in serial measurements (e.g., glucose) will use analysis of variance to quantify within and between treatment changes from baseline.

[redacted]

11.0 SPONSOR AND INVESTIGATOR RESPONSIBILITIES

The study will be conducted according to GCP as outlined by the ICH topic E6 R2, step 5 guideline. The CRO maintains a quality assurance system with written SOPs to ensure that clinical trials are conducted, and data are generated, documented, and reported in compliance with the clinical protocol, GCP, and applicable regulatory requirements. The Sponsor or designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

11.1 SPONSOR RESPONSIBILITIES

The Sponsor or CRO will provide protocol training to the study site research staff. Clinical monitors will conduct site visits, as needed, to ensure the site procedures are being carried out in accordance with the clinical study protocol and GCP. Throughout the study period, the clinical monitor will be available to address any issues that may arise. This availability includes access by phone and email.

11.2 INVESTIGATORS RESPONSIBILITIES

The Principal Investigator, together with any designated sub-investigators, has the overall responsibility for the conduct and compliance of this clinical trial according to this clinical protocol and GCP. Investigators and other key study staff shall provide *curriculum vitae* or equivalent, that will confirm

their suitability for the clinical study. All Investigators and key study staff will be listed with their responsibilities in the study on a signature and delegation log. It is the responsibility of the Investigator to ensure that all study staff are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

All written information and other material to be used by subjects and study staff must use vocabulary and local language that is clearly understood.

11.3 PROTOCOL AMENDMENTS

Amendments to the clinical protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study staff, and minor modifications that have no impact on the safety of subjects or the conduct of the study, will be classed as administrative amendments and submitted to the IRB/IEC and Regulatory Authorities for information only. The Sponsor or designee will ensure that acknowledgment is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval, as appropriate.

11.4 PROTOCOL DEVIATIONS

Should protocol deviations that could affect the subject's safety occur, the Sponsor must be informed within 24 h or as soon as possible. Protocol deviations will be included in the Clinical Study Report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

No prospective entry criteria protocol deviations are allowed; all subjects must meet all eligibility criteria to participate in the study. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. During a subject's participation in the study, if it is discovered that the subject did not meet all eligibility criteria, then the subject will be discontinued.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 STUDY MONITORING

The study will be monitored by the Sponsor or designee to ensure it is conducted and documented properly according to the clinical protocol, GCP, and all applicable regulatory requirements.

Before the study start at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and the eCRF with the Investigators and their staff. During the study, on-site monitoring visits will be made at appropriate times. Clinical monitors will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRF, the adherence to the clinical protocol and to GCP, the progress of enrollment, and to ensure that IP is being stored, dispensed, and accounted for according to specifications. Key study staff must be available to assist the clinical monitor during these visits.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and exploratory variables will be checked. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12.2 AUDITS AND INSPECTIONS

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the clinical protocol, SOPs, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

Investigators/Institution will permit trial related audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/documents. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13.0 ETHICS

13.1 ETHICS REVIEW

The final clinical protocol, including the final version of the IB, ICF and subject facing documents must be approved or given a favorable opinion in writing by an appropriately constituted IRB/IEC.

The Investigator is responsible for informing their IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the sponsor and IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing IRB/IEC reports of any reportable SAEs from any study conducted with ANG003. The Sponsor will provide this information to the Investigator. Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

13.2 ETHICAL CONDUCT

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 54, 56 and 312 of Title 21 of the CFR, in compliance with GCP guidelines, and other national, country, and regional regulations as applicable.

Declaration of Helsinki and amendments can be accessed via the website of the World Medical Association at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethicalprinciplesfor-medical-research-involving-human-subjects/.

13.3 INFORMED CONSENT

For each study subject, a written or electronic ICF will be obtained prior to any protocol-related activities. It must be signed and dated personally by the subject/legal representative and by the Investigator/designee permitted to conduct the informed consent procedure.

The Investigator or designee must explain orally and in writing the purpose, nature, duration of the study, and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences, or AE that may occur. The subject should be informed that they may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and ICH guidelines.

The ICF will be revised whenever important new information becomes available that may be relevant to the subject's consent, or when there is a protocol amendment that necessitates a change in the

content of the ICF. The Investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. The revised ICF must receive the IRB/IEC approval/favorable opinion in advance of use.

The Investigator must maintain the original, signed ICF. A copy of the signed and dated ICF must be given to the subject. The Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC approved ICF prior to study start.

14.0 DATA HANDLING AND RECORD RETENTION

14.1 DATA COLLECTION AND PROCESSING

Data will be collected by means of eCRFs. A subject identification number will be used to identify the subject. Completion instructions will be provided in the eCRF Completion Guidelines document or as prompts and short instruction on the eCRF pages.

The study will use an EDC system to collect the clinical trial data at the investigational sites. The system complies with U.S. 21 Code of Federal Regulations (CFR) Part 11 and ICH E6 GCP. Queries are generally sent to the investigational site using an electronic data query system which provides an automatic audit trail of the corrections made by designated staff. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

Source documents are information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source documents are to be retained to enable reconstruction and evaluation of the trial. No original observations will be entered directly into the computerized system without source documentation.

Concomitant medications entered in the database will be coded using the most recent version of the World Health Organization Drug Dictionary which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases, medical history, and AEs will be coded using the MedDRA dictionary.

Access to the EDC system is controlled with user identification and password and can only be granted to appropriately trained users. Distinct types of users will have different privileges assigned in the EDC system. A user access list is maintained throughout the study.

The eCRF must be completed within 5 working days after each subject visit and within 5 working days after the completion of the clinical phase of the study. All eCRF queries must be resolved within 10 working days. The Investigator will receive a password protected CD/DVD or USB drive of the subject data for archiving at the investigational site following the database lock but before the study site close out visit.

Database quality will be assessed early in the study conduct. Data queries will be quantified and reviewed by site, and by data type/program to highlight any data issues which can be addressed through additional training or enhancements to the data validation programs.

Formal quality control will also be conducted prior to database lock. All required changes to the database design and programming will be managed through a detailed change control process. Details of database lock will be documented in the appropriate Data Management Plan.

14.2 INSPECTION OF RECORDS

The Sponsor will be allowed to conduct clinical site visits for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the IP area, inventory, accountability records, subject charts, study source documents, and other records associated with study conduct.

14.3 RETENTION OF RECORDS

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or two years after the last approval of a marketing application in an ICH region or as per local requirements, whichever is the longer period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Directive 95/46/EC: Directive on the protection of individuals regarding the processing of personal data, on the free movement of such data, and in a form satisfactory to the Sponsor.

15.0 FINANCING AND INSURANCE

Prior to the study commencing, the Sponsor/designee and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (and/or the institution signatory) and the Sponsor/designee.

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations. Injury in subjects possibly arising from participating in this trial is covered by the liability insurance of the Investigator or Sponsor. This insurance provides coverage for damage to the subjects through injury or death caused by the trial.

[redacted]

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APPENDIX 1. INFECTION CONTROL GUIDELINES

Prior to, during, and after home / mobile clinic visits, Nurses will abide by detailed infection control protocols to ensure patient safety and minimize transmission of diseases.

I. Nurses wash and sanitize their hands at the following times throughout the home, neutral location or mobile unit visit:
   - Before and after having direct contact with patients
   - After contact with bare hands, instruments, equipment, and materials, and other objects likely to be contaminated by blood, saliva, or respiratory secretions
   - After removing gloves and/or all personal protective equipment (PPE)
   - When hands are visibly soiled
   - When moving from a contaminated site to a clean site

II. PPE will be donned correctly in proper order before entry into patient care areas. PPE includes but is not limited to:
   - Gowns that fully cover torso from neck to knees, arms to end of wrists, and wrap around back
   - Masks
   - Goggles or face shields
   - Gloves

III. PPE will be removed and disposed per provider guidelines and discarded in trash bag(s) for disposal or biohazards bag if contaminated with blood or body fluids

IV. Nurses will disinfect workspace before and after each procedure throughout the study visit until completed (injections, disposal of sharps / syringes / lances / point of care testing area).

APPENDIX 2. LIST OF SERVICE VENDORS