Statistical Analysis Plan (SAP)

Sponsor:	Anagram Therapeutics, Inc.
Study Title:	A Phase I Open-label, Multicenter Study to Assess the Safety and Efficacy of ANG003 in Patients with Exocrine Pancreatic Insufficiency Due to Cystic Fibrosis
Study Protocol Number	ANG003-22-101
Protocol Version/Date:	V006 22Mar2024 (Amendment 4)
SAP Version/Date:	2.0 18Aug2024
Supersedes SAP Version:	1.0
Appendices (external documents):	1. List of Tables, Listing, Figures (TLFs)

Approval

The Trial Statistician (TS) hereby confirms that the SAP was prepared in conformance with the procedures and principles set forth in the indicated protocol version and all established relevant guidelines.

Name Affiliation, Function	Signature:	Date:
[redacted] Ergomed, Sr. Biostatistician	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 20-Aug-2024 | 4:01:37 PM BST 3B78AC27B3D44BA09F1BE01B7ECF82BD	20-Aug-2024

By signing hereafter, I confirm that this Statistical Analysis Plan adequately describes the statistical analyses to be performed in the context of this study.

Name Affiliation, Function	Signature:	Date:
[redacted] Statistician	[redacted]	20-AUG-2024
[redacted] Anagram Therapeutics, Inc., [redacted]	[redacted] Signing Reason: I approve this document Signing Time: 20-Aug-2024 | 4:45:52 PM BST CB705E5CACA64C078A5E9DE56145E1B6	20-Aug-2024
[redacted] Anagram Therapeutics, Inc., EVP Regulatory Affairs	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-Aug-2024 | 5:10:46 PM BST EA29A49432BF449F941D89DBB3DD4B68	20-Aug-2024

Name **Affiliation, Function**	**Signature:**	**Date:**
[redacted] Medical Monitor	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-Aug-2024 | 5:34:13 PM BST B536C643953344368E1457D6E5DEF604	20-Aug-2024

Revision history

SAP Version	Version date	Reason(s) for change
1.0	22-Jul-2024	Original
2.0	18-Aug-2024	DRM updates to PPS & PK analyses

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area under the time by concentration curve
BMI	Body Mass Index
BP	Blood Pressure
BSS	Bristol Stool Scale
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Regulators
CGM	Continuous Glucose Monitor
CI	Confidence Interval
Cmax	Maximum Concentration
CRF	Case Report Form
CSR	Clinical Study Report
DBS	Dried Blood Sample
DHA	Docosahexaenoic Acid
DMC	Data Monitoring Committee
DRM	Data Review Committee
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EPA	Eicosapentaenoic acid
EPI	Exocrine Pancreatic Insufficiency
FA	Fatty Acid
FSH	Follicle Stimulating Hormone
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IP	Investigational Product
ITT	Intent To Treat
IWRS	Interactive Web Randomization System
LCPUFA	Long-Chain Polyunsaturated Fatty Acids
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
NAUC	Normalized AUC
NE	No Enzyme
PAGI-SYM	Patient Assessment of Gastrointestinal-Symptoms
PE	Physical Exam
PP	Per-protocol
PPS	Per-protocol Analysis Set
PT	Meddra Preferred Term
RBC	Red Blood Cell
SACT	Substrate Absorption Challenge Test
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

Abbreviation	Description
SAS®	Statistical Analysis Software Package
SD	Standard Deviation
SMM	SACT Morning Meal
SOC	Meddra System Organ Class, Standard Of Care
SP	Statistical Programmer
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, Figures
Tmax	Time of Peak Concentration
TS	Trial Statistician
ULN	Upper Limit of Normal
WHO	World Health Organization

1 STUDY INFORMATION

This Statistical Analysis Plan (SAP) is based on the protocol version 006 22Mar2024 and CRF dated 08Apr2024. This study is a phase I open-label, multicenter study to assess the safety and efficacy of ANG003 in patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). The purpose of this SAP is to define the variables and analysis methodology to address the study objectives.

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.

1.2 Exploratory objectives

- 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 plasma levels of amino acid equivalent, glucose and C-peptide.
- To evaluate erythrocyte composition (DHA, EPA, LCPUFAs, total FA) in subjects with CF.

1.3 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 and tolerability and the effect of four dose levels of ANG003 in a single treatment administration. ANG003 consists of three orally administered enzymes (lipase, protease, and amylase) of microbial origin. Each subject will be randomized with equal allocation to one of four possible dose combinations of lipase, protease, and amylase as shown in Table 1.

Table 1. Dosage Compositions

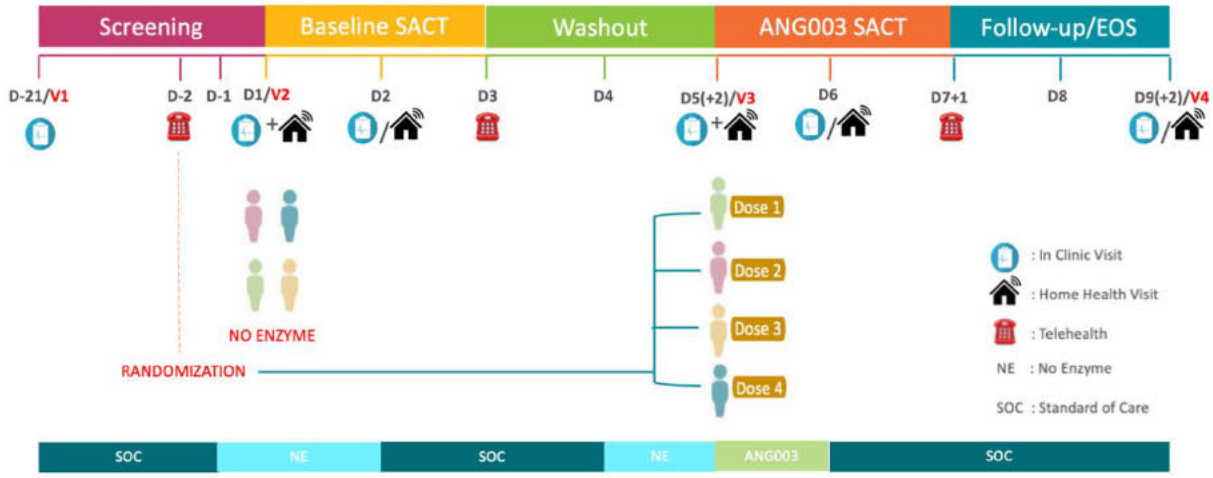
DOSE LEVEL	ANG003 DOSE (LIPASE / PROTEASE / AMYLASE)	[redacted]
1	20 mg / 25 mg / 40 mg	[redacted]
2	40 mg / 50 mg / 80 mg	
3	80 mg / 50 mg / 80 mg	
4	120 mg / 75 mg / 120 mg	

Approximately 48 to 60 eligible subjects with 12 to 15 subjects per dose level are expected to be enrolled in the study. The duration of the study will be approximately 30 days and the overall study design is displayed in Figure 1.

The study is composed of five periods:

1. Screening Period which allows a maximum of 21 days to complete all screening assessments.
2. Baseline Substrate Absorption Challenge Test (SACT) Period (24 h) which includes Day 1 and Day 2.
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 in-clinic and includes Day 6.
5. Safety Follow-up Period/EOS which includes telephone contact on Day 7 and the final study visit on Day 9 in-clinic or at home.

Figure 1. Study Schematic



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

During the 24-hour Baseline Substrate Absorption Challenge Test (SACT) period, a fasting baseline (t0) blood sample will be collected prior to the high-fat SACT morning meal (SMM). Subjects will receive Omega-3 fish oil triglycerides and two other substrates (whey and potato starch) with the SMM. Seven post SACT meal blood samples will be collected (1h, 2h, 4h, 6h, 8h, 10-12h, 24h).

During the 24-hour ANG003 SACT period on Day 5, a fasting baseline (t0) blood sample will be collected and subjects will receive a single dose of ANG003 with the SMM. Seven post SACT meal blood samples will be collected (1h, 2h, 4h, 6h, 8h, 10-12h, 24h).

The short-term lipolysis of DHA and EPA triglycerides and the absorption of DHA and EPA fatty acids will be assessed during each SACT period 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. The postprandial changes in plasma DHA and EPA levels with and without ANG003 will be compared during the two SACT periods.

Table 2. 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, 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						

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
Randomization		X							
Continuous Glucose Monitor q	X		X			X			
ANG003 Dosing						X			
SMM (Weights and Picture) [r]			X			X			
Concomitant Medi-cations	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

Footnotes:

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.

1.4 Randomization and Blinding

The study is unblinded. Eligible subjects will be randomly assigned to one of four dose levels with equal allocation according to a formal randomization schedule generated by an independent Statistician. Each subject will be randomized to a single dose level in Table 1 via the randomization module within the electronic data capture (EDC) interface. Initially, subjects will be stratified by use of Cystic Fibrosis Transmembrance Regulator (CFTR) modulator therapy or non-modulator therapy and then assigned a treatment dose within cohort. The randomization codes will be maintained by the sponsor and designated Statistician. The relevant randomization steps in the EDC will be fully described in a study specific Randomization Instructions document.

1.5 Planned sample size

The sample size of 48 to 60 subjects is from 4 treatment groups of equal sample size with at least 12 to 15 subjects per treatment dose (see Table 1). The sample size calculations are based on pre-clinical studies, however no formal sample size estimation was planned due to the exploratory nature of the trial.

Within-treatment changes in the baseline and test SACT periods increase precision as each subject serves as their own control. Between treatment differences in the change from baseline with 12 to 15 subjects per dose level will provide adequate point estimates and confidence intervals (CIs) for efficacy variables.

2 GENERAL INFORMATION

2.1 Background details

All study data will be transferred to a SAS database (version 9.4 or later) for statistical analysis purposes. Data will be imported from a Data Capture System Merative Clinical Development (formerly known as IBM Clinical Development) via validated SAS programs. [redacted]

The SAP will be finalized before database lock after agreement with the Sponsor on subject disposition and coding.

2.2 Individual protocol deviations

A detailed review of all documented and derived deviations from the protocol will be part of the data review meeting (DRM) before database lock. During this DRM the impact of protocol deviations on the analysis will be assessed and the conclusions recorded. A major protocol deviation will be identified as one having the potential to impact the rights, safety, and/or well-being of subjects, or the completeness, accuracy, and/or reliability of the results. A minor protocol deviation will be identified as one not having a potential impact on subjects or the results as described above.

A complete listing of documented and derived protocol deviations and the judgment for assessment of subject disposition will be signed before database lock. A description of protocol deviations that led to exclusion of a subject will be included in the Clinical Study Report (CSR). A listing and tabular summary of protocol deviations by type will be provided.

3 ANALYSIS POPULATIONS

The number of screened subjects will be presented. Any subject who signs informed consent and has a Screening visit conducted is considered screened. The Intent to treat, safety, and per-protocol populations are defined below.

3.1 Intent To Treat Analysis Set

The Intent to Treat Analysis Set (ITT) will include all subjects who signed the Informed Consent Document and were randomized.

3.2 Safety Analysis Set

The Safety Analysis Set (SAF) will include all subjects who received one dose of IP. Analysis of this population will be performed on an 'as treated' basis.

3.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPS) will include all SAF subjects who completed both the Baseline SACT Period and the ANG003 SACT Period, have both a t0 timepoint and at least 50% of the post-t0 timepoints collected for at

least one of the exploratory efficacy endpoints within each SACT Period, and with no major protocol deviations related to efficacy. Randomization errors will be classified as major protocol deviations, therefore 'as treated' and 'as randomized' analyses are identical in PPS.

4 STATISTICAL ANALYSES

SAS® software (Version 9.4 or later) will be the primary software for statistical analysis of safety (SAF population) and exploratory efficacy (ITT, SAF, and PPS).

Exploratory efficacy data represent the serial measurements for fatty acids, total amino acids , C-peptide, and glucose. Summary statistics (n, mean, standard deviation, median, minimum, maximum) of the actual value and change from baseline will be presented at each time point and SACT period. Summary statistics of within and between treatment changes in exploratory efficacy measures will generate P -values and confidence interval (CI) to quantify the magnitude of treatment effect and to inform dose selection in planning for future studies. Demographic and baseline characteristics may be listed for Screening failures. Otherwise, Screening failure data will not be analysed.

If not stated otherwise the following standard types of descriptive and inferential analyses will be presented:

- Descriptive statistics for continuous data

  N, mean, standard deviation (SD), minimum, median and maximum will be presented. These descriptive statistics will be determined for measured values and for differences from baseline. Summaries will be presented by dose level with overall summary where appropriate.

- Descriptive statistics for categorical data

  Absolute frequencies and percentages will be presented. Percentage (denominators) will be identified in the table title or footnote (i.e. all subjects at risk, all non-missing cases, all cases). For changes from baseline, shift tables will be generated as appropriate. Summaries will be presented by dose level with overall summary where appropriate.

- Inferential statistics

  Unless otherwise stated, all statistical tests will be performed two-sided and at a type I error probability of α=0.05.

  Unless otherwise stated, all Confidence intervals is will be derived two-sided and at a confidence probability of 1-α=0.95.

- Listings

  All recorded data will be listed by subject. Identification variables are centre number, subject number, and treatment using the ITT analysis set.

Change from Baseline: Baseline is t0 on Day 1 (baseline SACT) and t0 on Day 5 (ANG003 SACT). The change from baseline values will be calculated as post baseline values minus the baseline value within each SACT period and between SACT periods.

Change from Baseline = value – baseline.

4.1 Missing data

Generally, no missing data value imputation will be performed and all analyses will be conducted on observed data.

A AUC missing measurement is imputed using the values prior to and following the missing value computed trapezoidal area.

For each efficacy parameter, if the last corresponding timepoint is missing, the last timepoint is carried forward. AUC is not computed if the baseline measurement is missing.

For AE and concomitant medication partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the dose date, then impute the month and day of the dose date.
    b. Otherwise, assign "January."
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the dose date.
    b. Otherwise, assign "01."

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pre-treatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken, and the AE (or medication) is treatment emergent (or concomitant medication).
2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration for AEs or on or after the Screening/Visit 1 date for medications, then the most conservative approach is taken, and the AE (or medication) is treatment emergent (or concomitant medication).
3. If the start date is missing but the stop date is not missing and is before the day of study dose for AEs or before the Screening/Visit 1 date for medications, then the AE (or medication) is before treatment (or prior medication).
4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication is concomitant while the AE is defined by start date.

4.2 Demographic and other background data

The disposition of subjects will be tabulated by treatment and for the entire analysis set. Frequencies or different reasons for exclusions from analysis sets will be listed. Similarly, discontinued subjects will be described by frequencies for the reasons and in individual listings.

Demographic data (e.g., age, gender, race, ethnicity, weight, height, and body mass index (BMI)) and CFTR (yes, no) will be summarized in frequencies or summary statistics by dose level. Subject disposition, including numbers screened, screen failed, completing the study and prematurely withdrawing from the study, as well as reasons for discontinuation and/or withdrawal, will be reported.

4.3 PAGI-SYM

All assessments of Patient Assessment of Gastrointestinal Disorders – Symptom Severity Index (PAGI-SYM) sub-scale scores (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, lower abdominal pain) will be presented in a summary table.

4.4 Medical history, physical examination

Medical history will be summarized in frequency tables by dose level according to MedDRA V26.1 Sep 2023.

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.

Medical history will be summarized by system organ class (SOC) and preferred term (PT) by dose level in the SAF population.

4.5 Prior and concomitant medication

A 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. Prior & concomitant medications frequencies and percentages by ATC code level 4 and subject will be summarized by dose level using the ITT analysis set.

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 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. Routine PERTs are restricted after breakfast on Day -1, at least 24-hours prior to the Day 1 in-clinic visit, thru the 24 h blood sample on Day 2 AND after breakfast on Day 4, at least 24-hours prior to the Day 5 in-clinic visit, thru the 24 h blood on Day 6.

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

4.6 Exploratory endpoints

Exploratory efficacy data analyses will include analysis of variance methods. Summary statistics of within and between treatment efficacy measures will generate P-values and CIs to quantify the magnitude of treatment effect and to inform dose selection in planning for future studies. The primary exploratory efficacy comparisons in the PPS population of the exploratory efficacy measures are between SACT interventions as ANG003 SACT minus baseline SACT. The timepoints for analysis include:

Efficacy Parameter	Timepoint(s) to be analyzed
DHA & EPA	Over 10-12 & 24 hours
Total Fatty Acids	Up to 10-12 hours
C-Peptide	Up to 6 hours
Total Amino Acids	Up to 6 hours
Glucose	Up to 4 hours

Protocol-defined PK endpoints include AUC, normalized AUC (NAUC), maximum concentration (cmax) and time to maximum concentration (tmax). The PK analysis will include p-values within and between treatments using ANOVA with pairwise treatment comparison. PK measures include:

- C-Peptide: AUC 6 hr
- DHA & EPA Fatty Acid: AUC 10 hr & AUC 24 hr
- Total Fatty Acid: AUC 10 hr
- Blood Glucose: AUC 2 hr & AUC 4 hr
- Total Amino Acid: AUC 6 hr
- NAUC, maximum concentration (cmax) and time to maximum concentration (tmax) will be generated for all efficacy variables using the last timepoint available specified in the above table.

NAUC will be calculated as AUC of the last timepoint and divided by the corresponding SACT baseline value.

Analysis will focus on treatment differences in mean concentration at baseline and post baseline. Descriptive statistics (n, minimum, mean, median, maximum, standard deviation) of within and between SACT study periods pre-post prandial timepoints will be presented.

Exploratory efficacy analysis will include C-peptide, DHA/EPA fatty acid, total fatty acid, CGM, and total Amino Acids. For each exploratory endpoint, summary are generated within treatment, SACT period (baseline SACT, ANG003 SACT), and hour. Statistical significance of the change from baseline is by a one-sample 2-sided t-test. Summary statistics within treatment group and hour for SACT changes (ANG003 SACT minus baseline SACT) post baseline will be provided and assessed for statistical significance by a one-sample 2-sitded t-test.

The exploratory efficacy time intervals relative to baseline on Days 1 and 5 are computed (taken from the c-peptide, amino acid CRF page). For CGM, hours will be 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4 after t0. Fatty acid (DHA, EPA, DPA + EPA) time intervals include hours 0, 1, 2, 4, 6, 8, 10-12 and 24. C-Peptide time intervals include hours 0, 1, 2, 4 and 6. Amino acid time intervals include hours 0, 1, 2, 4, and 6. The primary population for exploratory efficacy analysis is the PPS population in the ANG003 SACT period. ANOVA with pairwise treatment comparisons will be used to generate between dose p-values. These pairwise comparisions will be included in the change from baseline SACT tables & PK tables for the exploratory efficacy endpoints.

PAGI-SYM questionnaire summary statistics at screening, Day 2, and Day 6 will be presented. Mean scores for each subscale and overall will be displayed. Bristol Stool Scale (BSS) will include descriptive summary statistics by visit and dose level.

4.7 Safety Analysis

Safety parameters will be summarized in the ITT and SAF population and presented by dose levels and overall.

The safety and tolerability primary endpoints include the following:

- Frequency of adverse events, serious adverse events, and AEs leading to discontinuation
- 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)
- Incidence of malabsorption symptoms (e.g., abdominal pain, constipation, diarrhea, distension/bloating, flatulence, indigestion/heartburn, nausea, steatorrhea, and vomiting)
- Vital signs (body temperature, heart rate, respiratory rate, blood pressure)
- Physical examination
- Concomitant medications

4.7.1 Adverse events

Adverse events will be presented by the Medical Dictionary for Regulatory Activities (MedDRA V26.1 Sep 2023) System Organ Class (SOC) and Preferred Term (PT) by dose level.

For each change in intensity, relationship, or seriousness of an AE, a new entry of the AE was recorded in the data capture database and such cases are analysed as different phases of the same AE.

Frequencies of adverse events identified from randomization through Day 9 will be listed as baseline SACT (Days 1-2), Washout (Day 3-4), ANG003 SACT (Days 5-6), and Follow-up (Days 7-9) will be presented by treatment dose and overall. Frequencies and percentages of AEs in the ITT & SAF population (screening & Days 1 – 9) and TEAEs (Days 5-9) will be presented separately. AE table for days off PERT (Day -1, Day 2 & Day 4) will also be summarized.

TEAEs are defined as AEs that emerge during treatment having been absent prior to Day 5 or worsened after treatment through Day 9. Incidence tables, i.e., frequency tables of subjects experiencing at least one occasion of the event while at risk (along with the number of different occurrences of the TEAE), will be presented in a data listing for the following types of adverse events and related SAEs:

- All TEAEs irrespective of the causality assessment
- Serious TEAEs (SAEs)
- Fatal TEAEs
- TEAEs leading to discontinuation
- TEAEs by worst severity
- TEAEs related to IP intervention

These tables will also include summary lines for all SOCs and PTs, and will be presented according to the Internationally Agreed Sorting Order (MedDRA V26.1 Sep 2023).

Multiple counts within a PT or SOC (repeated or different included terms or changes in descriptors) will be counted only once for the calculation of incidence.

All adverse events (i.e., TEAEs as well as non-treatment emergent events) will be listed in section 16.2 of the CSR.

4.7.2 Vital signs

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. Vital signs actual values and change from baseline (e.g. Day 5 (visit) to Day 6 (at home) will be summarized descriptively by visit and dose level.

4.7.3 Physical examination

At each follow-up physical examination and interval medical history will be obtained. New or worsened interval medical history will be captured as AEs.

Pulse Oximetry: Arterial 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. Actual values and change from baseline will be summarized descriptively by visit.

4.7.4 Laboratory variables

All laboratory samples for clinical laboratory assessments (Table 4) will be collected at the time points displayed in the Schedule of Assessments (Table 2).

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.

Clinical laboratory evaluations include hematology (blood cell count with differential and platelet count), serum biochemistry including blood urea nitrogen and creatinine, liver function tests, coagulation profile, and urinalysis).

Summary tables on actual values will be presented by dose level and visit. For qualitative analyses frequency tables will be provided. A subject listing of abnormal lab values (ICH CSR section 14.3.4) will be displayed. Data from scheduled visits will be used in in analyses and results from unscheduled visits will only be used in listings.

Table 4. 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

[redacted]

QUALITY CONTROL

The SAP will be reviewed by the TS before signature. Specifically, the TS has checked the consistency of the described methods and outputs with the actual version of the study protocol. In addition, a sponsor representative reviewed the SAP before final approval.

Log files of all SAS® programs used in the analysis will be checked for errors, warnings and suspicious notes by the statistical programmer. All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by an independent statistical programmer.

The agreement of the program outputs with the SAP, their consistency and plausibility will be checked by the TS. Moreover, the TS will review the outputs regarding completeness, readability and comprehensibility.

6 DERIVATIONS AND TRANSFORMATIONS

6.1 Formulas for derived variables

Variable	Definition / Derivation
BMI	Weight [kg] / (height [m])**2

7 STANDARDS USED IN PREPARATION OF STATISTICAL OUTPUTS

The below conventions will be followed as agreed with the Sponsor.

7.1 Programming

- One SAS program should create only one output.
- One output file can contain different output types (e.g., descriptive and inferential).
- Individual output files will be created in MS Word format (Rich Text Format, RTF).
- Once delivered to the client, numbering of TLFs will not be altered, unless agreed with the client.

7.2 Layout

- TLFs will be produced in landscape format
- TLFs will have a minimum 2 cm on every side
- TLFs will be produced using the Courier New font, size 8
- Section numbering of TLFs will follow ICH E3 guideline
- Titles and footnotes for figures will also be in Courier New font, size 8.
- Tables and listings will be in black and white (no colour), figures may include only colour that can be distinguished when printed on a grey-scale printer
- Text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will be used sparingly in the TLFs
- The ANSI character set will be used in the TLFs. Certain subscripts and superscripts (e.g., m^2, AUC_{norm}) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, unless they are derived directly from the data

7.3 Headers, Titles and Footnotes

- All output will have the following header at the top left of each page showing the study ID, the date of output generation and an internal pagination, where Y stands for the total number of pages in the pertaining output.

Study ID
Study description

[redacted]-DD
Page [X / Y]

- Also, all TLFs will have the following footer, identifying the generating SAS program (XXX.SAS), a reference to the relevant subject listing and the date of the data snapshot:

SAS program: <XXX>.sas	Ref. list X.X.X-YY	Data status: YYYY-MM-DD

- Each TLF will bear a title which is repeated on each page of the output.
- The title at the top of the page will be horizontally centered in bold font.
- A blank line will separate the title from the body of the output.
- The title will consist of an Output number, a descriptive title and a description of the presented analysis set (if applicable).
- The title will have the following general appearance:

Table / Figure / List XX.X.X-YY
Descriptive Title line 1
Descriptive Title line 2
(All subjects in the FAS, N=nnn)

- Each new footnote should start on a new line, where possible.
- Preferably, footnotes should be left justified. When extending beyond a single line, a manual linefeed should be inserted to avoid meaning distortion.
- An automatic footnote '(continued)' will appear at the bottom of TLFs that extend over more than one page.

7.4 General Conventions

- For measured variables column headers should include the unit in their description
- The order of dose levels in the TLFs will be consistent throughout the entire TLF presentation
- Alphanumeric values are preferably displayed left-justified;
- Dates are presented left-justified
- Integer numbers (e.g., counts) can be centered or right-aligned
- Numbers containing fractional portions will be decimal-aligned
- Fractional numbers with absolute value less than 1 will carry a leading zero, i.e. 0.123 not .123.
- Units of measured or derived variables will be included where appropriate
- Unless otherwise warranted, the estimated mean and median for a set of values will be displayed with 1 more significant digit than the original values, and standard deviations with 2 more significant digits. The minimum and maximum should report the same significant digits as the original values.
- P-values are output in the format: "0.xxxx", where xxxx is the value rounded to 4 decimal places. P-values less than 0.0001 will be presented as <0.0001.
- Precision of percentages displayed will depend on the total study size. For this study, values will be presented with one decimal place.
- Tabular display of data for medical history, prior/concomitant medications and all tabular displays of adverse event data are generally presented by body system, treatment class, or SOC according to the Internationally Agreed Sorting Order of the MedDRA V26.1 Sep 2023, unless otherwise agreed.
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant dose level (or overall) for the analysis (sub-) population presented.

- For categorical summaries (number and percentage of subjects) where a patient can be included in more than one category, an explanatory text will be added to clarify that multiple answers were possible.
- Missing values will be displayed either by a double-dash ("--") or as "NA" (='not available/applicable'), whichever is appropriate.
- Dates are displayed in according to ISO date/time format as YYYY-MM-DD, e.g. 2010 03 24. Missing dates may be represented as "NA", if not available/applicable.
- Clock times are displayed as HH:MM or HH:MM:SS based on 24-hour clock

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