Effective Date: FEB 01 2021

Protocol Title: ^{13}C-Spirulina Breath Test (^{13}C-GEBT) Lot-to-Lot and Biological Variability Study

Protocol Number: PRO-CD-050

Amendment Number: 00

Sponsor Name: Advanced Breath Diagnostics, LLC, dba Cairn Diagnostics

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SD 2/1/21

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1.0 STUDY SYNOPSIS

The purpose of this study is to collect information regarding lot-to-lot variability in ^{13}C-Spirulina GEBT test meal lots and within-subject biological variability.

^{13}C-Spirulina is the carbon-13 labeled substrate incorporated into the Gastric Emptying Breath Test (GEBT) test meal (100 mg of ^{13}C-Spirulina in 27 g of powdered egg). Consumption of the GEBT test meal and subsequent digestion, absorption and metabolism gives rise to $^{13}CO_2$ in human breath. The rate of $^{13}CO_2$ excretion arising from the carbon-13 labeled test meal reflects a patient's gastric emptying rate.

^{13}C-Spirulina used in the GEBT is produced at Cairn Diagnostics by culturing a pure axenic inoculum of Spirulina in a growth medium enriched in carbon-13, a safe, non-radioactive stable isotope of carbon. ^{13}C-Spirulina thus produced is uniformly labeled with carbon-13 to an abundance level of approximately 99% and contains a mixture of ^{13}C-labeled protein, carbohydrates, and lipids.

In this study participants will participate in one or two arms of the study. In one arm the participants will be administered GEBT tests that contain different ^{13}C-Spirulina/Egg mix drug lots. In the second arm, the participants will be administered GEBT tests from the same ^{13}C-Spirulina/Egg mix drug lot. All GEBT kit lots to be administered during the execution of this study have been manufactured under full cGMPs and will be administered according FDA-approved labeling.

2.0 DEFINITIONS

Term/Abbreviation	Definition
Carbon-13	Carbon-13, denoted as ^{13}C, is a stable, non-radioactive, safe, naturally occurring form of carbon. Carbon-13 occurs in nature in a natural abundance of approximately 1%.
Carbon-12	Carbon-12 (^{12}C) is the most abundant, non-radioactive form of carbon in nature. Natural abundance is approximately 99%.
ABCA GIRMS	Automated Carbon Breath Analyzer Gas Isotope Ratio Mass Spectrometer. Used to analyze stable, non-radioactive isotopes of carbon, ^{13}C and ^{12}C, in QC gases and human breath samples. The ABCA GIRMS is an FDA-approved instrument for use with Cairn Diagnostics' ^{13}C-Spirulina Gastric Emptying Breath Test ("GEBT"). For these purposes, the instrument measures the ratio of $^{13}CO_2/^{12}CO_2$ in QC gases and human breath.
ABCA2 GIRMS	Sercon's new model Automated Carbon Breath Analyzer-2 Gas Isotope Ratio Mass Spectrometer. Used to likewise analyze the ratio of $^{13}CO_2/^{12}CO_2$ in QC gases and human breath.
AE	Adverse Event
Delta values (δ^{13}C)	Amount of ^{13}C in a sample expressed as a ratio of carbon-13 to carbon-12: $\delta^{13}C(‰) = \frac{R_B - R_S}{R_S} * 1000$

Term/Abbreviation	Definition
	Where R_B is the ratio of $^{13}C/^{12}C$ of the sample and R_s is the ratio of $^{13}C/^{12}C$ in Pee Dee Belemnite (PDB), the reference standard for these measurements.
DOB	Delta Over Baseline i.e. the difference in delta value at any given time point and the pre-meal/baseline delta value
GEBT	Gastric Emptying Breath Test. The ^{13}C-Spirulina Gastric Emptying Breath Test ("GEBT") is an FDA-PMA approved, Class III combination drug medical device in vitro diagnostic product intended for measurements of the rate of solid phase gastric emptying and identification of gastroparesis (delayed gastric emptying).
GES	Gastric Emptying Scintigraphy
GRAS	Generally Recognized As Safe
PHI	Personal Health Information
SAE	Serious Adverse Event
WOCBP	Women of Childbearing Potential

3.0 BACKGROUND

3.1 Intended Use

The Gastric Emptying Breath Test (GEBT), to be used with the GEBT test meal, is a quantitative test intended for use in the measurement of the rate of gastric emptying of solids and to aid in the diagnosis of delayed gastric emptying (gastroparesis) in adults who are symptomatic for gastroparesis. For these purposes, the test system utilizes a Gas Isotope Ratio Mass Spectrometer (GIRMS) for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples.

The GEBT should be administered under supervision of a health care professional although no specialized facilities or specially licensed personnel are required.

3.2 Principle of the GEBT

After an overnight fast, a test meal containing non-radioactive ^{13}C-labeled Spirulina is administered to the patient. As the test meal is emptied from the stomach it is rapidly absorbed across the duodenum and metabolized giving rise to exogenous ^{13}C-labeled CO_2 which is excreted in the breath. The rate of $^{13}CO_2$ excretion in breath at any given GEBT measurement time is directly proportional to the rate of gastric emptying.

3.3 Description of the GEBT Device

Cairn's ^{13}C-Spirulina GEBT is a Class III in vitro diagnostic medical device that consists of three FDA regulated components:

- A diagnostic drug (^{13}C-Spirulina/Egg mix) that contains the active pharmaceutical ingredient (^{13}C-Spirulina) that gives rise to ^{13}C-labeled CO_2 in patients' breath when taking the test.
- A kit containing the diagnostic drug, repackaged saltine crackers, consumables used to prepare the meal, a breath collection kit (screw capped glass tubes and a straw),

materials to allow return of breath samples and approved labeling (instructions for use/package insert).

- An Automated Breath Carbon Analyzer Gas Isotope Ratio Mass Spectrometer (ABCA-GIRMS) used to determine the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples.

3.4 Components and Pictures of ^{13}C-Spirulina GEBT Kit, Prepared Test Meal and ABCA GIRMS Instruments

The components of the ^{13}C-Spirulina GEBT are addressed below.

- ^{13}C-Spirulina Gastric Emptying Breath Test (GEBT) – Test Meal (^{13}C-Spirulina/Egg)

  Ingredients: Desugared whole eggs, Dry non-fat milk solids, Salt, Smoke Flavoring (Char Oil), ^{13}C-labeled Spirulina

  Nutritional value: Fat 8.8 g; Carb 4 g; Fiber 0 g; Protein 12g
  Energy value; 150kCal
  Net weight; 27g

- ^{13}C-Spirulina Gastric Emptying Breath Test (GEBT) – Saltine Crackers (3 packages of 2 crackers)

  Ingredients: Unbleached enriched wheat flour (wheat flour, niacin, reduced iron, thiamine mononitrate, riboflavin, folic acid), canola oil, palm oil, sea salt, malted barley flour, baking soda, yeast.
  Nutritional value; Fat 1 g; Carb 14 g; Fiber 0 g; Protein 1g
  Energy value; 80 kCal
  Net weight; 18 g

- Overall Meal Nutritional/Energy Values

  Fat 9.8g, Carb 18g, Fiber 0g, Protein, 13g, 230kCal

Table 1. Contents of ^{13}C-Spirulina GEBT Kit

Meal preparation components of Kit	Breath Sample Collection Components of Kit
1 Instructions for Use/Package Insert	1 Test Request Form
1 ^{13}C-Spirulina/Egg Meal packaged in a foil pouch with oxygen absorber	2 Blue-Capped Exetainer tubes labeled for pre-meal collection
3 packages of 2 saltine crackers re-packaged in a foil pouch with oxygen absorber	6 White-Capped Exetainer tubes labeled for post-meal collection
1 large (~13 fl oz/390 mL) microwaveable cooking cup	2 drinking straws
1 filling cup (small (~3.5 fl oz/~100 mL) plastic cup with pour spout for transferring water)	1 Breath tube holder
1 plastic cutlery kit (knife, fork and spoon)	1 Pre-labeled Bubble Mailer

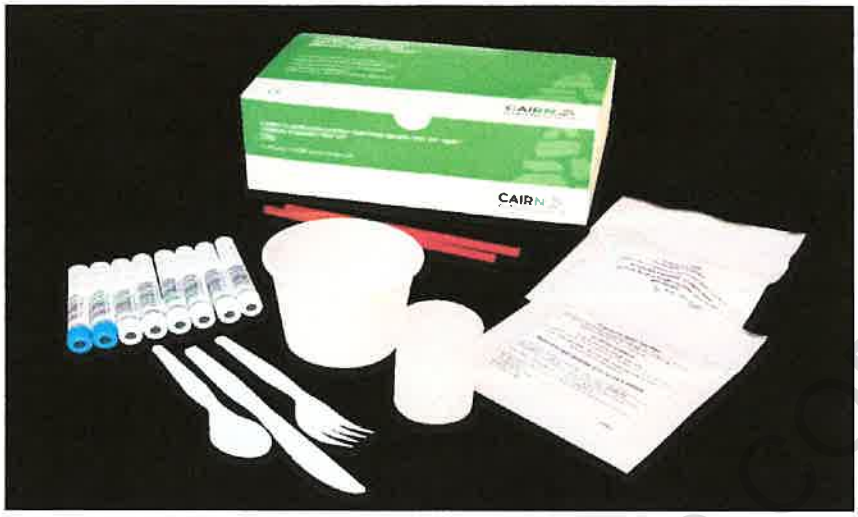

Figure 1. Contents of ^{13}C-Spirulina GEBT Kit Displayed

Figure 2. Prepared ^{13}C-Spirulina GEBT Test Meal and Breath Sample Collection Components

Figure 3. ABCA GIRMS instrument Currently Approved by FDA for Use with GEBT

3.5 Summary of Relevant Clinical Studies

The GEBT was validated in FDA-approved dual-labeled validation studies. The comparative method was a nuclear medicine procedure known as Gastric Emptying Scintigraphy ("GES"). GES is conducted by administering a radionuclide-labeled test meal to a fasting patient and measuring the rate of radiation decline with time as the stomach empties the labeled test meal. In the validation studies GEBT and GES were conducted concurrently (Mayo Clinic). GEBT demonstrated excellent agreement with diagnosis by GEBT vs. GES.

The FDA approved GEBT for commercial use in April 2015 (Pre-Market Approval PMA P110015: Gastric Emptying Breath Test). Exhibit A includes the FDA's public announcement of the approval and a copy of PMA 110015 Gastric Emptying Breath Test Letter of Approval.

GEBT has an excellent safety profile with no serious adverse events reported in pre-validation, validation and post validation studies. There have been no medical device reportable (MDR) events post approval (> 5,000 GEBT).

A recent international consensus statement recommended GEBT for use in the evaluation of gastroparesis "because of its careful validation, high concordance with scintigraphic data and FDA approval" (INTERNATIONAL CONSENSUS STATEMENT: Advances in the diagnosis and classification of gastric and intestinal motility disorders. Gastroenterology and Hepatology, Volume 15, May 2018).

GEBT is currently used in the majority of Phase II, and III pharmaceutical studies for new drugs for gastroparesis. In these studies, GEBT is used to identify gastroparetic patients for enrollment and to assess physiologic effects of new pharmacologic agents (U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); Gastroparesis: Clinical Evaluation of Drugs for Treatment; Guidance for Industry. July 2015, August 2019. Clinical/Medical).

Table 2 summarizes key peer-reviewed literature regarding ^{13}C-Spirulina GEBT.

Table 2. Summary of Key Peer-Reviewed Literature

Publication	Brief Description
J S Lee, M Camilleri, A R Zinsmeister, D Burton, L J Kost, P D Klein. A valid, accurate, office based non-radioactive test for gastric emptying of solids Gut 2000;46:768–773	Proof of principal study in healthy subjects showing the excellent correlation of simultaneous ^{13}C-Spirulina GEBT measurements with GES.
Viramontes B, Kim M, Camilleri M, et al. Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. Neurogastroenterology and Motility 2001; 13:567-574	In this study GEBT and GES were conducted simultaneously in subjects with conditions of delayed, normal and accelerated emptying. Data presented in this study showed a very high correlation between GES and GEBT values ($r = 0.86$; $P < 0.0001$). GEBT had a sensitivity of 86% and specificity of 80% for detecting abnormal emptying (delayed and accelerated).
Szarka L, Camilleri M, Vella A, et al. A stable Isotope Breath Test with a Standard Meal for Abnormal Gastric Emptying of Solids in the Clinic and in Research. Clinical Gastroenterology and Hepatology 2008; 8: 635-643. (Pivotal Validation Study and basis of FDA approval)	This study validated the ^{13}C-spirulina GEBT in a prospective manner among 129 symptomatic subjects meeting the criteria for referral to GES in a tertiary clinical setting. This study also demonstrated that the normal, day-to-day intra-patient biologic variability of gastric emptying is the same as measured by GES or GEBT.

PRO-CD-002, ^{13}C-Spirulina platensis GEBT – Biological Variation/Reference Range Study was designed to establish the diagnostic cutoff points (reference range) and the within subject biological variability of the GEBT method.

4.0 STUDY GOALS AND OBJECTIVES

Study objectives are as follows:

1) Estimate the difference, if any, in human *in vivo* response to different lots of ^{13}C-Spirulina GEBT test meals
2) Obtain additional data to estimate the within-subject biological variability of the ^{13}C-Spirulina GEBT in subjects with normal gastric emptying

This study will be conducted in compliance with this Protocol, GCPs, and IDE/IND regulations set forth in 21 CFR 812 and 21 CFR 312 and as applicable to this combination product.

5.0 SUBJECT SELECTION

Cairn personnel and their family and friends may volunteer to be a participant in this study.

Participants that participated in Cairn study PRO-CD-041, Determination of the Effect of ^{13}C-Spirulina Nitrogen Content on *In Vivo* ^{13}C-Spirulina Gastric Emptying Breath Test (^{13}C-GEBT) Results, will be invited to participate in this study.

This study requires a minimum of fifteen (15) and up to thirty (30) participants in each arm of this study. Volunteers may participate in one or both arms of the study.

Arm A - Lot-to-lot Variability: Participants in Arm A of the study will be administered up to six (6) different ^{13}C-Spirulina GEBT test meal lots.

Arm B – Biological Variability: Participants in Arm B of this study will be administered the same ^{13}C-Spirulina test meal lot on two different occasions.

5.1 Inclusion criteria

Participants are eligible to be included in the study if they meet the following criteria:

- Males and females, 18 – 85 years old at time of signing the informed consent form.
- Ability to eat test meal and provide breath samples.

5.2 Exclusion criteria

- History or physical exam suggestive of systemic disease such as diabetes mellitus or pathophysiologic disorders such as renal failure, chronic heart disease, chronic respiratory disease, liver disease, or malabsorption syndrome.
- History of abdominal surgery except appendectomy.
- Use of any medications that may alter gastric motility within two days of the study.
- Use of narcotics or anticholinergics within two days of the study.
- Females on hormone replacement therapy other than birth control medications.
- Pregnancy.
- Intolerance or allergy to any component of Gastric Emptying Breath Test meal
- History of neurologic or psychiatric disorders.

5.3 Participant Meal and Dietary Restrictions

Participants will fast for at least 8 hours (preferably overnight) prior to administration of the GEBT and during the GEBT (with the exception of eating the test meal). Alcohol should not be consumed within 8 hours prior to testing. Participants may consume a small amount of water up to 1 hour before the test, but not more than 4 fl oz.

Subjects should not smoke/use tobacco products (e.g. chewing tobacco, nicotine gum) before or during administration of the GEBT.

5.4 Participant Activity Restrictions

Participants will abstain from strenuous activity for at least 8 hours prior to administration of the GEBT. Participants may participate in light activities during administration of the GEBT (e.g. watching television, reading, using restroom) but otherwise will remain comfortably seated in the test administration location.

6.0 STUDY PROCEDURES/RESEARCH METHOD

6.1 Study Scheme

Arm A: Lot-to-Lot Variability Study

Visit 1 Screening and Enrollment: For each potential participant, perform a screening visit at the clinical study site (Cairn Diagnostics facility in Brentwood TN) or via a telehealth communications platform where the study is explained to the participant. Answer any questions about the GEBT test procedure and ask the participant to provide consent to participate in the study (see SPEC-CD-041 for informed consent form). The informed consent form will be signed in the presence of the research coordinator explaining the consent form. The consent form will be signed by the research coordinator and a copy will be provided to the participant.

If consent is performed via telehealth, a copy of the signed consent form will be sent (fax, email, etc) to the research coordinator to sign and return to the participant.

Complete the enrollment according to SOP-CD-025, Execution of Cairn Sponsored Clinical Trial Studies, to ensure that the participant is eligible to participate in the study. Participants are free to leave the facility or log out of telehealth platform upon completion of the screening and enrollment visit.

Visit 2 GEBT Administration: Within two weeks of visit 1, participants will either return to the clinical study site or log into the telehealth communication platform using the information provided by a Cairn telehealth administrator at which time the GEBT will be administered. After confirmation that the participant has met the fasting and dietary restriction requirements, the participant will provide a baseline (PRE-meal) breath sample by exhaling into two blue-capped glass Exetainer tubes. The participant will then consume the~~n~~ prepared GEBT test meal. After consuming the test meal, post meal breath samples will likewise be collected at 45, 90, 120, 150, 180, and 240-minute timepoints.

Follow up contact (e.g. phone call, email, in-person, etc) will be made with the participant within 48 hours following the GEBT administration to assess whether there are any post-administration adverse events.

Visit 3 GEBT Administration: The procedure for visit 3 is the same as visit 2 with a different ^{13}C-Spirulina test meal administered than was administered at Visit 2. The time period between Visit 2 and Visit 3 will be no less than 48 hours (note: washout period for GEBT is 24 hours).

Follow up contact (e.g. phone call, email, in-person, etc) will be made with the participant within 48 hours following the GEBT administration to assess whether there are any post-administration adverse events.

Visits 4-7 GEBT Administration: The procedures for visits 4-7 are the same as previous visits with different ^{13}C-Spirulina test meals administered than were administered at previous visits. The time period between visits will be no less than 48 hours (note: washout period for GEBT is 24 hours).

Follow up contact (e.g. phone call, email, in-person, etc) will be made with the participant within 48 hours following each GEBT administration to assess whether there are any post-administration adverse events. If participant does not want to continue further with this arm or participant in Arm B, the participant closeout will be performed.

Final Visit and closeout: Follow up contact (e.g. phone call, email, in-person, etc) will be made with the participant within 48 hours following the GEBT administration to assess whether there are any post-administration adverse events.

Table 3. Arm A: Lot-to-Lot Comparison Study Schedule of Activities (SoA)

Procedure	Screening and Enrollment (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Follow-up/Close-Out (Final Visit)	Early Termination (ET)	Notes
Informed Consent	X									
Inclusion and Exclusion Criteria	X									
Administration of ^{13}C-Spirulina GEBT		X	X	X	X	X	X			Test administration from different GEBT test meal lots
AE review								X	X	
SAE review								X	X	

Arm B: Biological Variability Study

Visit 1 Screening and Enrollment: For each potential participant, perform a screening visit at the clinical study site (Cairn Diagnostics facility in Brentwood TN) or via a telehealth communications platform where the study is explained to the participant. Answer any questions about the GEBT test procedure and ask the participant to provide consent to participate in the study (see SPEC-CD-041 for informed consent form). The informed consent form will be signed in the presence of the research coordinator explaining the consent form. The consent form will be signed by the research coordinator and a copy will be provided to the participant.

If consent is performed via telehealth, a copy of the signed consent form will be sent (fax, email, etc) to the research coordinator to sign and return to the participant.

Complete the enrollment according to SOP-CD-025, Execution of Cairn Sponsored Clinical Trial Studies, to ensure that the participant is eligible to participate in the study. Participants are free to leave the facility or log out of telehealth platform upon completion of the screening and enrollment visit.

Visit 2 GEBT Administration: Within two weeks of visit 1, participants will either return to the clinical study site or log into the telehealth communication platform using the information provided by a Cairn telehealth administrator at which time the GEBT will be administered. After confirmation that the participant has met the fasting and dietary restriction requirements, the participant will provide a baseline (PRE-meal) breath sample by exhaling into two blue-capped glass Exetainer tubes. The participant will then consume then prepared GEBT test meal. After consuming the test meal, post meal breath samples will likewise be collected at 45, 90, 120, 150, 180, and 240-minute timepoints.

Follow up contact (e.g. phone call, email, in-person, etc) will be made with the participant within 48 hours following the GEBT administration to assess whether there are any post-administration adverse events.

Note: Participants from Cairn study PRO-CD-041 will be administered the same GEBT test meal lot as was administered for the previous study. Visit 2 will serve as the second administration, therefore, these participants will not need to return for visit 3.

Visit 3 GEBT Administration: The procedure for visit 3 is the same as visit 2 using the same lot of GEBT test meal as administered at Visit 2. The time period between Visit 2 and Visit 3 will be no less than 48 hours (note: washout period for GEBT is 24 hours).

Visit 4 Follow-up and closeout: Follow up contact (e.g. phone call, email, in-person, etc) will be made with the participant within 48 hours following the GEBT administration to assess whether there are any post-administration adverse events. If the participant does not want to participate in Arm A, the participant closeout will be performed.

Table 4. Arm B: Biological Variation Study Schedule of Activities (SoA)

Procedure	Screening and Enrollment (Visit 1)	Visit 2	Visit 3	Follow-up/Close-Out (Visit 4)	Early Termination (ET)	Notes
Informed Consent	X					
Inclusion and Exclusion Criteria	X					
Administration of ^{13}C-Spirulina GEBT		X	X			Test administration from the same GEBT test meal lot
AE review				X	X	
SAE review				X	X	

6.2 Experimental Design

Arm A: Lot-to-Lot Variability Study

Participants in this arm will be administered up to six (6) different ^{13}C-Spirulina GEBT test meal lots.

Participants will be administered up to six (6) different ^{13}C-Spirulina GEBT test meal lots. The table below summarizes the ^{13}C-Spirulina GEBT test meal lot (D008), the ^{13}C-Spirulina lot(s) (API003) used in the production of the GEBT test meal lot and GEBT kit number.

Table 5. Summary table of lots to test (drug: ^{13}C-Spirulina/Egg Mix; Active Pharmaceutical Ingredient: ^{13}C-Spirulina and GEBT kit lots)

^{13}C-Spirulina/Egg mix drug lot	Lyophilized ^{13}C-Spirulina lot(s)	GEBT Kit lot
D008-052	API003-035	K025-008 TBD
D008-053	API003-035 API003-037	K025-009
D008-054	API003-037	K025-011
D008-055	API003-037 API003-039	K025-012
D008-057	API003-041	TBD
D008-058	API003-043	TBD

Arm B: Biological Variability

Participants will be administered the same ^{13}C-Spirulina test meal lot on two different occasions.

Participants that participated in Cairn study PRO-CD-041 will be administered a GEBT kit containing the same GEBT test meal as used in the previous study but may be a different GEBT kit lot number. Participants from this arm of the study may continue the study by rolling over into Arm A.

6.3 Administration of ^{13}C-Spirulina GEBT

^{13}C-Spirulina GEBT will be administered to participants according to the instructions enclosed in the GEBT kit in the approved package insert.

6.4 Analysis of Breath samples

Breath samples will be analyzed using Cairn's approved ABCA-GIRMS instrument according to SOP-CD-005, Breath Test Processing.

6.5 End of Study

- Participants may withdraw from the study at any time, without prejudice.
- An authorized investigator may discontinue any test subject at any time if medically indicated or in the best interest of the individual.

- Participants who do not complete all components of the testing, all data completed prior end of study will be included in statistical analysis.
- Participants who were not in compliance with procedures will be excluded from the statistical analysis.
- Withdrawn participants may be replaced to achieve the specified number of subjects.
- The trial may be terminated prematurely if, in the judgment of Cairn's Medical Director, the severity or frequency of adverse events so warrants.

Each participant is considered to have completed the study when they have completed all GEBT test administrations and the AE review follow-up and all collected breath samples have been analyzed on the ABCA-GIRMS systems.

The end of the study is defined as the date on which all of the participants' breath samples have been analyzed on the ABCA-GIRMS and all follow-up (AE review) has been completed.

7.0 RISK/SAFETY INFORMATION

7.1 Established Contraindications, Warnings and Precautions of GEBT

The following contraindications, warnings and precautions have been established for the ^{13}C-Spirulina GEBT in FDA-approved labeling:

- Individuals with known hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT
- Because the GEBT is an indirect multi-compartmental method of measuring gastric emptying, GEBT results may be inaccurate in individuals compromised with significant small bowel, pancreatic, liver, and/or lung disease. Consequently, GEBT should not be administered to patients with pulmonary dysfunction (e.g. COPD) and/or small bowl malabsorption.
- Individuals with severe lactose intolerance may wish to avoid the GEBT, as the test meal contains a small amount of lactose, approximately 2.7 grams.
- The performance characteristics for individuals under the age of eighteen (18) years have not been established for this test.
- The performance characteristics for pregnant women have not been established for this test.
- False positive and false negative results can occur with this test.
- Follow the directions for collecting breath samples carefully. Errors in the timing and/or procedures for collecting breath samples may affect test results and necessitate retesting.
- The GEBT should not be performed in individuals who have taken medications known to influence the rate of gastric emptying (e.g. erythromycin, metoclopramide, opiates and anticholinergics) within three (3) days prior to testing. Individuals should stop such medications only after consulting with and obtaining approval from their attending physician or the physician ordering the test.

- Fasting serum glucose levels of diabetic subjects should be checked before administration of GEBT and the test should only be administered to subjects with a fasting serum glucose level of <275mg/dl.
- After 24 hours there is no residual $^{13}CO_2$ signal in the breath arising from the ^{13}C label contained in the GEBT meal; thus, the GEBT may be administered as frequently as every 24 hours.
- The GEBT should not be administered within 24 hours (or the relevant washout period) of other ^{13}C breath tests (e.g. the ^{13}C-Urea breath test for H. pylori).

7.2 Potential Risk to Participant Associated with this Study

This study involves the following risks:

- Allergic reactions such as rash, itching, hives or problems breathing are a possibility if the participant were unknowingly and severely allergic to the GEBT test meal ingredients. The ingredients are 100 mg Spirulina, 27 grams of dried scrambled eggs (with nonfat milk added), saltine crackers (containing wheat) and water.

Any unanticipated problems will be reported to the IRB within ten (10) calendar days of being reported.

8.0 MONITORING AND REPORTING OF ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

An Adverse Event (AE) is any untoward medical occurrence in the participant associated with administration of GEBT, whether or not considered related to GEBT.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity

AE's will be reported by the participant (or, when appropriate, by a caregiver, a surrogate of the participant or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the GEBT test procedure or study procedures that caused the participant to discontinue the study.

8.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs or SAEs will be collected from the day of each GEBT test administration until the follow-up visit as outlined in Tables 3 and 4, Schedule of Activities.

In the event any serious adverse events are reported, or observed during the GEBT administration procedure, whether or not attributable to the GEBT test procedure, the event will be reported within 24 hours to the IRB and to Cairn's medical director.

The following information will be provided in writing: study protocol number, patient's identification code, date of birth, date and nature of the serious adverse event and the causality assessment. The report of an SAE will be completed and signed by the next working day.

8.2 Intensity of an Event

The intensity/severity of an event will be classified as follows:

- Mild: that is an awareness of sign or symptom, but easily tolerated
- Moderate: that is discomfort of sign or symptom, but easily tolerated
- Severe: at least partially incapacitating (or restricting usual activity)

8.3 Relationship to Study Procedures

Adverse events will be considered associated with the study procedure if the attribution is possible, probable or very likely. The relationship can be classified as follows:

- Not related: an adverse event that is not related to the study procedure
- Doubtful: an adverse event for which an alternative explanation is more likely
- Possible: an adverse event, which might be due to the study procedure
- Very likely: an adverse event which is listed as a possible adverse reaction and cannot be reasonable explained by an alternative explanation
- Unknown: it is not possible to assign the reaction to any of the above categories because of insufficient, pending or contradictory information

8.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, Cairn's medical director will follow the participant at subsequent visits, contacts, etc. All SAEs and non-serious AEs of special interest will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

If an adverse event results in withdrawal, the patient will be followed up until the cause of the event is established, if possible, and the outcome resolved, or the patient's condition stabilized.

8.5 Regulatory Reporting Requirements for SAEs

Prompt notification of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Cairn has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of GEBT. Cairn will comply with country-specific (U.S. FDA) and IRB-specific regulatory requirements relating to safety reporting.

8.6 Pregnancy

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Exhibit D.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillborn, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.0 STUDY OVERSIGHT

Samantha Bouldin, PhD, or another qualified Cairn employee specifically designated by Cairn's medical director, Alex Ryder, MD, PhD, will provide oversight of this study protocol and supervise all study activities. The designee will ensure that all personnel associated with the study are adequately trained in the study protocol and delegations of study duties will be given to the appropriately trained personnel.

Cairn Diagnostics Quality Assurance and Compliance personnel will assure:

- The study protocol is being followed as approved by Cairn Diagnostics and the IRB
- Informed consent is being obtained before GEBT test administration is conducted
- Accurate, complete and current records are being maintained
- Responsibilities have not been delegated to unspecified or untrained personnel

10.0 PRODUCT STORAGE AND ACCOUNTABILITY

GEBT kits will be distributed to Cairn personnel as needed for the course of the study. The kits are stored in a controlled, limited access area at controlled room temperature (20°C-25°C). The kits have an expiry date and should not be used beyond the expiration date displayed on the GEBT test kit box. Collected breath samples should be stored at room temperature and analyzed within 28 days of collection. Kit receipt, usage or destruction will be recorded in the GEBT kit inventory to assure all kits are accounted for during the study.

11.0 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

No pre-specified randomization scheme is needed. Qualified participants will be entered into the study on a random, first come, first serve basis.

12.0 DATA MANAGEMENT

12.1 Breath Sample Analysis

Perform sample analysis on the participant(s) breath samples using the ABCA GIRMS system according to SOP-QC-017, Operation, Calibration and Maintenance – ABCA GIRMS. Analysis will be conducted by trained and qualified clinical laboratory personnel with verified and documented training appropriate for operation of the ABCA GIRMS systems.

12.2 ^{13}C-Spirulina GEBT reporting

Prepare reports for each ^{13}C-Spirulina GEBT according to Cairn SOP-CD-005, Breath Test Processing. Enter data from each individual report into a spreadsheet for statistical analysis.

12.3 Sample retention

Retain all participant breath samples collected for at least 28 days after the sample collection date recorded on the GEBT Test Request Form. Dispose of the samples according to SOP-CD-021, GEBT Breath Sample Accessioning and Chain of Custody.

12.4 Data Retention

- Maintain data as hard copies and scan and store electronic copies on Cairn's server.
- Review all data generated during execution of the validation protocol for completeness and accuracy in accordance with SOP-QC-030, Data Generation and Review.

12.5 Statistical Analysis

12.5.1 Arm A: Lot-to-lot Variability Study

Participant kPCD values at each measured timepoint from each lot of ^{13}C-Spirulina GEBT test meal will be plotted to compare the *in vivo* results across each lot of material.

The pooled kPCD and standard deviations at each measured timepoint from each lot of ^{13}C-Spirulina GEBT test meals will be calculated and compared for the lot-to-lot comparisons.

Each set of pooled ^{13}C-Spirulina test meal lot kPCD values will be calculated using a t-test or ANOVA to determine statistical equivalence if the underlying assumptions of the tests (equal variances and normality of the distribution) are met. The test will have a significance level of 0.05.

12.5.2 Arm B: Biological Variability Study

Participant kPCD values at each measured timepoint from the same ^{13}C-Spirulina GEBT test meal will be plotted to compare against each other.

The pooled, within-subject standard deviations of duplicate measurements of kPCD values at each measured timepoint from the same lot of ^{13}C-Spirulina GEBT test meal will be calculated for biological variation using Bartlett's test for homogeneity of variances (or the Levene test for equality of variances if the kPCD values do not appear to be normally distributed). The test will have a significance level of 0.05.

12.6 Reporting

Collate the results of the executed protocol, including all associated data, and document the completion of the protocol in a report. The report must be approved by the same individuals who approved the associated protocol.

13.0 IRB REVIEW/ETHICS/INFORMED CONSENT

13.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with this protocol and in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organization of Medical Sciences International Ethical Guidelines
- Applicable ICH Good Clinical Practice Guidelines
- Applicable U.S. laws and regulations

This protocol, protocol amendments, Informed Consent Form and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before initiation of this study.

Any amendments to this protocol will be submitted for IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

13.2 Informed Consent Process

Obtain a signed consent from the participant prior to any participation in study activities. Participants may ask questions and/or withdraw from the study at any time.

A copy of the Informed Consent Form (SPEC-CD-041) must be provided to the participant.

13.3 Data Protections

Assign each participant a unique identifier. Since Cairn Diagnostics is the study investigator as well as the sponsor, Cairn, its principal investigator, and study team will need to receive and use certain personal information of the study subjects. If Cairn needs to share a subject's study related data with an individual or entity outside of Cairn, other than the subject's study doctor or his/her staff, it will replace any information which could identify the subject with a unique code number. Only study tea members will have access to the key that links the assigned code to the study subject.

Inform the participant that his/her personal study-related data will be used by Cairn Diagnostics in accordance with local data protection law.

Inform the participant that his/her medical records may be examined by Cairn Diagnostics auditors, other authorized personnel appointed by Cairn Diagnostics, by appropriate IRB/IEC member and by inspectors from regulatory authorities.

Obtain a HIPAA authorization to collect, use and disclose the study subject's personal information and protect health information as needed to conduct the study (refer to SPEC-CD-041).

13.4 Data Quality Assurance

All participant data relating to the study will be recorded on printed case report forms (CRFs). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

The investigator must permit study related monitoring, audits, IRB/IEC review and regulatory agency inspectors and provide direct access to source data documents.

Cairn Diagnostics is responsible for the data management of this study including quality data checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete and verifiable from source documents; the safety and rights of the participants are being protected and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Cairn Diagnostics. No records may be transferred to another location or party without written notification to Cairn.

14.0 INTENDED USE OF DATA

Data obtained in this study will be added to data previously obtained from Cairn sponsored clinical trials to gather more information regarding lot-to-lot comparisons and within-subject biological variation.

15.0 REFERENCES

A. J S Lee, M Camilleri, A R Zinsmeister, D Burton, L J Kost, P D Klein. A valid, accurate, office based non-radioactive test for gastric emptying of solids Gut 2000;46:768–773
B. Viramontes B, Kim M, Camilleri M, et al. Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. Neurogastroenterology and Motility 2001; 13:567-574
C. Szarka L, Camilleri M, Vella A, et al. A stable Isotope Breath Test with a Standard Meal for Abnormal Gastric Emptying of Solids in the Clinic and in Research. Clinical Gastroenterology and Hepatology 2008; 8: 635-643.
D. Jennison C and Turnbull BW. Group Sequential Trials with Applications to Clinical Trials. Chapman and Hall/ CRC. 2000.

16.0 EXHIBITS

A. PMA P110015 Approval Letter and FDA Press Release
B. COVID19 Transmission Mitigation Plan
C. Study Participant Health Questionnaire
D. Contraceptive Guidance & Collection of Pregnancy Information

17.0 REVISION HISTORY

Revision Level	Brief Description of Revision(s)	Effective Date
00	Initial Document	See first page of this document.

18.0 PRINCIPAL INVESTIGATOR AGREEMENT:

By signing this protocol, I commit to conducting the clinical investigation in accordance with the procedure all requirements of the investigational plan, IDE regulations, other applicable regulations of the FDA, and any conditions of approval imposed by the Institutional Review Board (IRB) or FDA. I agree to abide by all of the responsibilities of investigators addressed in 21 CFR Part 812, Subpart E and Subpart G.

	NAME (Print)	SIGNATURE	DATE
Principal Investigator:	SEE	ATTACHED SD	2/1/21

18.0 PRINCIPAL INVESTIGATOR AGREEMENT:

By signing this protocol, I commit to conducting the clinical investigation in accordance with the procedure all requirements of the investigational plan, IDE regulations, other applicable regulations of the FDA, and any conditions of approval imposed by the Institutional Review Board (IRB) or FDA. I agree to abide by all of the responsibilities of investigators addressed in 21 CFR Part 812, Subpart E and Subpart G.

	NAME (Print)	SIGNATURE	DATE
Principal Investigator:	Alex Ryder		1/29/21

SD 2/1/21

19.0 EXHIBIT A: PMA P110015 APPROVAL LETTER AND FDA PRESS RELEASE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

April 6, 2015

MR. KERRY BUSH
PRESIDENT
ADVANCED BREATH DIAGNOSTICS, LLC
105 WESTPARK DRIVE, SUITE 150
BRENTWOOD, TN 37027

Re: P110015
Gastric Emptying Breath Test (GEBT)
Filed: July 11, 2012
Amended: September 18, 2012, December 26, 2012, April 5, 2013, September 19, 2013, May 15, 2014
Procode: PGE

Dear Mr. Bush:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Gastric Emptying Breath Test (GEBT). This device, to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastoparesis. For these purposes, the test system utilizes a Gas Isotope Ratio Mass Spectrometer (GIRMS) for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples. The GEBT procedure should be administered under supervision of a health care professional although no specialized facilities or specially licensed personnel are required. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at three years for 20 °C - 25 °C (68 °F – 77 °F) with excursions permitted to 15 °C - 30 °C (59 °F - 86 °F). This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required

under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR)

regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the

amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Sunita Shukla at 301-796-6406.

Sincerely yours,

Alberto Gutierrez -S

Alberto Gutierrez
Director
Office of In Vitro Diagnostics and
Radiological Health
Center for Devices and
Radiological Health

20.0 EXHIBIT B: COVID-19 TRANSMISSION MITIGATION PLAN

COVID-19 TRANSMISSION MITIGATION PLAN

Screening/Enrollment visit

Cairn personnel designated to participate in screening visit with the potential study participant will be required to wear a facemask and practice social distancing while in contact with the potential participant.

The potential study participant will enter the facility where they will be met by Cairn personnel and will be asked a series of questions regarding symptomology or exposure to COVID-19 (refer to Exhibit C for Study Participant Health Questionnaire). A copy of the questionnaire will be signed by the participant and Cairn personnel and will be stored in the participants file.

- If participant answers any of the questions that indicate potential symptomology or exposure to COVID-19, they will be asked to leave the facility and be advised to consult a healthcare professional. They will not be able to participate in the study at that time.
- If the participant answers the questions indicating no potential symptomology or no known exposure to COVID-19, they will meet with a qualified Cairn employee designated by the medical director and/or the medical director to give an overview explanation of the study, answer questions regarding the GEBT test procedure and provide consent to participate in the study.

Upon completion of this screening visit, the study participant will leave the facility and all PPEs worn by Cairn personnel will be disposed of in a biohazard container.

GEBT Administration Visits

Cairn personnel designated to participate in GEBT administration with the study participant will be required to wear a disposable laboratory coat, gloves and facemask while in contact with the potential participant.

The study participant will enter the facility where they will be met by Cairn personnel and will be asked a series of questions regarding symptomology or exposure to COVID-19 (refer to Exhibit E for Study Participant Health Questionnaire). A copy of the questionnaire will be signed by the participant and Cairn personnel and will be stored in the participants file.

- If participant answers any of the questions that indicate potential symptomology or exposure to COVID-19, they will be asked to leave the facility and be advised to consult a healthcare professional. They will not be able to participate in the study at that time.
- If the participant answers the questions indicating no potential symptomology or no known exposure to COVID-19, they will meet with the a qualified Cairn employee designated by the medical director and/or the medical director to give an overview explanation of the study, answer questions regarding the GEBT test procedure and provide consent to participate in the study.

The participant will be administered the GEBT under the supervision of Cairn's medical director via a telecommunication platform (e.g. FaceTime, Microsoft Teams, etc) by qualified Cairn personnel. The participant will remain in the area where the GEBT is being

administered and will only be in contact with the qualified personnel during sample collection times.

Upon completion of the GEBT administration visit, the study participant will leave the facility and all PPEs worn by Cairn personnel will be disposed of in a biohazard container.

Follow up/Closeout visit

Cairn personnel designated to participate in follow up contact with the participant will do so via a phone call, email, or a telecommunication platform. If the follow up if performed via a phone call or telecommunication platform, a memo noting the follow up will be placed in the participant's file.

21.0 EXHIBIT C: STUDY PARTICIPANT HEALTH QUESTIONNAIRE

CAIRN DIAGNOSTICS

Study Participant Health Questionnaire

In order to prevent the spread of COVID-19 (novel coronavirus) and reduce the exposure of our personnel, their families, and our visitors, we would appreciate you completing the following health questionnaire.

1) Do you have a fever currently or in the past 14 days? ☐ **Yes** ☐ **No**

2) Are you currently experiencing a cough, sore throat, shortness of breath, muscle aches/pains, or diarrhea? ☐ **Yes** ☐ **No**

3) Have you had contact with anyone who has confirmed, suspected, or has been tested and is awaiting results for COVID-19? ☐ **Yes** ☐ **No**

4) Have you been tested for COVID-19? ☐ **Yes** ☐ **No**

   a. If yes, when and results: _____

_____ _____
Study Participant Signature Date

_____ _____
Cairn Personnel Signature Date

22.0 EXHIBIT D: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1.

Table 1: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable

Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) There is no scientific reason to believe that ^{13}C-Spirulina GEBT will interact with hormonal contraception and reduce the efficacy of the contraceptive method.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.
- Perform pregnancy testing with a minimum sensitivity of 25 mIU/mL on WOCBP within 48 hours prior to each Gastric Emptying Breath Test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, and while there are not expected to be any adverse effects of ^{13}C-Spirulina GEBT on a pregnancy, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.