SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: [13C]-Spirulina Platensis Gastric Emptying Breath Test

Device Trade Name: Gastric Emptying Breath Test (GEBT)

Device Procode: PGE

Applicant's Name and Address: ADVANCED BREATH DIAGNOSTICS LLC
105 Westpark Drive Suite 150
Brentwood TN 37027

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110015

Date of FDA Notice of Approval: April 6, 2015

Priority Review: Not applicable

II. INDICATIONS FOR USE

The Gastric Emptying Breath Test (GEBT), 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.

III. CONTRAINDICATIONS

- 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 bowel malabsorption.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Gastric Emptying Breath Test labeling.

V. DEVICE DESCRIPTION

The Gastric Emptying Breath Test (GEBT) is a non-radioactive, non-invasive, orally administered test for measurement of the rate of solid phase gastric emptying in adults. The GEBT has been validated against the reference method of gastric scintigraphy.

The GEBT utilizes the stable isotope carbon-13, denoted as ^{13}C. The GEBT may be administered in a primary care facility, clinic or tertiary care setting.

The GEBT measures how fast the stomach empties solids after ingestion of a cooked egg test meal, labeled with ^{13}C-Spirulina particles. The GEBT procedure is conducted over a 4 hour period. Following an overnight (or ≥8 hour) fast, duplicate pre-meal breath samples are collected from the test subject (used to establish a subject's baseline $^{13}CO_2$ level). Following pre-meal breath sample collection, the subject is administered the test meal. Single post-meal breath samples are subsequently collected at 45, 90, 120, 150, 180, and 240 minutes from the end of test meal consumption. Breath samples, collected in capped glass tubes before and after test meal administration, are returned to a central laboratory for analysis by Gas Isotope Ratio Mass Spectrometry (GIRMS) to determine the ratio of $^{13}CO_2/^{12}CO_2$ in each sample. By measuring the change in this ratio over time as compared to the pre-meal value, the rate of $^{13}CO_2$ excretion can be calculated and the individual's gastric emptying rate determined.

The key components of the GEBT system include:

- GEBT Kit (See table below)
- GIRMS System: The Automated Breath Carbon Analyzer (ABCA) is a continuous flow Gas Isotope Ratio Mass Spectrometer (GIRMS) System intended for use in the measurement the carbon content of breath samples ($^{13}CO_2/^{12}CO_2$ ratio) collected as part of the GEBT procedure.

Component	Description
Test Meal	[^{13}C]-GEBT Diagnostic Dosage: Polyethylene-lined foil pouch of Smoke-Flavored Scrambled Egg Mix containing 43 mg ^{13}C in approximately 100 mg [^{13}C]-*Spirulina platensis* with oxygen absorber
	Cracker Package: Six (6) Nabisco PREMIUM saltine crackers (3 two-cracker packs) in a heat-sealed foil pouch containing an O_2 absorber
Meal Preparation Components	Plastic cutlery – Pre-packaged plastic knife and fork, pre-packaged plastic spoon
	Filling Cup – 3 fl. oz. plastic cup for transferring potable water
	Cooking Cup – 8 oz. plastic cup for cooking the egg mix

	GEBT Administration Instructions
Breath Collection Assembly	Eight (8) glass breath collection tubes with screw-caps – Exetainer® brand, 510(k) K880622; Labco, Ltd., Establishment Reg. #8021930
	Two (2) wrapped plastic drinking straws
	Breath sample transport container and pre-addressed overnight courier pack
Packaging	Device Box – corrugated cardboard, white exterior, houses ALL components
	Meal Kit Box – corrugated cardboard, white exterior, houses test meal and test meal preparation components
	Breath Collection Tube Transport Container – white polyethylene foam insert with detachable cardboard sleeve, houses glass breath collection tubes

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection of gastroparesis, such as gastric scintigraphy and the SmartPill, described below. Each alternative has its own advantages and disadvantages.

Gastric scintigraphy is considered the standard method for the diagnosis of gastroparesis. This method entails recording and imaging the transit time of a standardized meal through the stomach. The meal is labeled with a radioactive compound, ^{99m}Tc sulfur colloid. Scintigraphic scanning is conducted over time (typically two to four hours) and the fraction of meal emptied (% emptied) is determined at each measurement time. Scintigraphic measurements require specialized nuclear medicine facilities.

The SmartPill Gastrointestinal (GI) Monitoring System can also be used as an aid in evaluating patients with suspected motility disorders, such as gastroparesis. The SmartPill is a wireless, ingestible capsule that is capable of measuring transit time, pH, and pressure in the GI tract. Transit time through the entire digestive tract is normally 24-48 hours in healthy individuals, but may be up to 72 hours in patients with various GI dysmotilities. As it passes through the G1 tract, acquired data are transmitted to a receiver worn on the patient's belt. Once the SmartPill device is passed from the patient's GI tract, the data are downloaded on to a laptop computer. Special software provides a summary of the GI tract information. SmartPill is contraindicated in patients that have difficulty swallowing, are suspected of having strictures, fistulas or other GI track obstructions, Crohns disease or diverticulosis, recent GI surgery, and history of long-standing undigested food in the stomach.

VII. MARKETING HISTORY

The GEBT has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

There were 13 non-serious adverse that occurred during the clinical validation study.

Total number of subjects who completed the study: 129
Incidence of Adverse Events: 13

Events included (number of subjects per event):

Nausea/Fullness (3)
Heartburn (1)
Diarrhea (2)
Emergency Room Visit (1)
Dry Heaves (1)
Abdominal Pain (1)
Severe reflux (1)
Dizziness (1)
Heart rate elevation following atropine bolus injection (1)
Head cold (1)

It was determined that the following 9 of 13 adverse events were not related to the GEBT or dual-label test procedure: ER visit, nausea/fullness (2 events), heartburn, diarrhea (1 event), severe reflux, dizziness, heart rate elevation and head cold. It was uncertain whether the following 4 of the 13 adverse events were related to the GEBT: nausea (1 event), dry heaves, abdominal pain and diarrhea (1 event). These 4 subjects reported post-GEBT administration complaints, such as postprandial fullness and nausea, which is consistent with gastroparesis symptomology.

There are also potential risks associated with false positive and false negative test results. The consequences of a false positive result, i.e. a positive test result in a patient with symptoms who does not have gastroparesis, would be treatment for gastroparesis at the risk of missing another diagnosis that is the actual cause of the patient's symptoms. Therapeutic interventions for gastroparesis include dietary changes, nutritional support, and pharmacologic intervention with antiemetic and prokinetic agents and correction of glycemic control in diabetes. Some additional risks of false positive results are as follows:

- Consequences of inappropriate dietary adjustments and nutritional support most likely would be minimal.

- Pharmacologic intervention with inappropriate agents may expose patients to adverse side effects of the unnecessary or inappropriate drug therapy. At present time there are few drugs available to treat gastroparesis. Metoclopramide is the only one on the

market, and long term use of this drug is not recommended due to risk of neurologic events (tardive dyskinesia). However future drugs that are motility agents (5-HT-4 antagonists, ghrelin receptor antagonists) may have some cardiovascular effects. The newer ones are more selective for the 5-HT-4 receptor so they are supposed to have less potential for CV AEs.

- A patient presenting with signs and symptoms of gastroparesis (nausea, vomiting, early satiety, postprandial fullness) could have another underlying cause of clinical presentation (such as infection, malignancy, etc.). A false positive test in such a patient could result in a missed diagnosis and missed opportunity for appropriate treatment.

The consequences of a false negative result, i.e. a negative test result in a patient with symptoms who does have delayed gastric emptying, could be a missed diagnosis and treatment of gastroparesis leading to additional unnecessary work up to evaluate other causes of the patient's symptoms. However, if no other etiology is identified and the patient continues to have symptoms, then the patient will more than likely be treated even if the test is negative.

IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical studies were not conducted for the GEBT test meal for the following reasons:

1. The GEBT test meal contains only food-derived ingredients; these ingredients are Spirulina (a widely consumed nutritional supplement), powdered egg and saltine crackers.

2. The active ingredient in the GEBT test meal is carbon-13 labeled Spirulina. Spirulina species, including Spirulina platensis (synonym Arthrospira platensis), are blue-green microalgae with a long history of use in the human diet as a source of protein (Ciferri 1983). Naturally abundant Spirulina (98.9% [^{12}C], 1.1% [^{13}C]) was acknowledged by the US FDA as a legally marketed food in 1981 and is recognized as safe when contained in foods at levels from 0.5 to 3.0 grams per serving. The dose of Spirulina in each GEBT test meal is only 0.1 gram.

3. ^{13}C is a naturally occurring, non-radioactive stable isotope of carbon.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The PMA included data from five (5) clinical studies as summarized in the table below:

Study Name and Protocol Number	Study Objective(s)	Number of Study Site(s)
1. GEBT Dose	Selection of a safe and effective [^{13}C]-*S. platensis*	

Finding Study, PRO-CD-001	dose and test meal composition for use in further studies	Two
2. GEBT Biologic Variation / Reference Range Study, PRO-CD-002	1. Estimation of time-related, within-subject total variability (imprecision) with GEBT 2. Estimation of the GEBT Reference Range for normal adults	Two
3. GEBT Dual-Label* Calibration Trial, PRO-CD-003	1. Estimation of the Reference Range for scintigraphic results using the GEBT test meal 2. Collection of additional Reference Range data for normal adults 3. Estimation of total variability (imprecision) of scintigraphy and GEBT measurements on normal and marginal† gastroparetic test subjects	One
4. GEBT Dual-Label* Validation Trial, PRO-CD-004	Validation of the GEBT for use in diagnosis and monitoring of delayed gastric emptying	One
5. Test Meal Equivalence Study, PRO-CD-005	Demonstrate that the GEBT test meal produced by a modified manufacturing process (MP) is equivalent to that produced by the original manufacturing process (OP)	One

* The term "dual-label" refers to a GEBT test meal that contains both ^{13}C-Spirulina and ^{99m}Tc sulphur colloid, the labeling substance used in gastric scintigraphy. After consuming the test meal, gastric emptying testing of the subject is then conducted simultaneously by scintigraphy and by the GEBT.

† "Marginal gastroparetics" are defined as those with gastric emptying metrics ranging from slow (low) normal to mild gastroparesis.

The first three studies listed in the table above (PRO-CD-001, PRO-CD-002 and PRO-CD-003) were pre-validation exploratory trials. Study PRO-CD-004 was the pivotal validation trial, in which the overall diagnostic concordance, sensitivity and specificity of the GEBT were compared with scintigraphic diagnoses. Shortly after completion of the validation trial (PRO-CD-004), a key contract manufacturer became unavailable to produce the lyophilized egg/^{13}C-Spirulina test meal used in the GEBT. An alternative contract manufacturer was selected to produce the GEBT test meal, and PRO-CD-005 (the Test Meal Equivalence Trial) was added to the original investigational plan to demonstrate functional equivalence of the original and modified test meals.

With regard to the five studies summarized above:

1. The results from Study PRO-CD-001, the GEBT dose-finding study, established the composition of the GEBT test meal and dose of carbon-13 for use in all subsequent studies. Part A of the study was a prospective, open-label, cross-over study with 7 normal and 7 gastroparetic subjects. Each participant received the GEBT at 3 different [^{13}C]-Spirulina doses at various visits. Part B of the study was a prospective, open-label, crossover study, using a subset of normal/gastroparetic subjects (from part A) to test a reduced calorie GEBT test meal. Part B also examined the effect of a

reduced calorie meal on GEBT results. Combined, Parts A and B demonstrated that the GEBT can be administered once every 24 hours, the reduced calorie GEBT meal was appropriate for the GEBT device with regard to tolerability and performance, and 40 mg of carbon-13 was selected as the dose for the GEBT meal.

2. The results of Studies PRO-CD-002 and PRO-CD-003 were used to establish diagnostic cut-off points (COPs) for the GEBT and scintigraphy methods. Study PRO-CD-002 was a Phase 2 exploratory trial. In this study, GEBT results were compared in subjects who consumed different GEBT test meal preparations (hand mixed meal vs. pre-mixed test meal). A "hand-mixed" meal refers to a GEBT test meal in which the dose of' ^{13}C-Spirulina powder and the dry, formulated egg powder were individually packaged and manually combined and cooked at the test administration site. A "pre-mixed" meal refers to a GEBT test meal in which the dose of ^{13}C-Spirulina and dry formulated egg powder (in the same proportions as the hand-mixed configuration) have been combined site into a single packaged unit and is cooked at the test administration site. Reference ranges (Normal Range), and respective cut-off points (COPs) used to classify patients as gastroparetic versus normal, were determined for each measurement time using the hand mixed (N=40) and pre-mixed (N=30) test meals. At the conclusion of PRO-CD-002, reference ranges were calculated for both test meals, however it was determined that the GEBT pre-mixed meal was diagnostically comparable to the hand-mixed meal.

3. PRO-CD-003 was a prospective, open-label study conducted in order to collect additional reference range data using the pre-mixed test meal. Data collected from normal subjects who received the pre-mixed GEBT test meal (N=30) were combined with data collected for normal subjects who received the pre-mixed GEBT test meal (N=30) in Study PRO-CD-002 to calculate a reference range (Normal Range) for each time point.

4. Study PRO-CD-004 was the pivotal validation trial, in which the overall diagnostic agreement between the GEBT and gastric scintigraphy was demonstrated. This study provided the basis for the evaluation of device performance, as compared to scintigraphy. Further details regarding this study are provided under sub-sections A through C below.

5. Study PRO-CD-005 was a prospective, open-label study intended to demonstrate that the GEBT test meal produced by a modified manufacturing process (MP) was equivalent to that produced by the original manufacturing process (OP). The OP and MP meals differed in the way that the ^{13}C-Spirulina and egg mixture were prepared and combined together. The study confirmed that the weight, meal matrix and caloric value of the MP and OP meals were identical. Additionally, the study concluded that the GEBT test meal produced by the proposed MP provided statistically equivalent GEBT (N=44) and scintigraphic (N=20) test results to that produced by the OP test meal.

The expiration dating period for the GEBT drug product has been established and approved for three years. The recommended labeling storage condition is: "Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature*]. The stability protocol has been fully described in the PMA and is sufficient to establish the expiration date and FDA agrees the protocol can be used to support an extension of the expiration date.

*Note that the USP defines temperature requirements for drug storage, including permissible temperature excursions. USP editions are updated every year.

A. Study Design

The pivotal validation study (PRO-CD-004) was a single-site, prospective, cohort study of patients from the intended use population.

The GEBT was validated against gastric scintigraphy and testing was conducted at a clinical site in the U.S.

This study determined the diagnostic concordance (overall diagnostic agreement), sensitivity, specificity, positive predictive value, and negative predictive value of GEBT compared to gastric scintigraphy for the diagnosis of delayed gastric emptying (gastroparesis). A total of 132 subjects were enrolled and 129 of those completed the study. Enrollment is summarized as follows:

1. One-hundred and two (102) subjects were recruited from patients suspected of gastroparesis and scheduled for gastric scintigraphy, including diabetic subjects.
2. Twenty-four (24) subjects were enrolled who had been previously suspected of and evaluated for gastroparesis.
3. To supplement the number of scintigraphically positive subjects, five (5) healthy individuals were enrolled for pharmacological induction of delayed gastric emptying by intravenous injection of atropine.
4. One (1) asymptomatic diabetic patient from the Diabetology Clinic.

To eliminate the effects of natural, day-to-day variation in gastric emptying on comparative diagnostic results from scintigraphy and GEBT in this validation study, each individual was simultaneously tested by scintigraphy and GEBT using a dual-label test meal. The term dual-label refers to a test meal that contains both the GEBT labeling material (^{13}C-Spirulina) and the labeling substance used in scintigraphy (^{99m}Tc sulphur colloid). After consuming the standardized GEBT meal containing both labels, gastric emptying testing of each individual was conducted simultaneously by scintigraphy and GEBT at 45, 90, 120, 150, 180 and 240 minute post-meal measurement times. Of the 129 study subjects who completed the study, protocol deviations affected results for 14 subjects, yielding 115 evaluable subjects. Performance statistics are based on the 115 evaluable subjects.

GEBT results are reported using kPCD, which is defined as percent dose ^{13}C excreted at time t x 1,000 (relative to the test meal), as the primary GEBT metric. Statistical analysis included clinical sensitivity, specificity, positive predictive value, and negative predictive value calculations at 45, 90, 120, 150, 180, and 240 minutes post-baseline, with two-sided 95% confidence intervals for each time point. Diagnostic GEBT cut-off points were determined based on data analysis of PRO-CD-002 and PRO-CD-003.

Clinical Inclusion and Exclusion Criteria

Enrollment in the GEBT dual-label validation trial was limited to patients who met the following inclusion criteria:

1. Initially scheduled for gastric scintigraphy at the study site or previously stated a willingness to participate in future clinical trials at the study site.
2. Males and females (18 - 85 years old). Females of childbearing potential must have negative pregnancy urine test within 48 hours of the dual-label gastric emptying test.
3. Ability to eat test meal and provide breath samples.
4. Written informed consent.

Diabetic subjects also met the following inclusion criteria:

1. Prior diagnosis of Type I or Type II diabetes mellitus.
2. Recommended by the patient's attending physician for participation in the dual-label gastric emptying clinical trial.
3. Asymptomatic for delayed gastric emptying.

Exclusion Criteria:

1. Intolerance or allergy to any component of dual-label gastric emptying test meal.
2. Identified clinically significant neurologic or psychiatric disorders that could interfere with compliance to experimental procedures.
3. History of malabsorption due to mucosal disease, pancreatic disease, liver dysfunction, or other causes.
4. Use of medications, such as narcotics or anticholinergics, that can alter gastric motility within 48 hours of the study (with the exception of short-acting intravenous fentanyl as used for conscious sedation for endoscopy which can be administered up to 12 hours prior to the gastric emptying breath test).
5. Receipt of an investigational drug within 4 weeks prior to the study.
6. Pregnancy.

The following exclusion criteria were used for the Healthy Volunteers for Induced Gastroparesis:

1. 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.
2 Glaucoma.
3. History of abdominal surgery except appendectomy.
4. Current use of any medication that is contraindicated for use in combination with atropine.
5. Females on hormone replacement therapy other than birth control medications.

Follow-up Schedule

Follow-up contact (e.g., phone call, email, etc.) was made with all test subjects within 1 to 3 business days (excluding weekends/holidays) after the dual-label testing to determine if there were any new and/or ongoing adverse events.

The key time points are shown below in the tables summarizing safety and effectiveness.

Clinical Endpoints and Statistical Analysis

The clinical validation study determined diagnostic concordance (overall diagnostic agreement), sensitivity, specificity and positive predictive value/negative predictive value of GEBT compared to gastric scintigraphy for the diagnosis of delayed gastric emptying as primary end points.

Safety was also evaluated by assessing adverse events during the administration of the test and during the follow-up period (as described below).

B. Accountability of PMA Cohort

One hundred thirty-four subjects were screened for enrollment in this study. Of the 134 subjects screened, 2 failed screening and were not enrolled and 132 were enrolled. Of the 132 subjects enrolled, 126 consumed the entire test meal and completed the dual-label test procedure. Three enrolled subjects withdrew from the study and did not receive the test meal. Three enrolled subjects were unable to consume the entire test meal. Of the 126 subjects who completed the test procedure, test results for 115 were considered evaluable and used in data analysis.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are consistent with the intended use population. The table below shows the patient demographics of the study population.

Subjects Screened by Type	New Motility Clinic Patient	103
	Previously Tested Motility Clinic Patient	24
	Healthy Subjects for Atropine-induced gastroparesis	6
	Asymptomatic Diabetics (Type I or II)	1

Subjects Enrolled by Type	New Motility Clinic Patients	102
	Previously Tested Motility Clinic Patients	24
	Healthy Subjects for Atropine-induced gastroparesis	5
	Asymptomatic Diabetics (Type I or II)	1
Subjects Completed by Type	New Motility Clinic Patients	99
	Previously Tested Motility Clinic Patients	24
	Healthy Subjects for Atropine-induced gastroparesis	5
	Asymptomatic Diabetics (Type I or II)	1
Subjects Withdrawals by Type	Withdrawals due to Adverse Events	2
	Withdrawals for other reasons	1
Adverse Events	Adverse Events	13
	Serious Adverse Events	0
Age Demographics (Enrolled Subjects)	Range of Ages	21-77
	Median Age	50
Sex Demographics (Enrolled Subjects)	Male	37
	Female	95
Race Demographics (Enrolled Subjects)	American Indian/Native Alaskan	1
	Asian	1
	Black	2
	White	127
	Other	1

D. Safety and Effectiveness Results

The diagnostic concordance of the GEBT to scintigraphy and other performance measures are shown in the table below on page 13. The 95% reference interval and cut-off points (COPs) for the GEBT at each time point was determined in the pre-validation studies.

1. Safety Results

The analysis of safety was based on the intended use cohort of 129 patients/procedures, etc available for the 10 month evaluation period. The key safety outcomes and adverse effects are reported below. There were no deaths and no serious adverse events associated with the GEBT device in any of the five clinical studies described above. In total, 20 adverse events were reported across all studies. Of these events, 15 were determined to be unrelated to the GEBT, 4 were determined to be of uncertain relation to the GEBT, and 1 was determined to be associated with the GEBT. All four events for which the relationship to the GEBT was considered uncertain were reported by subjects previously determined to be gastroparetic. Additionally, the one event that was determined to be related to the GEBT was reported by a gastroparetic subject. The reporting subjects complained of nausea and abdominal discomfort after ingesting the test meals,

which are symptoms consistent with gastroparesis, especially following food consumption.

Adverse effects that occurred in the PMA clinical study:

In total, 321 adult subjects were administered the GEBT during development and validation studies. There were no deaths associated with GEBT studies. There were no serious adverse events associated with the GEBT device or the dual-label test procedure conducted in GEBT studies. There were 13 non-serious adverse that occurred during the validation study.

Validation Trial:
Total number of subjects who completed the study: 129
Incidence of Adverse Events: 13

Events included (number of subjects per event):

Nausea/Fullness (3)
Heartburn (1)
Diarrhea (2)
Emergency Room Visit (1)
Dry Heaves (1)
Abdominal Pain (1)
Severe reflux (1)
Dizziness (1)
Heart rate elevation following atropine bolus injection (1)
Head cold (1)

It was determined that the following 9 of 13 adverse events were not related to the GEBT or dual-label test procedure: ER visit, nausea/fullness (2 events), heartburn, diarrhea (1 event), severe reflux, dizziness, heart rate elevation and head cold. It was uncertain whether the following 4 of the 13 adverse events were related to the GEBT: nausea (1 event), dry heaves, abdominal pain and diarrhea (1 event). These 4 subjects reported post-GEBT administration complaints, such as postprandial fullness and nausea, which is consistent with gastroparesis symptomology.

2. Effectiveness Results

The analysis of effectiveness was based on the comparison of GEBT and scintigraphy at six different time points. Key effectiveness outcomes are presented in the table below. The GEBT demonstrates higher concordance rates with scintigraphy at the earlier time points, ranging from 77%-87% at 45 to 150 minutes post GEBT meal ingestion. Furthermore, the GEBT demonstrates specificity values of 89%-98% between 45 and 240 minutes and PPV values of

73%-97% between 45 and 240 minutes across all time points post meal ingestion (see table below).

	Diagnosis by kPCD vs. Scint_FE at 45, 90, 120, 150, 180 and 240 minutes from the end of test meal consumption					
Classification (N = 115)	**45**	**90**	**120**	**150**	**180**	**240**
TP*	16	30	31	29	20	11
TN†	84	63	57	60	57	67
FP‡	6	2	1	2	7	2
FN§	9	20	26	24	31	35
Performance Statistics (%)						
Specificity (95% CI)	93.3 (88.1-98.5)	96.9 (92.8-100)	98.3 (94.9-100)	96.8 (96.8-100)	89.1 (81.4-96.6)	97.1 (93.3-100)
Sensitivity (95% CI**)	64.0 (42.2-83.0)	60.0 (45.2-72.9)	54.4 (40.7-65.7)	54.7 (40.2-67.5)	39.2 (27.1-53.3)	23.9 (11.6-37.6)
Concordance	87.0	80.9	76.5	77.4	67.0	67.8
PPV¶ (95% CI)	72.7 (55.5-89.6)	93.8 (88.4-100)	96.9 (90.9-100)	93.5 (85.3-100)	74.1 (59.5-89.8)	84.6 (66.3-100)
NPV†† (95% CI)	90.3 (85.1-95.0)	75.9 (63.7-78.0)	68.7 (62.4-74.1)	71.4 (65.0-77.3)	64.8 (59.7-70.8)	65.7 (61.9-70.0)

* TP: true positive; † TN: true negative; ‡ FP: false positive; § FN: false negative; ¶ PPV: positive predictive value; **CI: confidence interval, bootstrap; †† NPV: negative predictive value

Since approximately 50% of the Motility Clinic patients recruited for the study were positive for delayed gastric emptying, as defined by scintigraphy, the overall diagnostic concordance across multiple time points was established as one of the primary performance measures. Concordance is computed as follows:

Concordance=TN+TP/TN+TP+FN+FP

where:

TP: The number of patients with both GEBT and scintigraphic results Positive for delayed gastric emptying

TN: The number of patients with both GEBT and scintigraphic results Negative for delayed gastric emptying

FN: The number of patients with the GEBT result Negative and scintigraphic result Positive for delayed gastric emptying

FP: The number of patients with the GEBT result Positive and scintigraphic result Negative for delayed gastric emptying

Sensitivity=TP/TP+FN
Specificity=TN/TN+FP
PPV=TP/TP+FP
NPV=TN/TN+FN

Note: The estimations of true positive and true negative above are relative to scintigraphy only.

3. Subgroup Analyses
   No subgroup analyses were performed.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 1 principal investigator and 3 co-investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the review of this device, including consideration of its potential benefits and risks, did not raise new questions for which panel input was needed.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Taken together, the concordance, specificity and PPV values presented above (clinical endpoints) demonstrate efficacy of the GEBT device across multiple time points from the clinical validation study. The GEBT appears to be most sensitive (compared to scintigraphic results) in the early time points of 90 minutes and 120 minutes. The specificity is >89% throughout all time points evaluated, which is important to confirm the diagnosis.

Expiration dating period for the GEBT drug product has been established and approved for three years. The recommended labeling storage condition is: "Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature*]. The stability protocol has been fully described in the PMA and is sufficient to establish the expiration date and FDA agrees the protocol can be used to support an extension of the expiration date.

*Note that the USP defines temperature requirements for drug storage, including permissible temperature excursions. USP editions are updated every year.

B. Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above. There were no significant life-threatening or serious adverse events associated with the GEBT device from all studies that were conducted, however minor adverse events that were/weren't associated with the GEBT are referenced in Section VIII above.

There are potential risks associated with false positive and false negative test results. The consequences of a false positive result, i.e. a positive test result in a patient with symptoms who does not have gastroparesis, would be treatment for gastroparesis at the risk of missing another diagnosis that is the actual cause of the patient's symptoms. Therapeutic interventions for gastroparesis include dietary changes, nutritional support, and pharmacologic intervention with antiemetic and prokinetic agents and correction of glycemic control in diabetes. Some additional risks of false positive results are noted in Section VIII above.

The consequences of a false negative result, i.e. a negative test result in a patient with symptoms who does have delayed gastric emptying, could be a missed diagnosis and treatment of gastroparesis leading to additional unnecessary work up to evaluate other causes of the patient's symptoms. However, if no other etiology is identified and the patient continues to have symptoms, then the patient will more than likely be treated even if the test is negative.

C. Benefit-Risk Conclusions

The potential benefit of this test to clinicians and patients is summarized as follows: Assessment of gastric motility can be important for the purpose of differential diagnosis and proper treatment planning in patients symptomatic for or suspected of having gastorpareisis. The etiology of gastroparesis is diverse; the main categories are diabetic, idiopathic and post-surgical. Virtually any disease or condition that can induce neuromuscular dysfunction of the GI tract may cause gastroparesis. Since the GEBT is a non-radioactive, non-invasive, orally administered test for the measurement of gastroparesis, positive test results can be used as confirmatory evidence (along with symptoms) for treatment efforts. Some of the probable benefits of the device are based on acceptable device performance as demonstrated by data

collected in the clinical validation study conducted to support PMA approval (described above). Results from the validation study showed that the GEBT demonstrated specificity, as compared to scintigraphy, ranging from 89%-98% (between 45 and 240 minutes). The GEBT test is non-radioactive and non-invasive, which will make testing less burdensome than scintigraphy. Furthermore, the results of the GEBT test will be utilized in conjunction with a complete clinical profile of the patient to assess diagnosis and treatment options.

Additional factors to be considered in determining probable risks and benefits for the GEBT included risk mitigation by clear labelling and description of the potential benefits, risks and limitations of the system. Furthermore, risks associated with false positive and false negative test results can be mitigated by use in appropriate patient population, i.e. patients with signs and symptoms of delayed gastric emptying, following proper instructions pre-test and during test administration and interpreting test results in light of the overall clinical assessment (including any other GI-based testing) of the patient. Additional risks can be mitigated by careful patient selection and clinician education, knowing the limitations of the test.

As stated above, there are potential risks associated with false positive and false negative test results. However, the results of the test will be assessed in conjunction with a patient's clinical profile.

GEBT results are intended to provide supplemental information to the clinician when evaluating a patient for gastric dysmotility. GEBT results are best used as a component of an overall evaluation plan that includes the patients' clinical history and other laboratory results findings from procedures, such as endoscopy.
The GEBT diagnostic procedure is relatively simple and straightforward to understand and carry out. Patients may tolerate the risks of GEBT for the benefit of a test that does not require the ingestion of radiative material.

In conclusion, given the available information above, the data support that for the diagnosis of gastroparesis using the GEBT, the probable benefits outweigh the probable risks.

D. Overall Conclusions

Based on the data in this application, there is a reasonable assurance of safety and effectiveness of this device when used in accordance with the instructions for use. The clinical validation study was conducted under conditions intended to mimic real use, in a representative intended use population.

XIII. CDRH DECISION

CDRH issued an approval order on April 6, 2015. The final conditions of approval are cited in the approval order.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.
Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Ciferri O. Spirulina the Edible Microorganism. Microbiol Rev. Dec. 1983: 551-578.