ARJ Medical C13 Urea Breath Test Kit and Analyzer Clinical Trial Protocol

ARJ Medical, Inc.
209 State Street East
Oldsmar, FL 34677

ARJ MEDICAL, INC.
Clinical Trial Protocol
UREA C13

Protocol Number:	ARJ 2014-01
Version Date:	June 26, 2015
Investigational Product:	ARJ C13 Urea Breath Test System
IND Number:	
Development Phase:	
Sponsor:	ARJ Medical, Inc. 209 State Street East Oldsmar, Fl 34677
Funding Organization:	Gulf Coast Medical
Principal Investigator:	Name: [redacted] MD Telephone: [redacted] Fax: E-mail:
Medical Monitor:	Name: [redacted], MD Telephone: [redacted] Fax: E-mail:
Coordinating Center:	N/A

Approval:

Philip Ross, President — June 26, 2015 (Date)

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the Study Subjects enrolled under my supervision and providing ARJ Medical, Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: ARJ 2014-01 Rev.6

Protocol Title: ARJ C13 Urea Breath Test System

Protocol Date: June 26, 2015

_____ 6/29/15

Investigator Signature *Date*

[redacted]

Print Name and Title

Site # 1

Site Name South Lake Gastroenterology

Address 2040 Oakley Seaver Dr.

Clermont, FL 34711

Phone Number [redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious Adverse Experience

PROTOCOL SYNOPSIS

TITLE	ARJ C13 Urea Breath Test: An Open-Label, Comparator Group Study to Evaluate the equivalency of the ARJ C13 Urea Breath Test System to the predicate device ARJ Pylo Plus.
SPONSOR	ARJ Medical, Inc.
FUNDING ORGANIZATION	Gulf Coast Medical
NUMBER OF SITES	3
RATIONALE	Patients who are experiencing the effects of gastritis, which is an inflammation, irritation, or erosion of the lining of the stomach require an identification of the status and generation of urease in the stomach to provide a definitive diagnosis. Historically, this has been achieved via an upper endoscopy, where a thin tube containing a tiny camera, is inserted through your mouth and down into your stomach to look at the stomach lining. The doctor will check for inflammation and may perform a biopsy, a procedure in which a tiny sample of tissue is removed and then sent to a laboratory for analysis. By ingesting a low dosage of C13 urea, the patients' exhaled breath is then measured to record the level of change of ^{13}C labeled urea detectable in a patient's breath. This is measured before and after the ingestion of the urea mixture. The exhaled breath is read by the analyzer which provides an immediate diagnoses and is non-invasive. Although other C13 Urea Test Kits and analyzers are in the market, the ARJ C13 Breath Test System is believed to be equivalent in functionality and will be manufactured in the U.S. which can provide a cost effective equivalent product.
STUDY DESIGN	Up to 3 centers, non-randomized, comparative study to compare the ARJ C13 Urea Breath Test System to the ARJ Pylo Plus rapid urease test.
PRIMARY OBJECTIVE	To demonstrate the ARJ C13 Breath Test System equivalency to the predicate ARJ Pylo Plus rapid urease test.
SECONDARY OBJECTIVES	None
NUMBER OF SUBJECTS	Test Group: Approximately 100 - 300 Study Subjects
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • Male or Female ≥ 18 years of age • Patients who are experiencing the effects of gastritis • Written informed consent (and assent when applicable) obtained from subject and ability for subject to comply with the requirements of the study. Exclusion Criteria: • Pregnant or lactating female • Study Subjects currently taking antibiotics • Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data • Fasting required one hour prior to testing • Study Subjects shall not consume the following items prior to the test o Mouthwash

	○ Chewing gum ○ Carbonated beverages ○ Cigarette smoke ○ Acetone (to simulate the effect of ketone production that may result from some diets) ○ Alcohol
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	ARJ C13 Breath Test System will be administered one time during a one-time visit per Study Subject, according to the standard procedure described in the device's instructions. The administration shall be done orally followed by a series of specifically timed exhalations of the subject's breath.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	The ARJ Pylo Plus comparator product will be administered once at a follow-up appointment where the ARJ Pylo Plus test will be administered by the physician using a biopsy from the patient to test the presence of h. Pylori.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for 2 days **Screening:** up to 90 days **Test:** 2 days **Reporting:** 30 days The total duration of the study is estimated to be 120 days. 3 months for subject screening and testing 1month for final analysis and reporting.
CONCOMITANT MEDICATIONS	Allowed: • No exclusions with the requirement of fasting one hour prior to testing Prohibited: • Antibiotics
EFFICACY EVALUATIONS	The efficacy evaluations shall compare, per study subject, the results of the ARJ C13 Breath Test System to the results of the proven ARJ Pylo Plus test and the biopsy histology, rapid urease and culture tests.
PRIMARY ENDPOINT	• Results of the test study patients' breath tests demonstrate acceptance criterion of $\geq$ 95% to the ARJ Pylo Plus test readings.
SECONDARY ENDPOINTS	None
OTHER EVALUATIONS	None
SAFETY EVALUATIONS	When approximately 20% of patients have completed the study, an interim analysis for safety will be conducted. Serious Adverse Events will be monitored on an ongoing basis throughout the study.
PLANNED INTERIM ANALYSES	When 20% of the study group patients have completed testing, analysis of the study results shall be processed and repeated monthly until the end of the study to evaluate the study progression.

STATISTICS **Primary Analysis Plan**	Each review of the subject(s) shall be recorded including documentation of status at selection and again during the comparative study test visit. The baseline reading and each subsequent breath test shall provide a complete series of breath readings per Study Subject. The analyzed breath readings shall be documented. The analysis of the results shall be graphed for the Study Group. This is to illustrate progression from start of the testing through the most recent day's tests of the study. At the end of the study, the results of the Study Group's ARJ C13 Breath Test System shall be compared to the results of the ARJ Pylo Plus, histology, rapid urease and culture results as compared per study subject. The Study Group's results shall be calculated and compared for equivalency. Adverse Events shall be documented by subject. All identified Adverse Events shall be given a level of adversity per Table 3- AE Severity Grading. The analysis of the results shall be graphed per subject and overall of all subjects per study group. This is to illustrate adversity from start of testing through the most recent testing per study group.
Rationale for Number of Subjects	The clinical studies for the ARJ C13 Urea Breath Test predicate device Pylo-Plus (K052708) included 100 study subjects. The recent clearance (May 2013) of the Exalenz Bioscience Ltd. Breath ID Hp System (K130524) included 79 pre-treatment study subjects. The rationale to use approximately 100 - 300 study subjects shows equivalency to the two (2) related clinical studies.

1 BACKGROUND

Peptic ulcer disease is a chronic inflammatory condition of the stomach and duodenum. Despite the fact that the disease has relatively low mortality, it results in substantial suffering of those affected.

A strong association between H. pylori, chronic superficial gastritis and gastrointestinal disease has been well established. H.pylori is associated with type B gastritis, duodenal ulcer, gastric ulcer, gastric cancer, and non-Hodgkin's lymphoma.

H. pylori was first cultured successfully from human gastric mucosa in 1982. The organisms, spiral gram negative bacteria, are found in the human stomach between the gastric epithelium and the mucosa. Isolates implicated in the above mentioned diseased states are distinguished by the production of copious amounts of endogenous urea amidohydrolase (urease). The enzyme catalyzes the breakdown of urea to carbon dioxide and ammonia, which are absorbed into the bloodstream.

Methods available for detecting current infection of the human stomach by H. pylori are generally divided into two general types: Invasive and Non-invasive. Invasive methods are so called because they include, as a first step, an esophagogastroduodenoscopy ("EGD") with collection of gastric biopsies. These biopsies are then examined by one or more detection methods: histological examination of stained tissue, microbiological culture of the organism, or direct detection of urease activity in the tissue (for example, the CLOtest®). Biopsy based methods are expensive, entail some patient risk and discomfort, and may give false negative results due to sampling errors when colonization of the gastric mucosa is patchy.

The C13 Urea Breath Test kit is intended for use with the ARJ Breath Test Analyzer, which is a combined product referred to as the ARJ C13 Breath Test System for the qualitative detection of urease associated with Helicobacter pylori as an aid in detecting H.pylori.

2 STUDY RATIONALE

Gastritis describes a group of conditions with one thing in common: inflammation of the lining of the stomach. The inflammation of gastritis is most often the result of infection with the same bacterium that causes most stomach ulcers. Injury, regular use of certain pain relievers and drinking too much alcohol also can contribute to gastritis Helicobacter pylori (H. pylori): A bacteria that lives in the mucous lining of the stomach; without treatment, the infection can lead to ulcers, and in some people, stomach cancer.

Patients who are experiencing the affects of gastritis, which is an inflammation, irritation, or erosion of the lining of the stomach require an identification of the status and generation of urease in the stomach to provide a definitive diagnosis.

By ingesting a low dosage of C13 urea, the patients' exhaled breath is then measured to record the level of change of ^{13}C labeled urea detectable in a patient's breath. This is measured before and after the ingestion of the urea mixture. The exhaled breath is read by the analyzer which provides an immediate diagnoses and is non-invasive. Although other C13 Urea Test Kits and analyzers are in the market, the ARJ C13 Breath Test System is believed to be equivalent in functionality and will be manufactured in the U.S. which can provide and cost effective equivalent product.

2.1 Risk Benefit Assessment

2.1.1 Risk

- For in vitro diagnostic use only. The 13C-urea powder and Citric Powder are dissolved in a glass of water and the resulting solution is taken orally as part of the diagnostic procedure. In the case of accidental overdose – drink water and call the physician.
- A negative result does not rule out the possibility of H. pylori infection. False negative results can occur with this procedure. If clinical signs suggest H. pylori infection, retest with a new sample or an alternate method.
- A false positive test may (rarely) occur due to urease associated with other gastric spiral organisms observed in humans such as Helicobacter heilmanni.
- A false positive test could occur in patients who have achlorhydria.

2.1.2 Benefit

- Noninvasive diagnosis of H. pylori.
- High degree of testing accuracy.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the clinical efficacy of the ARJ C13 Breath Test System as compared to the ARJ Pylo Plus test which tests the Study Subject's biopsy to determine the Study Subject's level of H.pylori.The results of the testing of C13 urea presence in the Study Subjects' breath and read via the breath analyzers is compared to the results of the ARJ Pylo Plus test per study subject.

3.2 Secondary Objectives

None

4 STUDY DESIGN

4.1 Study Overview

This will be up to three sites, open label, comparative trial. Approximately 100 – 300 (number) of subjects are planned. Each subject will be administered a single dose of study drug one time during a single visit. Evaluations will be taken at baseline and at a specified time during the testing session.

Screening data will be reviewed to determine subject eligibility. Upon patient's consent, subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following testing regimens will be used:

- Using three independent sites, a total of 100-300 clinical samples are to be obtained from a population of symptomatic individuals who have been prescribed endoscopic examination for the detection of H.Pylori infection. The physician(s) will schedule test subjects per standard of care for an endoscopy procedure in which a gastric mucosal biopsy will be obtained. In addition to the physician's standard testing, the obtained tissue will also be used to perform the following tests:
  - Histology
  - Rapid Urease Test
  - Culture
- Experimental treatment ARJ C13 Urea Test dosage shall be a one-time dosage at time of initial testing.
- Comparator – ARJ Pylo Plus shall be a one-time test performed during a follow-up visit to examine the study subject's biopsy to determine the level of urease presence.
- Total duration of subject participation will be two visits. Total duration of the study is expected to be 4 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Upon the completion of the four (4) months of testing, the test results of ARJ C13 Urea are expected to demonstrate equivalency to the ARJ Pylo Plus test results and equivalency to the results of the histology, rapid urease and culture tests results.

5.2 Secondary Efficacy Endpoints

The Study Subjects shall show no adverse conditions during the study. If adverse conditions are realized during the study, the root cause analysis shall be performed and a determination shall be made as to the safety of the study product.

5.3 Safety Evaluations

Incidence of adverse events shall be addressed immediately and appropriate action shall be taken to ensure the safety of the Study Subjects. Any adverse event occurrences shall be analyzed and documented.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a potential diagnosis of peptic ulcer disease who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

- Male or female ≥18 years of age at the time of the visit.
- Patients who are experiencing the effects of gastritis.
- Written informed consent (and assent when applicable) obtained from subject and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

- Pregnant or lactating women.
- Study Subjects currently taking antibiotics
- Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
- Fasting required one hour prior to testing.
- Study Subjects shall not consume the following items prior to the test.
  - Mouthwash
  - Chewing gum
  - Carbonated beverages
  - Cigarette smoke
  - Acetone (to simulate the effect of ketone production that may result from some diets)
  - Alcohol

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications through the individual's entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for gastritis is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.
Prohibited Medications and Treatments

- The patient should have fasted at least one hour before administering the ARJ C13 Breath Test System.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Approximately 100 - 300 eligible patients will be assigned to the ARJ C13 Breath Test System.

8.2 Formulation of Test and Control Products

The study is to be performed the same across the entire population of each study group. Each Study Subject shall be tested with the study product which is ARJ C13 Breath Test Kit. Each Study Subject shall be observed by the Investigator or designee during the testing. This is common for all Study Subjects.

8.2.1 Formulation of Test Product

ARJ Medical's C13 Urea Test Kit consists of one sealed packet of premeasured C13 urea, one packet of premeasured citric acid and sweetener and two breath bags to be used for the exhaled breath to be measured. At the time of testing, the sealed packet of premeasured C13 urea shall be opened and the citric acid and sweetener shall be added to the packet. The packet will then be filled with water and the Study Subject shall drink the contents of the packet until empty. See Table 1 for the formulation of ARJ C13 Urea Test.

Table 1: Formulation and Measurement

	ARJ C13 Urea Breath Test
13C Urea	75 mg
Citric Acid Flavoring Packet	Range of 2-4 g

8.2.2 Formulation of Control Product

The ARJ Pylo Plus test is performed by evaluating a sample of the study subject's biopsy.

8.2.3 Packaging and Labeling

Study drug is supplied in single use kits.

Each carton (kit) of study drug will be labeled with the required FDA warning statement, the protocol number, a treatment number, the name of the Sponsors, and directions for patient use and storage. Each test kit will be labeled with Protocol ID and Protocol Title and the statement "For investigational use only":

8.3 Supply of Study Drug at the Site

The Study Sponsor (or designee) will deliver study product to the investigational site. The initial study product delivery will be delivered after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study product deliveries will be made after site request for resupply.

8.3.1 Dosage/Dosage Regimen

The test subjects shall mix the urea and citric acid together in the provided packet and fill the cpacket with water. After mixing the contents of the packets the Study Subject shall ingest the packets liquid until the packet is empty.

8.3.2 Dispensing

The test subjects shall be provided with the study product or the comparator product by the Investigator or designee who shall administer the testing.

8.3.3 Administration Instructions

Upon the Study Subject's initial arrival at the study site, the study Investigator shall provide the study subject with their study record which includes their Study Subject identification and log into the study by entering:

- Study Subject ID (Name or Number)
- Date

The study Investigator or designee shall record the Study Subject's arrival by documenting it on the Study Subjects' Study Activity Form which will include:

- Study Subject's ID
- Date of Test
- Review of current health and health statistics
- Study Product ID Distributed to the Study Subject
- Consumption Time of Study Product
- Exhale Time and Analyzer Reading
- Review of current health and health statistics
- Adverse Events documentation

8.4 Supply of Study Drug at the Site

The study Sponsor shall supply the study product and comparator test product to the test site to ensure sufficient quantities to maintain the testing without interruption. The Sponsor and Investigator shall agree on the minimum quantity of study product to be available on the premises of the study site to ensure availability of the study product for the Study Subjects through the term of the study.

8.4.1 Storage

ARJ C13 Urea Test System shall be stored at room temperature which would be approximately 25°C (77°F); excursions permitted to 15-30°C (59-86°F). The following components of the test kits have expiration dates: the 13C-urea powder and the Citric Acid Powder. Do not use either of these components beyond the expiration date stated on the respective labels.

The comparator product, ARJ Pylo Plus storage is at room temperature for up to two (2) years. Do not use beyond the expiration date.

8.5 Measures of Treatment Compliance

Subjects will be asked to log into the Study Subject Test Log by entering their respective Study Subject Identification and date.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at day of testing. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at the subject's Screening. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at day of Subject's testing. New abnormal physical exam findings must be documented and will be reviewed with the physician prior to continuing with the Subjects test.

9.1.5 Vital Signs

Upon arrival for the second testing, the body temperature, blood pressure, pulse and respirations will be performed per physician typical protocol.

9.1.6 Adverse Events

Incidence of Adverse Events shall be identified and documented by the Study Subject and also by the Investigator during the testing and observation review. Any and all Adverse Events shall be documented in the Study Subjects' testing log and also recorded and tracked by the Investigator to be analyzed within the study statistics. If the Study Subject and/or the Investigator determine the Adverse Event was presented by the use of the C13 Urea Test kit the use of the study product shall be immediately terminated and necessary actions shall be taken to improve the Study Subject's condition.

9.2 Clinical Laboratory Measurements

None

10 EVALUATIONS BY VISIT

10.1 Visit 1 Screening and Test (Day 1)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including a history of gastritis, diagnosis date, and prior gastritis treatments.
5. Record concomitant medications.
6. Perform and record vital signs.
7. Schedule subject for Visit 2 to perform study test (may be same day).
8. List all additional procedures, Dispense study drug (if same day)

10.2 Visit 2 - Study Test

1. Concomitant medications review (if not same day).
2. Perform and record vital signs.

10.3 Early Withdrawal Visit

1. Record any Adverse Experiences and/or for adverse experiences and exclusionary medication use.

2. Record changes to concomitant medications.
3. Perform and record vital signs.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 12.

Table 1. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization

- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

The study site will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

[redacted], MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Telephone: [redacted]

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible to ensure proper closure of the subject's participation in the study and to confirm the subject has no adverse conditions.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.2 Replacement of Subjects

Subjects who withdraw from the study will be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by: race, gender, age, height and weight.

14.3 Interim Analysis

Interim study analysis shall be performed after the initial two weeks of testing and again at the end of one month of testing. Analysis will continue on a monthly basis until the end of the study.

14.4 Sample Size and Randomization

The sample size for this protocol was determined by:

The ARJ C13 Urea Breath Test predicate device Pylo-Plus (K052708) included 100 study subjects.

The recent clearance (May 2013) of the Exalenz Bioscience Ltd. BreathID Hp System (K130524) included 79 study subjects.

The rationale to use approximately 100 – 300 study subjects shows equivalency to the 2 related clinical studies.

14.5 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

14.6 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

14.7 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. *For EDC studies:* Queries are entered, tracked, and resolved through the EDC system directly. *For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.8 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

14.9 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.
All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

14.10 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

14.11 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all Study Subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).
To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

15.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

15.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.
Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.
Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.
The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.3 Informed Consent Form

Informed consent will be obtained in accordance with the US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.
The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on

Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.
A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

15.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.

Personally conduct or supervise the study (or investigation).
Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. EXAMPLE OF SCHEDULE OF STUDY VISITS

	VISIT 1 Selection/Breath Test	**VISIT 2 Test/Pylo Plus, Histology, Rapid Urease and Culture**
Informed Consent	X	
Medical History	X	
Abbreviated Physical Exam		X
Height	X	X
Weight	X	X
Vital Signs	X	X
Dispensing or Administration of Study Drug		X
Counting of Returned Study Drug		X
Concomitant Medication Review	X	X
Adverse Experiences		X