SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Urea Breath Test (UBT)

Device Trade Name: PyloPlus UBT System

Device Procode: OZA

Applicant's Name and Address: ARJ Medical, Inc.
209 State Street East
Oldsmar, FL 34677

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170022

Date of FDA Notice of Approval: February 18, 2020

II. INDICATIONS FOR USE

The PyloPlus UBT system is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis of *H. pylori* infection in adults 18 years old and older. The PyloPlus UBT system consists of the PyloPlus UBT Kit and the PyloPlus UBT analyzer. The analyzer is an infrared Spectrometer used for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples. The PyloPlus UBT system is for use by trained health care professionals as prescribed by a physician.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PyloPlus UBT System labeling.

V. DEVICE DESCRIPTION

The PyloPlus UBT is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* (*H pylori*) in the human stomach. The PyloPlus UBT is a combination product that includes a diagnostic drug component, ^{13}C urea/citric acid. The USP monograph for ^{13}C-urea was provided and supports a stability claim of 24 months at room temperature under stable humidity. In the PyloPlus UBT, the pouched ^{13}C-urea and pouched flavoring packet are reconstituted with water and then ingested by the patient.

The ^{13}C-urea is decomposed by urease associated with gastric *H pylori* forming $^{13}CO_2$ and NH4+. The $^{13}CO_2$ is absorbed into the blood, and then exhaled in the breath. The result of the PyloPlus UBT is provided as the Delta Over Baseline (DOB) which is the difference between the ratio of $^{13}CO_2/^{12}CO_2$ in the post-dose sample and the corresponding ratio in the baseline sample. Analysis of the breath samples is performed by the PyloPlus UBT Analyzer. The analyzer is an infrared spectrophotometer that can distinguish the difference between ^{13}C isotope and ^{12}C that is most predominant in air. The Spectrophotometer is manufactured by FAN and is a standalone unite that measures the amount of ^{13}C in each breath bag and then calculates the change in ^{13}C between the baseline breath sample and post-dose breath sample. From the change in ^{13}C levels a ratio or DOB can be calculated. A DOB result $\geq$3.0 is interpreted as positive for *H pylori* infection, and a result < 3.0 is interpreted as negative for *H. pylori* infection in adult patients.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternative methods for the detection of *H. pylori* in human specimens. One of the diagnostic methods entails an endoscopy procedure to obtain gastric biopsy and perform histology, immunohistochemical stains, culture, and rapid urease tests. Additional methods include, serological assays to detect immunoglobulins (A, G, or M antibodies) to *H. pylori*, stool antigen test and other urea breath tests. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The PyloPlus UBT is not marketed anywhere in the US or outside the US.

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.
Adults postmarket experience:
During post-approval use of UBTs, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in stomach, tingling in the skin, vomiting, and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

There have been no adverse effects associated with the use of the device in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Reproducibility:

Analytical studies were conducted to evaluate the reproducibility and precision of the PyloPlus UBT System with different operators, instruments, days, and sites. The studies used samples stored at a minimum of 60 days at stable room temperature and humidity conditions.

Three gas isotope pairs were used with DOB values of 2.2 (high negative), 3.1 (low positive), and 9.5 (moderate positive). The study was conducted over 5 days at three different sites, with two operators/site to measure the DOB values for samples from each of the three sample pairs. The reproducibility study results demonstrated minimal differences in the standard deviation over different samples for both the operator, the devices and between days. Table 1 summarizes the results of the reproducibility study.

Table 1 PyloPlus Reproducibility

Sample	Average DOB		Within Run	Between Runs (operator)	Between Days	Between Sites
High Neg 2.2	2.27	SD	0.123	0.000	0.027	0.084
		%CV	5.417	0.000	1.180	3.690
Low Pos 3.1	3.18	SD	0.145	0.046	0.000	0.047
		%CV	4.559	1.442	0.000	1.469
Mod Pos 9.5	9.53	SD	0.144	0.000	0.042	0.000
		%CV	1.513	0.000	0.442	0.000

CV=coefficient of variation

Repeatability (Precision)
The study was conducted at one site over 12 days with 2 measurements/day of three gas isotope pairs with DOB values of 2.2 (high negative), 3.1 (low positive), and 9.5 (moderate positive). The repeatability results demonstrated that minimal differences the standard deviation over different samples and different days. Table 2 summarizes the results of the repeatability study.

Table 2. PyloPlus Repeatability

Sample	Average DOB		Within Run	Between Runs	Between Days
High Neg 2.2	2.20	SD	0.077	0.000	0.056
		%CV	3.486	0.000	2.300
Low Pos 3.1	3.15	SD	0.051	0.000	0.048
		%CV	1.633	0.000	1.403
Mod Pos 9.5	9.66	SD	0.100	0.053	0.000
		%CV	1.035	0.546	0.000

CV=coefficient of variation

Stability of breath bag samples:
Contrived gasses for the reproducibility and repeatability study support the clinical claim of $^{13}CO_2$ stability for seven (7) days when held at room temperature.

Carryover
A study was conducted to evaluate the potential for sample to sample carry-over or cross contamination in the PyloPlus UBT System. Five runs were conducted using contrived gas, each run consisting of 10 tests. Testing consisted of alternating between contrived gas samples alternating between high negative 2.2 and high positive 29.3. Data from tests 1-10 in each run were used in the analysis.
The standard deviation for either the high negative or the high positive was $\underline{<}$ 0.10. The results indicate potential carryover between 2.2 and 29.3 is not a clinically significant amount. Table 3 summarizes the results of the Carryover study.

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Table 3. PyloPlus Carryover

	High Negative 2.2			High Positive 29.3		
Day	Within-run SD	Within-Run Variance	Mean	Within-run SD	Within-Run Variance	Mean
1	0.07	0.030	2.3	0.05	0.002	29.2
2	0.07	0.030	2.3	0.08	0.003	29.3
3	0.05	0.022	2.2	0.007	0.000	29.2
4	0.1	0.043	2.3	0.007	0.000	29.3
5	0.07	0.030	2.3	0.1	0.003	29.2

B. Animal Studies
N/A

C. Additional Studies
N/A

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the PyloPlus UBT System for the qualitative detection of urease associated with *H. pylori* in the human stomach and for the indication as an aid in the initial diagnosis of *H. pylori* infection in adults 18 years old and older. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between August 2015 and November 2016. The dataset for this application reflected data collected through November 2016 and included 324 patients. There were six (6) investigational sites.

The clinical performance was determined based on data collected from a multi-center, open-labeled study designed to compare the PyloPlus UBT System to endoscopic method to aid in the diagnosis of *H. pylori*. The use of endoscopy is considered as part of standard of care for diagnosis of *H. pylori* for some individuals. During endoscopy, tissue samples are taken for a Rapid Urease Test (RUT), histology and culture when available. Depending on availability, results from three or only two tests (RUT and histology) were used as the Composite Reference Method (CRM) to determine if the final reference results was evaluable for the purpose of determining patient status (infected/not infected). When results from only two tests were available, patient status was recorded as "infected" if culture was positive. In cases where culture was negative and a single negative for RUT or histology was available, patient infected status was considered "not infected". When culture was not obtained, either concurrent positive or concurrent negative for the other two tests were considered evaluable for determining patient infected status as infected and not infected, respectively. When discrepant results for those two tests were obtained, in the absence of a culture result, the patient infected status was considered non-evaluable. Subjects in the pivotal study were symptomatic adults 18 years and older undergoing diagnostic upper endoscopy at the determination of their treating gastroenterologist. Study enrollment was based on esophagogastroduodenoscopy (EGD) performed on each subject in proximity to the administration of the PyloPlus UBT. The study enrolled 324 patients at U.S. investigational sites in the Tampa/Orlando area. No adverse events were reported during this clinical investigation.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the PyloPlus UBT System study was limited to patients who met the following 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

Patients were not permitted to enroll in the ARJ 2014-01 study if they met any of the following 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
    - Mouthwash
    - Chewing gum
    - Carbonated beverages
    - Cigarette smoke
    - Acetone (to simulate the effect of ketone production that may result from some diets)
    - Alcohol

Use of proton pump inhibitors (PPIs) should have disqualified a patient from enrollment because it has been shown to potentially negatively affect the biopsy result, but the protocol did not specify this as an exclusion criterion and patients on PPIs were enrolled. A false negative rapid urase test (RUT) result may occur in patients on PPIs.

2. Follow-up Schedule

All patients were first identified as candidates for enrollment into the study. They were randomized to either being first given the PyloPlus UBT System test and then upper endoscopy, or upper endoscopy first then followed by the PyloPlus UBT System test. Results between the two test procedures were blinded to the operators. Patients were enrolled for initial diagnosis of *H. pylori* infections without prior knowledge of disease status. Upper endoscopy was performed on patients who were already undergoing gastric biopsy as part of routine care.

Preoperatively, patients were requested to follow standard medical procedures for upper endoscopy. Postoperatively, the objective parameters measured during the study required that the biopsy sample be tested by the rapid urease test at the time of collections, that a biopsy be sent for histological examination, and that a third biopsy be sent for culture if available. A composite result of these three tests was used to determine patient infected status. Adverse events and complications were recorded at all visits.

The PyloPlus UBT System test was performed once and the results were compared to

the CRM results to determine performance.

3. Clinical Endpoints
   With regards to safety, the consumption of the urea/citric acid mix, is considered low risk. The collection of breath prior to drug consumption and post drug consumption is considered non-invasive with minimal risk.

   With regards to effectiveness, the non-invasive clinical test demonstrated a sensitivity of 100% and a specificity of 100% when compared to the patient infected statues determined by upper endoscopy and the results for the CRM.

   Of the 324 patients enrolled 324 patients had endoscopy results from which an evaluable result was established and corresponding UBT result that could be used for analysis.

B. Accountability of PMA Cohort

At the time of study completion, November 2016, of the total 324 patients enrolled in the PMA study, results from 97.5% (N=316) of patients were available for analysis.

Three hundred twenty-four patients had endoscopy results and were determined to be evaluable and had a corresponding UBT result that was used for analysis. One (1) of the 324 patients had discrepant CRM results and is considered non-evaluable. Seven (7) of the 324 patients were later determined to have been taking antibiotics when enrolled and tested by endoscopy and UBT. Use of antibiotics is one of the exclusion criteria. Therefore, eight patients were excluded from the per protocol (primary) analysis.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a prospective study performed in the US.

Of the 316 patients tested 216 were female and 102 were male. The patients ranged in age from 18 years old to 90 years old. Even though reporting of race was voluntary, 111 patients declined to report race and 205 patients provided this information. Three (3) patient were reported as Asian, 13 as Black, 60 as Hispanic/Latino, and 129 as White. Race, age and gender did not appear to affect the performance of the PyloPlus UBT System in the sample population.

D. Safety and Effectiveness Results

1. Safety Results
   The analysis of safety was based on the 324 prospectively enrolled over a 16-month time span.

Adverse effects that occurred in the PMA clinical study:
No adverse events where reported for the ingestion of ^{13}C urea/citric acid during the clinical study.

2. Effectiveness Results

The analysis of effectiveness was based on the 316 evaluable per protocol patients that were enrolled over 16-months. Of the 316 patients 144 patients were determined to have abstained from the use of PPI for at least 2 weeks prior to CRM testing. The remaining 172 patients were determined to have been taking a PPIs within 2 weeks of the CRM test. Because PPIs are known to cause false negative CRM results, the patients taking PPIs were excluded from the primary analysis. All patients taking PPIs and abstaining from PPIs were later pooled in an additional analysis.

The effectiveness of the PyloPlus UBT System was assessed by determining test results pre and post ingestion of ^{13}C urea for initial diagnosis of persons suspected of *H. pylori* infections in the stomach. There were 34 patients positive by the CRM and 110 patients determined to be negative by CRM. The analysis contained only congruent results among the CRM tests (histology and rapid urease test). The calculated performance is provided in Table 4 below for 144 patients. Patients on PPIs (172) are omitted from the primary analysis because of the potential for a false negative result from the CRM.

Table 4. PyloPlus primary analysis

		Composite Reference Method		
		Positive	Negative	Total
ARJ PyloPlus UBT System	Positive	34	0	34
	Negative	0	110	110
	Total	34	110	144
Sensitivity	100%	95% CI	89.9%-100%	
Specificity	100%	95% CI	97.4%-100%	

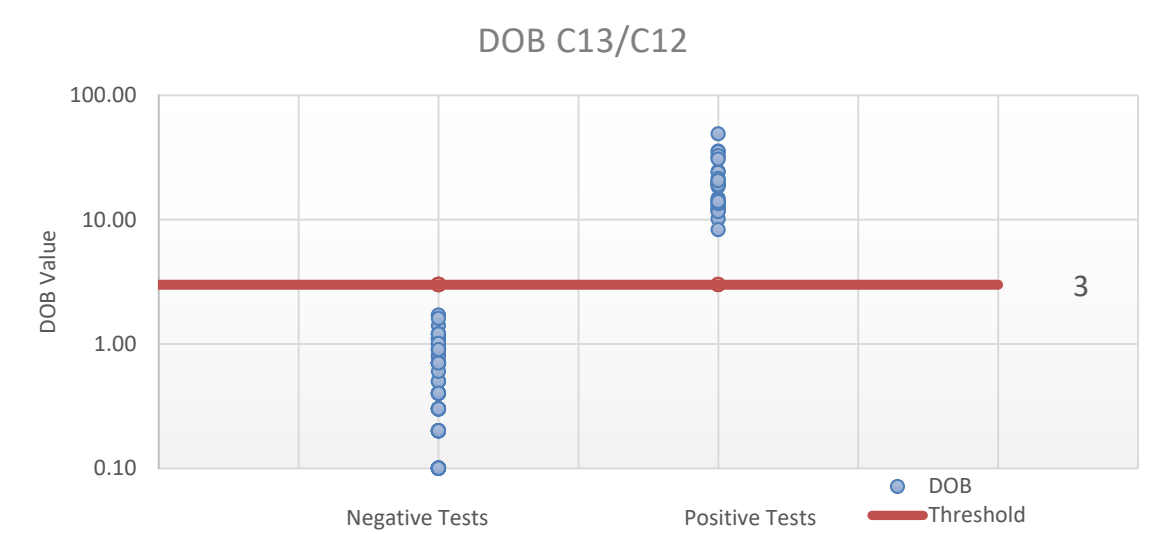
An additional analysis was performed by including all 316 patients (i.e. irrespective of the use of PPIs at the time of testing). The analysis contained only congruent results among the CRM tests (histology and rapid urease test). There were 64 patients positive by the CRM and 252 patients determined to be negative by CRM. There were 63 true positive results and 250 true negative results, two (2) false positive results and one (1) false negative results when the PyloPlus UBT System was compared to the CRM. The calculated performance is provided in Table 5 below. Patients on PPIs are included as a secondary analysis.

Table 5. PyloPlus additional analysis

		Composite Reference Method		
		Positive	Negative	Total
ARJ PyloPlus UBT System	Positive	63	2	65
	Negative	1	250	251
	Total	64	252	316
Sensitivity	98.40%	95% CI	91.7%-99.7%	
Specificity	99.20%	95% CI	97.2%-99.8%	

A subset of the first 115 patients was used to confirm the DOB of $\geq$ 3.0 is a positive result for the PyloPlus UBT System when compared to the CRM. The PyloPlus UBT system positive and negative test results, compared to the CRM, are graphically represented in figure 1 below. The left column graphically represents all the negative results with each circle representing the DOB measurement. The right column graphically represents all the positive results with each circle representing the DOB measurement. Patients on PPIs are included in the cutoff study analysis.

Figure 1. DOB Cutoff Confirmation



The same 115 patient samples used to confirm the clinical cutoff study were also used for a breath bag stability study. None of the positive bags turned negative and none of the negative bags turn positive during the breath bag stability study. Variations over time existed but did not change any of the results over a 7 day period after the collection of breath samples, when stored at room temperature.

3. Subgroup Analyses
   A subgroup analysis showed that performance was similar across site, age, gender, race or ethnicity.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 six (6) 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. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Performance characteristics of PyloPlus UBT System for *H. pylori* were similar across age groups, race, gender and study sites. The primary endpoint analysis was conducted to determine the sensitivity and specificity of the PyloPlus UBT kit for *H. pylori* to the CRM results for the 144 patients who abstained from PPIs. When compared to the CRM, the observed sensitivity and specificity values were 100%, and 100%, respectively. When patients taking PPIs, were included in the analysis in addition to the 144 patients not taking PPIs, the observed sensitivity and specificity values compared to CRM were 98.4% and 99.2% respectively.

B. Safety Conclusions

The adverse effects (AE) of the device are based on data collected in clinical studies to support PMA approval as described above. No adverse effects were reported during this clinical trial

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical study conducted to support PMA approval as described above. The benefits include providing a means of rapid, non-invasive detection of *H. pylori* in the stomach for adults with active peptic ulcer disease (PUD), certain types of gastric lymphoma or gastric cancer, or other conditions where suspicion of *H. pylori* infection warrants

testing, and treatment if present. The device, along with others like it that utilize the same mechanism for detection of *H. pylori*, provide an alternative to other means of *H. pylori* diagnosis that may require an invasive procedure, or may be unable to detect active, current infection.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The risks associated with the device, when used for pre-treatment diagnosis of *H. pylori*, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the instrument. A false positive *H. pylori* diagnostic test risks overtreatment with antimicrobials used in treatment regimens for *H. pylori*. A false negative result may result in delays in treatment of *H. pylori* infection, which could result in worsening of certain associated gastrointestinal illnesses, such as peptic ulcer disease. Adverse events related to use of the device were not observed during the clinical study and are expected to be rare.

No additional factors to be considered in determining probable risks and benefits for the PyloPlus UBT System are included.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data supports the intended use of PyloPlus UBT system in the qualitative detection of urease associated with *H. pylori* in the human stomach and for use as an aid in the initial diagnosis of *H. pylori* infection in adults 18 years old and older. The probable benefits outweigh the probable risks for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device and drug (^{13}C urea/citric acid) when used in accordance with the indications for use. The submitted clinical studies have shown that the PyloPlus UBT System when used for the detection of *H. pylori* has a similar performance as the CRM, to aid in the initial diagnosis of *H. pylori* infection in adult patients.

XII. CDRH DECISION

CDRH issued an approval order on February 18, 2020. The final conditions of approval cited in the approval order are described below.

Provide a Certificate of Analysis (CoA) for all future batches of ^{13}C-Urea testing as required by the USP monograph, specifically to include residue on ignition testing.

Testing is to be conducted at release of ^{13}C-Urea and test results will be included in future annual reports.

XIII. 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: N/A.

XIV. REFERENCES

N/A