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(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170022/S003

Date of FDA Notice of Approval: January 11, 2024

The original PMA (P170022) was approved on February 18, 2020, and is indicated 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 SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the PyloPlus® UBT System

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 and post treatment monitoring of *H. pylori* infection in adults and pediatric patients ages 3-17 years old. 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 System (Urea Breath Test (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 (U.S. Pharmacopeia) 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 subject. 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 unit 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 subjects.

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 subject 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 has been marketed in the US since its original approval on February 18, 2020.

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.

Historical 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 NON-CLINICAL STUDIES

A. Laboratory Studies

No new laboratory studies were conducted for the added target population claims.

B. Animal Studies

N/A

C. Additional Studies

N/A

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of detection of *H. pylori* with 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 and post treatment monitoring of *H. pylori* infection in adults and children 3-17 years old. Data from this clinical study were the basis for the Panel track PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Adult subjects were treated between March 29, 2023, and May 16, 2023. The database for this Panel Track Supplement reflected data collected through May 2023 and included 80 subjects. There were 2 investigational sites.

The pediatric subjects were tested between November 14, 2022, to June 6, 2023. The database for this Panel Track Supplement reflected data collected through June 2023 and included 57 subjects. There were 5 investigational sites.

The studies were separate, multi-center, non-randomized, open label, clinical studies. Subjects were enrolled on a walk-in basis. Enrollment sites utilized a PyloPlus UBT Analyzer to document the results, but the results remained blinded to the investigator and treating physicians and no treatment decisions were made based on the investigational device results. Pediatric subjects were treatment naïve and adult subjects had been treated for *H. pylori* within the past 6 months at the time of testing.

The urea breath test uses a breath sample, pre-drug consumption as the baseline. Post drug consumption, a breath sample is collected and analyzed for an elevation in C13 which is indicative of detection of a urease metabolizing bacteria in the stomach. All subjects in both cohorts are compared to an FDA cleared stool antigen test using a 2x2 table and calculation the positive and negative percent agreement with a 95% two-sided confidence interval to determine clinical performance. Each subject acts as their own control by collecting a base line breath sample pre-drug treatment.

1. Clinical Inclusion and Exclusion Criteria for Adults
   Enrollment in the adult post-therapy study was limited to subjects who met the following inclusion criteria:

   - Inclusion criteria:
     a. Male or female age > 18 years of age
     b. subjects who have been diagnosed with *H. pylori* and have been treated within the past 6 months
     c. Naïve to *H. pylori* treatment in the past 4 weeks (including Proton Pump Inhibitors)

   Patients were not permitted to enroll in the adult post-therapy study if they met any of the following exclusion criteria:

   - Exclusion criteria:
     a. Pregnant and/or lactating women.
     b. 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.
     c. Participation in other interventional trials.
     d. Allergy to test substrates.

e. Antibiotics taken within 4 weeks of the testing.
f. Study subjects shall not consume the following items at least 1 hour prior to the PyloPlus UBT:
    - Mouthwash
    - Chewing Gum
    - Carbonated Beverages
    - Cigarette Smoke
    - Acetone (to simulate the effect of ketone production that may result from some diets)
    - Alcohol
    - Food

2. Clinical Inclusion and Exclusion Criteria for Pediatric

Enrollment in the pediatric initial diagnosis study was limited to subjects who met the following inclusion criteria:

- Inclusion criteria:
    a. Male or female age 3-17 at the time of visit.
    b. Subject/Legal guardian (and subject when relevant) is willing to sign the Informed Consent/Assent Form
    c. Naïve to *H. pylori* treatment in the past 4 weeks

Patients were not permitted to enroll in the pediatric study if they met any of the following exclusion criteria:

- Exclusion criteria:
    a. Pregnant and/or lactating women.
    b. 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.
    c. Participation in other interventional trials.
    d. Allergy to test substrates.
    e. Antibiotics taken within 4 weeks of the testing.
    f. Study subjects shall not consume the following items at least 1 hour prior to the PPUBT test:
        - Mouthwash
        - Chewing Gum
        - Carbonated Beverages
        - Cigarette Smoke
        - Acetone (to simulate the effect of ketone production that may result from some diets)
        - Alcohol
        - Food

g. Children 12 years and older – to be excluded after a written notification from the sponsor is received at the site that the limit of approximately 1/3 of the sample size was achieved for this group.

2. Follow-up Schedule
All subjects were first identified as candidates for enrollment into the study. Results between the two test procedures were blinded to the operators. Adult subjects were enrolled who had a positive test for *H. pylori* win the past 6 months and had completed treatment at least 4 weeks prior to entering the post-therapy cohort. Pediatric subjects were enrolled for initial diagnosis of *H. pylori* infections without prior knowledge of disease status. The PyloPlus UBT System test was performed once, and the results were compared to the stool antigen 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 sensitivity and specificity values of 76%, and 98%, respectively for the adult post -therapy cohort and sensitivity and specificity values of 100%, and 89.9%, respectively for the pediatric initial diagnosis cohort.

With regard to success/failure criteria, of the 80 adult subjects enrolled, 76 subjects had a stool antigen result from which an evaluable result was established and corresponding UBT result that could be used for analysis. Of the 57 pediatric subjects enrolled, 40 subjects had a stool antigen result from which an evaluable result was established and corresponding UBT result that could be used for analysis. The primary analysis of the pediatric cohort was safety with efficacy being a secondary analysis.

B. Accountability of PMA Cohort

At the time of study completion, June 2023, a total of one hundred thirty-seven (137) subjects enrolled in the PMA study were available for safety analysis, with results from 84.7% (N=116) of subjects available for efficacy analysis. Table 1. Below is the study breakdown for the number of subjects in each study cohort.

One hundred sixteen (116) subjects (76 adults and 40 pediatric) had stool antigen results with a corresponding UBT result available and were determined to be evaluable for efficacy.

Table 1. Breakdown of adult and pediatric analysis

Study analysis cohorts.	Safety analysis	Efficacy analysis is a subset of the safety analysis cohort	Total
Adult safety	80	76	80
Pediatric safety	57	40	57
Total			137

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an all-comers study performed in the US.

Of the one hundred thirty-seven (137) subjects tested, 80 were adults and 57 were children. All adult and pediatric subjects were evaluable for safety analysis. As noted below, the analysis of effectiveness was based on 116 evaluable subjects (76 adults and 40 pediatric subjects).

There were 80 evaluable adult subjects included in the safety analysis. There were 76 evaluable adult subjects in the efficacy analysis who completed both the UBT and stool antigen test. Of the evaluable 80 adult subjects, 67.5% (54/80) were female and 32.5% (26/80) were male. Subjects were aged 21 to 93 with 29% (23/80) over aged 65. The collected demographic information combined race and ethnicity data. Therefore only 1 subject was listed as Black/Hispanic with the remaining 79 subjects listed as Caucasian/Hispanic.

There were 57 evaluable pediatric subjects included in the safety analysis. There were 40 evaluable pediatric subjects in the efficacy study who completed both the UBT and the stool antigen test. Of the evaluable 57 subjects for safety, 42% (24/57) were male and 58% (33/57) were female. Subjects were aged from 3-17 years, with 68.4% (39/57) under the age of 12. Hispanic subjects comprised 47% (27/57) of the study population, Caucasian subjects 26.3% (15/57), African American subjects 7% (4/57) and Asian subjects 1.8% (1/57). 10 subjects (17.5%) were listed as Caucasian/Hispanic, other or unknown.

D. Safety and Effectiveness Results

1. Safety Results
   The analysis of safety was based on the 137 prospectively enrolled over a 7-month time span.

Adverse effects that occurred in the PMA clinical study:

No adverse events were 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 116 evaluable subjects, 76 adults and 40 pediatric subjects tested over the 7-month enrollment period. Key effectiveness outcomes are presented in Table 2 for adults and Table 3 for the pediatric cohort.

Table 2. Adult post-therapy efficacy compared to stool antigen.

	Stool Antigen Test		
PyloPus UBT system	Positive	Negative	Total
Positive	19	1[2]	20
Negative	7[1]	49	56
Total	26	50	76

[1]Seven (7) of the false negative results were followed up with an FDA reviewed UBT and found to be negative by UBT.
[2]The false positive result was followed up with an FDA reviewed UBT and found to be positive by UBT.

Positive Percent Agreement 73.1% [95% CI (54.0%-86.3%)]
Negative Percent Agreement 98% [95% CI (89.7%-99.7%)]

Table 3. Pediatric initial diagnosis secondary analysis (efficacy) compared to stool antigen.

	Stool Antigen Test		
PyloPus UBT system	Positive	Negative	Total
Positive	1	4	5
Negative	0	35	35
Total	1	39	40

Positive Percent Agreement 100%
Negative Percent Agreement 90% [95% CI (76.4.8%-96.0%)]

3. Subgroup Analyses

No other subgroup analysis was conducted.

4. Pediatric Extrapolation

The data in this premarket application as well as leveraging existing clinical data were used to support the reasonable assurance of safety and effectiveness of the proposed device in pediatric subjects.

a) The framework set forth by the FDA Guidance entitled "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" was utilized to determine the acceptability of the sponsor's proposal. As stated in the guidance, "Leveraging relevant available clinical data, when appropriate, may lead to more devices being granted

marketing authorization for pediatric indications, which will increase the availability of medical devices with appropriate labeling to support safe and effective device use in pediatric" subjects. Valid scientific evidence in the guidance is defined as well-controlled investigations, partially controlled studies, case histories and reports of significant human experience from which FDA can be reasonably assured that device will be safe and effective when used as intended. The scientific evidence provided by the sponsor was considered sufficient to allow pediatric extrapolation from adult data for initial and post- treatment efficacy.

b) The Sponsor additionally performed a literature search and provided the following references for FDA review. The literature search identified Leal et al., 2011, a meta-analysis which included thirty-one articles and 135 studies which overall demonstrated a sensitivity of 95% and specificity of 93.5% in children. They also included four other studies published from 1997 to 2009. These included Rowland et al., 1997 and Bazzoli et al., 2000 which both demonstrated a high sensitivity with a DOB of 3.5. Elitsur et al, 2009 demonstrated high sensitivity with a DOB of 2.4 and Machado et al., 2004 which demonstrated no relationship between the DOB value and age including in young children down to 1 year of age.

c) The sponsor fully leveraged clinical data from their device and literature to extrapolate effectiveness for the pediatric post-therapy detection of urease activity.

d) The literature search and pediatric extrapolation from adult efficacy is appropriate because of the large margin of safety associated with the drug, the risk profile of the diagnosis and the over 10 years experience we have with this class of UBT using the same drug formulation with the pediatric population. Therefore, the provision of only safety data from the clinical study is acceptable. Based on the literature search, maintaining the same DOB of 3 in adult and pediatric populations is also acceptable.

XI. 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 five (5) 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.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

N/A

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

Device did not go to Panel.

XIV. 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 an FDA cleared stool antigen test for the adult post-therapy cohort with results for the 76 subjects who abstained from PPIs. When compared to the stool antigen test, the observed sensitivity and specificity values were 76%, and 98%, respectively. When subjects were compared to an FDA cleared breath test, the sensitivity and specificity were 100% and 100%, respectively.

Performance characteristics of PyloPlus UBT System for *H. pylori* were similar across age groups, race, gender, and study sites. The secondary endpoint analysis of efficacy for pediatric subjects 3-17 years of age was conducted to determine the sensitivity and specificity of the PyloPlus UBT kit for *H. pylori* to an FDA cleared stool antigen test. Results were available for 40 subjects; when compared to the stool antigen test, the observed sensitivity (n=1) and specificity (n=39) values were 100%, and 89.9%, 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, or the information did not serve as part of the basis of the decision to approve or deny the PMA 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 and children 3-17 years old aid in the post therapy detection of urease associated with *H. pylori* infection in adult subjects and children 17 years old. 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 a stool antigen test, to aid in the post-therapy detection of urease associated with *H. pylori* infection in adult subjects. Furthermore, the data and evidence provided indicate results do not differ in the pediatric population as the ^{13}C-enriched urea dosage amount and DOB cut-off point would be the same. ARJ Medical, Inc. has effectively used the CDRH guidance titled *Leveraging Existing*

Clinical Data for Extrapolation to Pediatric Uses of Medical Devices to support the claim that the PyloPlus UBT analyzer is safe, effective and provides results as intended when used in children 3-17 years of age.

XV. CDRH DECISION

CDRH issued an approval order on January 11, 2024.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. 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

XVII. REFERENCES

N/A