DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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January 5, 2017

C2 Therapeutics, Inc.
Ms. Theresa Brandner-Allen
VP of Regulatory Affairs and Quality Assurance
303 Convention Way, Ste. 1
Redwood City, CA 94063

Re: K161202
Trade/Device Name: C2 CryoBalloon Ablation System
Regulation Number: 21 CFR 878.4350
Regulation Name: Cryogenic unit and accessories
Regulatory Class: Class II
Product Code: GEH
Dated: November 21, 2016
Received: November 23, 2016

Dear Ms. Brandner-Allen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Binita S. Ashar -S

Binita S. Ashar, M.D., M.B.A., F.A.C.S.
Director
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
*See PRA Statement below.*

510(k) Number *(if known)*
K161202

Device Name

C2 CryoBalloon™ Ablation System

Indications for Use *(Describe)*

The C2 CryoBalloon™ Ablation System is intended for use as a cryosurgical tool in the field of general surgery, specifically for endoscopic applications, to include ablation of Barrett's Esophagus with dysplasia.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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# 510(k) Summary

This 510(k) summary is being submitted in accordance with the requirements of 21 CFR §807.92.

## I. SUBMITTER

Submitter Name: C2 Therapeutics, Inc.

Address: 303 Convention Way, Suite 1
Redwood City, CA 94063

Phone Number: 650-521-5921

Fax Number: 650-556-1145

Contact Person: Theresa Brandner-Allen
VP of Regulatory Affairs and Quality Assurance

Date Prepared: December 14, 2016

## II. DEVICE

Name of Device: C2 CryoBalloon™ Ablation System

Common Name: Cryosurgical Unit, Cryogenic Surgical Device

Classification Name: Cryosurgical Unit, Cryogenic Surgical Device
21 CFR§878.4350(a)(2)

Regulatory Class: Class II

Product Code: GEH

## III. PREDICATE DEVICES

Coldplay CryoBalloon™ Ablation System: K152329

The Coldplay CryoBalloon™ Ablation System predicate device has not been subject to a design-related recall.

## IV. DEVICE DESCRIPTION

The subject device is a cryosurgical system with a nitrous oxide cooled balloon that is compatible with a commercially available endoscope with a minimum working channel inner diameter (ID) of 3.7 mm and length of 100 cm. The subject device is a

system comprised of a Catheter (sterile), Controller (non-sterile), and Cartridge (non-sterile).

The subject device is used to ablate unwanted tissue by application of extreme cold to a 360° circumference, 90° circumference, or 45° circumference and is identical to the respective predicates. The balloon at the distal end of the Catheter comes in contact with tissue and is inflated with nitrous oxide. Tissue is visualized through the pre-inflated balloon, and the treatment site is selected by adjusting the endoscope and Controller position. The nitrous oxide spray cools the balloon to ablate the unwanted tissue, and the nitrous oxide exhausts through the Controller.

## V. INDICATIONS FOR USE

The C2 CryoBalloon™ Ablation System is intended for use as a cryosurgical tool in the field of general surgery, specifically for endoscopic applications, to include ablation of Barrett's Esophagus with dysplasia.

## VI. COMPARISON OF TECHNOLOGICAL CHARACTERISTICS WITH THE PREDICATE DEVICE

Cryoablation is the fundamental technological principle for the subject C2 CryoBalloon™ Ablation System and the predicate device. Both the subject device and predicate device are used as endoscopic instrumentation for ablating unwanted tissue.

The only modification to the subject device is to modify the labeling. The labeled indication for use is changing from ablation of Barrett's Esophagus with high grade dysplasia to also include ablation of Barrett's Esophagus with low grade dysplasia (collectively, dysplasia) and to change a portion of the product name from Coldplay CryoBalloon to C2 CryoBalloon. The subject devices have identical technological characteristics to the legally marketed predicates. The subject device and predicate devices are based on the following same technological elements:

- Inserted through an endoscope to access the treatment site
- Apply extreme cold to ablate (freeze) the unwanted tissue
- Use of a compliant balloon to position the treatment diffuser
- User-controlled activation to release and apply the therapy
- Software controlled

There have been no technological changes to the subject device, and there are no technological differences between the subject device and predicate device. The subject device remains substantially equivalent to the predicate device.

## VII. PERFORMANCE DATA

Because there have been no technological changes to the subject device, no additional

bench testing, electrical safety testing, preclinical testing, sterilization, and biocompatibility testing were performed. A confirmatory bench evaluation was conducted to demonstrate the ability of the subject device to deliver temperatures sufficient for cell necrosis to the treatment area as demonstrated in the literature. A pre-clinical study reported in the literature was previously included in K152329 and is summarized below. These data support the safe and effective use of the device as intended.

In a prior study, Schölvinck 2014 conducted a prospective preclinical evaluation in the porcine model to evaluate the short-term and long-term histopathological effects and safety of the subject device.[1] Cryoablations were first performed in swine that were survived between 12 hours and 28 days. There were no adverse events. At 48 hours, inflammation, cell necrosis, and edema extended throughout the entire esophageal wall and extended to the serosa. After 28 days, no signs of necrosis or fibrosis remained in any esophageal wall layer. Based on these findings, a subsequent human clinical safety study was performed in 4 patients directly prior to a scheduled esophagectomy. Ablations showed moderate inflammation mainly limited to the submucosa with a median score of 6 (range 5 to 8). The investigator concluded that in both humans and animals, the cryoablation penetrates deeply into the esophageal wall, but after 4 weeks, little injury and no fibrosis remain. The publication of additional follow up data is in progress.[1]

Clinical data were provided to support the modification of the indications for use to include ablation of Barrett's esophagus with low-grade dysplasia. The supporting studies conducted by Schölvinck 2015 and by Canto 2016 were prospective studies of patients presenting with Barrett's esophagus.[2, 3] These clinical data for the low-grade dysplasia patients are summarized in **Table 1** below.

**Table 1 – Subject Device Prospective Clinical Data Summary**

| Characteristic / Clinical Data | Literature (Schölvinck 2015)[2] | Literature (Canto 2016)[3] |
|---|---|---|
| Inclusion Criteria Summary | - Known Barrett's epithelium scheduled for surveillance, endoscopic resection, or ablative therapy<br>- Prague classification score of at least C ≥ 2 and/or M ≥ 3, and/or a Barrett's epithelium island ≥ 1 $cm^2$ | - Patients scheduled for ablation, EMR, and/or surveillance for BE (with or without dysplasia)<br>- Age ≥ 18 years<br>- Pathologically confirmed BE with a C&M classification of C≥0 and/or M≥1 |

[1] Schölvinck D, Weusten B, Triadafilopoulos G, Valli T, Friedland S. Deep Tissue Ablation with Little or No Late Fibrosis: Animal and Human Data on Esophageal Cryoablation Using the New CryoBalloon Focal Ablation System. GastrointestEndosc 2014. 79(5S):AB520.

[2] Schölvinck DW, Künzli HT, Kestens C, Siersema PD, Vleggaar FP, Canto MI, Cosby H, Abrams JA, Lightdale CJ, Tejeda-Ramirez E, DeMeester SR, Greene CL, Jobe BA, Peters J, Bergman J, Weusten B. Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy. 2015 Dec; 47(12):1106-12.

[3] Canto M, Almario JA, Cosby H, Voltaggio L, Montgomery E, Lightdale CJ. Multifocal Nitrous Oxide Cryoballoon Ablation With or Without EMR for Treatment of Neoplastic Barrett's Esophagus: Preliminary Results of a Prospective Clinical Trial in Treatment-Naive and Previously Ablated Patients. Presented by M Canto at the 2016 United European Gastroenterology Meeting. October 18, 2016.

| Characteristic / Clinical Data | Literature (Schölvinck 2015)[2] | Literature (Canto 2016)[3] |
|---|---|---|
| | - Flat treatment area (according to the Paris classification)<br>- Age 18 – 80 years | - Flat lesions |
| Exclusion Criteria Summary | - Presence of active inflammation<br>- Visible nodules within 4 cm of the treatment area at endoscopy<br>- Stenosis within 4 cm of the treatment area that would prevent advancement of the endoscope<br>- Prior treatment with any energy-based ablation system | - Endoscopically active inflammation in the treatment zone<br>- Esophageal stenosis preventing advancement of a therapeutic endoscope<br>- Endoscopically visible abnormalities such as masses or nodules within 4 cm of the treatment zone |
| Barrett's Esophagus with LGD | 9/39 (23%) | 13/40 (33%) |
| Follow-up duration (LGD) | 64 days (median) | 1 year |
| Device used | Coldplay CryoBalloon Focal Ablation System | C2 CryoBalloon Focal Ablation System |
| Resolution at follow-up (LGD, 10 second ablation) | 5/5 (100%)[4] | 12/13 (92%)[5] |
| Serious Adverse Events (LGD, requiring treatment) | | |
| Dysphagia | 0/9 (0%) | 0/13 (0%) |
| Stricture | 0/9 (0%) | 1/13 (8%)[6] |
| Bleeding | 0/9 (0%) | 0/13 (0%) |
| Perforation | 0/9 (0%) | 0/13 (0%) |
| Pain requiring prolonged course of narcotics | 0/9 (0%) | 0/13 (0%) |
| Non-Serious Adverse Events (LGD) | | |
| Dysphagia ≥ 24 hours | 0/9 (0%) | 2/13 (15%) |
| Stricture | 0/9 (0%) | 0/13 (0%) |
| Mucosal laceration | 2/9 (22%) | 0/13 (0%) |
| Pain requiring narcotics ≥ 24 hours | 0/9 (0%) | 1/13 (8%)[7] |

The combined 22 LGD patient data from Schölvinck 2015 and Canto 2016 support safety and effectiveness with no new concerns. One LGD patient had an SAE of stricture that required treatment, which is an expected event in endoscopic ablative or resective therapies. There was no dysphagia or bleeding that required treatment. For Non-SAE, there were two patients with mucosal laceration and two patients with dysphagia at 24 hours. One patient required narcotics (Lortab) at 24 hours. Both studies demonstrated high levels of effectiveness. In summary, the SAE rate of 4.5% for the subject device compares favorably with SAE rates ranging from 2.4% to 4.4%, particularly given the more conservative definition used for the safety analysis of the subject device.

[4] 5/5 patients had full (100%) conversion with no residual LGD as determined with biopsy. This represents 8 lesions in 5 patients with full (100%) conversion.
[5] 12/13 patients had full (100%) conversion with no residual LGD as determined with biopsy.
[6] One patient with pre-existing post-EMR and RFA stricture was treated with Kenalog at 2 months after first cryoablation.
[7] Post-discharge only one subject required narcotics for pain management (Lortab) at 24 hours.

The data from both studies are consistent and demonstrate definitive, prospective safety and efficacy of the subject device. The outcome data for the Schölvinck 2015 study was used to determine the 10 seconds dose for the Canto 2016 study and supports the safety and efficacy of the additional data reported in the Canto 2016 study with no new concerns.

The published safety and efficacy rates of the clinical studies for the subject device are within the same range as the safety and efficacy rates for the RFA ablation and other cryoablation devices for ablating Barrett's esophagus with LGD. The literature data combined with the nonclinical and clinical tests demonstrate that the device is as safe, effective, performs as well as, and is substantially equivalent to the predicate device and 510(k) cleared ablation devices.

The outcomes of patients with LGD in terms of resolution of all dysplasia and metaplasia are included in **Table 1**.

In addition to the published data for use of the subject device, data are reported in the literature from prospective, multicenter studies using RFA and other cryotherapy ablation devices that have demonstrated the safety and efficacy for ablation of low-grade dysplasia.

- In a sham-controlled multicenter study by Shaheen et al. that treated 42 LGD patients with Barrett's esophagus using RFA, efficacy rate for LGD was 90% at 12-month follow-up. There was 1 SAE in 42 LGD patients (2.4%) of upper gastrointestinal bleeding. There were 11 non-SAEs in 42 LGD patients (26%). The events included one patient with stricture that required dilation (this would be considered an SAE by the definition used for the subject device). The other non-SAEs were chest and throat pain with nausea (n=1); vomiting (n=1), stricture/scarring (n=1); narrowed esophagus (n=1); esophageal varices (n=1); fever and diarrhea (n=1); bloated, reflux sensation with difficulty swallowing (n=1); painful swallowing and chest pain (n=1); premature fullness with meals (n=1); painful swallowing with abdominal and chest pain (n=1); fever with laryngitis and bronchitis (n=1).[8, 9]
- In a randomized controlled study by Phoa et al. that treated 68 LGD patients with Barrett's esophagus using RFA, efficacy rate for LGD was 93% at a median 36-month follow-up. Two LGD patients experienced 3 SAEs (2/68, 4.4%). One patient hospitalized for abdominal pain was treated with

[8] Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. NEJM May 2009: V360 N22 pp2277-2288.

[9] Ablation of Intestinal Metaplasia Containing Dysplasia. (Copyright: U.S. National Library of Medicine; Last updated: December 28, 2015). In ClinicalTrials.gov. Retrieved on November 18, 2016 from: https://clinicaltrials.gov/ct2/show/results/NCT00282672?term=NCT00282672&rank=1.

analgesics. One patient experienced bleeding after Endoscopic Mucosal Resection (EMR). This same patient was later hospitalized for fever and chills post-dilation for stricture. Twelve (12) non-SAEs (12/68, 18%) in LGD patients were reported. Three patients experienced minor mucosal lacerations. One patient had retrosternal pain 3 weeks post-procedure, which was treated with analgesics after endoscopic evaluation (by the definition used for analysis of the subject device safety, the intervention would classify this pain as an SAE). Eight (8, 12%) patients developed stricture that required dilation. Note that stricture requiring dilation is considered an adverse event by the definition used for the safety analysis of the subject device.[10]

- In a multicenter study by Ghorbani et al. that treated 32 LGD patients with dysplastic Barrett's esophagus, the efficacy rate reported for LGD using CSA spray cryotherapy was 91% at a mean of 21-month follow-up for LGD patients with Barrett's Esophagus. The safety results specific to the LGD patients subgroup was not reported.[11]

The LGD efficacy rate of 92% and SAE rate of 5% (1/22) for the subject device are within the same range as the safety and efficacy rates for the RFA ablation and other cryoablation devices reported in the literature, including the LGD Barrett's conversion rates and incidence of adverse events reported in the literature for the subject device.

## VIII. CONCLUSION

The subject C2 CryoBalloon™ Ablation System is substantially equivalent to the predicate device. There have been no technological changes to the subject device, and there are no technological differences between the subject device design and predicate device design. The 92% efficacy rate and 5% SAE rate indicate use of the device for treatment of Barrett's esophagus with low-grade dysplasia does not raise different questions of safety and effectiveness.

Based on the benefit-risk factor assessment, prospective clinical data, and pre-clinical data reported in the literature, the safety and effectiveness rates reported for the subject device are substantially equivalent to the safety and effectiveness rates reported for the RFA ablation device and other cryoablation device. The nonclinical and clinical performance data support the indication for use modification and demonstrate that the subject device is as safe, effective, and performs as well as the predicate device.

[10] Phoa KN, van Vilsteren FGI, Weusten BLAM, Bisschops R, Schoon EJ, Ragunath K, Fullarton G, Di Pietro M, Ravi N, Visser M, Offerhaus GJ, Seldenrijk CA, Meijer SL, ten Kate FJ, Tijssen JGP, Bergman JJGHM. Radiofrequency Ablation vs Endoscopic Surveillance for Patients with Barrett Esophagus and Low-Grade Dysplasia a Randomized Clinical Trial. JAMA. 2014;311(12):1209-1217. doi:10.1001/jama.2014.2511.

[11] Ghorbani S, Tsai FC, Greenwald BD, Jang S, Dumot JA, McKinley MJ, Shaheen NJ, Habr F, Coyle WJ. Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the National Cryospray Registry. Diseases of the Esophagus. 2016 Apr;29(3):241-7. 2016 Apr;29(3):241-7. DOI: 10.1111/dote.12330.