

# **SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

## **I. GENERAL INFORMATION**

Device Generic Name: Thermal Endometrial Ablation Device

Device Trade Name: Cerene® Cryotherapy Device

Device Procode: MNB

Applicant's Name and Address: Channel Medsystems, Inc.  
5858 Horton Street, Suite 200  
Emeryville, CA 94608

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180032

Date of FDA Notice of Approval: March 28, 2019

## **II. INDICATIONS FOR USE**

The Cerene® Cryotherapy Device is indicated for endometrial cryoablation in premenopausal women with heavy menstrual bleeding due to benign causes for whom child bearing is complete.

## **III. CONTRAINDICATIONS**

The Cerene® Cryotherapy Device is contraindicated for use in the following:

- A patient who is pregnant or who wants to become pregnant in the future. **PREGNANCIES FOLLOWING ABLATION CAN BE DANGEROUS FOR BOTH MOTHER AND FETUS.**
- A patient with known or suspected uterine cancer or pre-malignant conditions of the endometrium, such as unresolved adenomatous hyperplasia.
- A patient with any anatomic condition (e.g., history of previous classical cesarean section or transmural myomectomy, including hysteroscopic and/or laparoscopic myomectomy performed immediately prior to the Cerene procedure) or pathologic condition (e.g., requiring long- term medical therapy) that could lead to weakening of the myometrium.
- A patient with a history of endometrial ablation and/or resection (including endometrial ablation/resection performed immediately prior to the Cerene procedure), regardless of the modality by which it was performed. **REPEAT ABLATION MAY RESULT IN SERIOUS PATIENT INJURY.**
- A patient with active genital or urinary tract infection (e.g., cervicitis, vaginitis,

endometritis, salpingitis, cystitis, pelvic inflammatory disease, or tubo-ovarian abscess) at the time of treatment.

- A patient with an intrauterine device (IUD) currently in place.
- A patient with undiagnosed vaginal bleeding.

#### **IV. WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the Cerene Cryotherapy Device labeling.

#### **V. DEVICE DESCRIPTION**

The Cerene Cryotherapy Device is designed to treat pre-menopausal women with heavy menstrual bleeding due to benign causes for whom childbearing is complete. The Cerene Cryotherapy Device uses nitrous oxide (N<sub>2</sub>O) to freeze and ablate the endometrium to reduce future menstrual bleeding.

The Cerene Cryotherapy Device (Figure 1) uses cryothermic energy to achieve ablation throughout the uterine cavity. The cryothermic energy is provided by a liquid-to-gas phase change of N<sub>2</sub>O. During the 2½ minute treatment cycle, liquid N<sub>2</sub>O (originating from a small Cylinder located in the device handle) flows through a delivery line and into an inflow line with multiple jets. This liquid N<sub>2</sub>O is infused into an ultra-thin polyurethane Liner, where it converts into gas. The gaseous N<sub>2</sub>O is exhausted through the Exhaust Hose exiting the bottom of the handle. An Exhaust Collection Bag (FGS-5009, Figure 2 below), which connects to the Exhaust Hose exiting the bottom of the device, is provided as an accessory to the Cerene Cryotherapy Device to minimize patient and physician exposure to the vented nitrous oxide. The Exhaust Collection Bag is provided individually labeled, packaged, and non-sterile in boxes of 10.

**Figure 1 - Cerene Cryotherapy Device**



**Figure 2 - Exhaust Collection Bag, shown here hanging from an IV pole**



The Cerene Cryotherapy Device is able to treat uterine cavities ranging in length between 2.5 and 6.5 cm with corresponding uterine soundings up to 10 cm. The user rotates the Sheath Retraction Knob to retract a thermally-insulating Sheath to the appropriate cavity length, based upon prior uterine sound measurements. Retraction of the Sheath also controls the number of N<sub>2</sub>O jets exposed within the Liner. The conformable Liner enables coverage of the irregular surfaces of the uterine cavity and effective thermal transfer.

The device status and sequential operating instructions are displayed on the device's LCD Screen. After removal from sterile packaging, the end of the Exhaust Hose is connected to the Exhaust Collection Bag. The Twist Ring is rotated to open the N<sub>2</sub>O Valve and turn on the device. The user is then prompted to press the Button and insert the device to the fundus. After insertion, the device prompts the user to partially retract the Sheath and press the Button a second time to slowly inflate and deploy the distal portion of the Liner. Once the preset pressure is reached, the device prompts the user to retract the Sheath to the full, pre-measured cavity length (shown on the LCD). A third Button press initiates treatment. The Liner is gradually pressurized with filtered air, deflated, and re-pressurized a second time. A final Liner leak detection test is completed and then the N<sub>2</sub>O flow is automatically initiated. At any time, the user can pause or stop the procedure. After 2½ minutes, N<sub>2</sub>O flow is stopped and the user is prompted to rotate the Twist Ring to vent the remaining N<sub>2</sub>O. The uterine cavity is allowed to thaw, and vacuum is initiated within the Liner to expedite device removal. After use, the entire device and Exhaust Collection Bag are disposed per local practice.

For additional details, please read the Instructions for Use for the Cerene Cryotherapy Device.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are several alternatives for the treatment of heavy menstrual bleeding due to benign causes. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets her expectations and lifestyle. The following alternative practices and procedures are currently available to treat excessive uterine bleeding due to benign causes, in the absence of structural abnormalities such as fibroid tumors or polyps:

- **Drug Therapy**

Drug therapies, using estrogen-progesterone combinations (such as those found in oral contraceptives) or progesterones (progesterone) by themselves, are approaches frequently employed for the treatment of heavy menstrual bleeding. Other classes of drugs used include androgens such as Danocrine, gonadotropin-releasing hormone (GnRH) agonists, and non-steroidal anti-inflammatory drugs (NSAIDs). Drug therapy is typically the first order of treatment to alleviate heavy menstrual bleeding. Drug therapies usually require long-term treatment. Drug therapy is successful for some women but may be ineffective or cause unpleasant side effects in others. This treatment approach does, however, allow a woman to maintain her fertility.

- **Dilatation and Curettage (D&C)**

D&C historically has been the treatment of choice for profuse uterine bleeding in women who are hemodynamically unstable and refractory or intolerant to drug therapy. First the cervix is dilated, and then the endometrial lining of the uterine cavity is either scraped by an instrument or removed/evacuated through vacuum aspiration. D&C may reduce bleeding for a few cycles. If a polyp is present and removed, the bleeding may stop. In most cases, D&C does not provide the patient with long-term definitive results, but may be useful for those women who desire to maintain their fertility.

- **Hysteroscopic Endometrial Ablation**

Hysteroscopic endometrial ablation is a surgical procedure which utilizes a resectoscope or operating hysteroscope, a video monitor, a fluid distention medium such as Glycine or Sorbitol, and a surgical ablation device such as an electrode loop, rollerball, or laser to destroy the endometrial lining of the uterus. The procedure is typically performed under general or regional anesthesia. The cervix must be dilated to accommodate the hysteroscopic instrument, and the uterine cavity must be properly distended to enable visualization. The most common risks associated with hysteroscopic endometrial ablation are

hyponatremia from fluid overload, which is a life-threatening condition, and uterine perforation. This treatment is intended for women who no longer desire fertility.

- **Second Generation “Global” Endometrial Ablation (GEA)**

Second Generation Global Endometrial Ablation (GEA) technologies are faster, less complex, and, in most cases, allow for a significant reduction in the incidence of complications associated with endometrial ablation, when compared to hysteroscopic endometrial ablation. There are currently seven (7) endometrial ablation systems approved by FDA:

- The ThermaChoice Balloon Endometrial Ablation System (Gynecare, P970021) uses thermal energy from heated sterile fluid (5% dextrose in water) contained within a silastic balloon.
- The HydroTherm Ablation System (Boston Scientific, P000040) uses USP 0.9% saline heated externally and injected into the uterine cavity.
- The Her Option CyroAblation System (Cooper Surgical, P000032) uses cryoablation.
- The NovaSure RF Endometrial Ablation System (Hologic, P010013) uses bi-polar RF energy to create heat and destroy the endometrium to a pre-determined depth using tissue impedance.
- The Microsulis Microwave Endometrial Ablation System (Microsulis Medical, P020031) uses microwave energy to heat the endometrial layer using a thermocouple at the tip of the device for ablation depth control.
- The Minerva Endometrial Ablation System (Minerva Surgical, P140013) uses bi-polar RF energy and ionized argon gas to create heat and destroy the endometrium.
- The AEGEA Vapor System™ (AEGEA Medical, P160047) uses heated water vapor to ablate the endometrium.

All of these therapeutic approaches are intended for women who no longer wish to maintain their fertility.

- **Hysterectomy**

The most definitive surgical treatment for heavy menstrual bleeding is hysterectomy, or complete removal of the uterus. Hysterectomy is a procedure performed in the hospital (or surgical center) under general anesthesia and is associated with the risks and complications of major surgery. Depending on the technique, hysterectomy may require a lengthy recovery period.

## **VII. MARKETING HISTORY**

The Cerene Cryotherapy Device was issued a CE Mark (CE 656054) by BSI (Notified Body Number 2797) on June 14, 2017. The Cerene Cryotherapy Device has not been marketed in the United States or any foreign country.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Below is a list of the potential adverse events (i.e., complications) associated with the use of the Cerene Cryotherapy Device:

- Emesis
- Fever
- Bacterial Vaginosis
- Endometritis
- Vulvovaginitis
- Groin pain
- Presyncope
- Urinary incontinence
- Dyspareunia
- Menstrual cramps
- Pelvic pain
- Uterine Cramps
- Uterine Tenderness
- Vaginal Discharge
- Hypertension

For any endometrial ablation procedure, commonly reported postoperative symptoms include the following:

- Postoperative cramping can range from mild to severe. This cramping will typically last a few hours and significantly decrease by the first day following the procedure.
- When present, nausea and vomiting typically occur immediately following the procedure, are associated with anesthesia, and can be managed with medication.
- Vaginal discharge
- Vaginal bleeding/spotting

The following adverse events could occur or have been reported in association with the use of other endometrial ablation systems and may occur when the Cerene Cryotherapy Device is used:

- Post-ablation tubal sterilization syndrome
- Pregnancy-related complications

**NOTE: Pregnancy following endometrial ablation is very dangerous for both the mother and the fetus.**

- Thermal injury to adjacent tissue, including bowel, bladder, cervix, vagina, vulva and/or perineum
- Perforation of the uterine wall
- Cervical or vaginal laceration
- Transient change in appearance of the cervical epithelium
- Thermal injury to extremity
- Mechanical bowel injury
- Diarrhea
- Headache
- Hemorrhage
- Hematometra
- Difficulty with defecation or micturition
- Uterine necrosis
- Air or gas embolism
- Infection or sepsis
- Complications leading to serious injury or death

Some or all of these risks may require a need for reoperation or subsequent treatment and/or may lead to permanent disability or death.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

## **IX. SUMMARY OF NONCLINICAL STUDIES**

### **A. Sterilization Validation**

The Cerene Cryotherapy Device is a single-use device. The sterilization method is ethylene oxide (EO). EO process validation results along with bioburden resistance test results support that Cerene Cryotherapy Device has a Sterility Assurance Level of  $\leq 10^{-6}$  and complies with ANSI/AAMI/ISO 11135:2014 and 11737-1:2006/(R)2011.

The Cerene Cryotherapy Device was adopted into the AAMI TIR28:2009, Product Adoption and Process Equivalence for Ethylene Oxide Sterilization. EO and Ethylene Chlorohydrin (ECH) residual levels met ISO 10993-7:2008 limits for limited exposure type.

The Exhaust Collection Bag accessory is provided non-sterile.

Packaging and tray seal integrity were tested to ensure sterility following shipping and environmental conditioning.

## **B. Biocompatibility**

The Cerene Cryotherapy Device is classified as a surface device that contacts mucosal membranes (vagina, cervix, and uterus) with a limited contact duration (less than 24 hours). Therefore, per ISO 10993-1:2009, assessment of the cytotoxicity, sensitization, and irritation potential of the patient-contacting components of the Cerene Cryotherapy Device was required. Acute systemic toxicity was also assessed.

The applicant completed the following biocompatibility testing on distal end samples that incorporated all patient-contacting components from the Cerene Cryotherapy Device and had been exposed to -90° C to reflect actual conditions of use:

- Cytotoxicity – ISO Elution Method (ISO 10993-5:2009)
- Sensitization – Guinea Pig Maximization Test (ISO 10993-10:2010)
- Irritation – Vaginal Irritation Test (ISO 10993-10:2010)
- Acute Systemic Toxicity – ISO Acute Systemic Injection Test (ISO 10993-11:2006)

The protocol and results of the above biocompatibility tests are acceptable and demonstrate that the patient contact components of the Cerene Cryotherapy Device are non-cytotoxic, non-sensitizing, non-irritating, and not systemically toxic.

## **C. Thermal Modeling**

Channel Medsystems performed thermal modeling by numerical simulation to investigate the effects of tissue thermal properties and treatment duration on ablation depths as part of the initial development of the Cerene Cryotherapy Device. The results of the thermal model were consistent with literature values for cryoablation temperatures and correlated with pathology results from peri-hysterectomy testing to demonstrate adequate safety.

## **D. Design Verification Testing**

Channel Medsystems conducted bench testing to verify the design of the Cerene Cryotherapy Device. These tests are outlined below.

- **Device Removal Strength Test** – The distal end of the device did not detach when the specified maximum removal force ( $\leq 7$  lbs) was applied to the device frozen in tissue.
- **Tip Perforation Test** – The mean force required to perforate the representative uterine tissue model was greater than the mean force of representative intrauterine devices, satisfying the requirement that the device have an atraumatic tip.

- **Liner Material Test** – The liner film thickness was measured to be in the specified range, and the pull strength and elongation met specifications. The liner was able to withstand cryothermic temperatures without a loss of integrity. When externally constrained, the Liner saw no localized plastic deformation under maximum operating pressure. When unconstrained, the Liner volume increased beyond the minimum volume expansion.
- **Perforation Detection Test** – The perforation fault was triggered when the test device was inserted into a representative tissue model with a perforation, and the device alerted the user that a possible perforation had been detected.
- **Liner Integrity Test** – When a leak was simulated in the test device, the leak was detected by the device during the liner integrity test.
- **Exhaust Tube Test** – The flexible portion of the exhaust tube was cycled 20 times without the exhaust tube fracturing or kinking. When compared to a commercially available uterine sounding tool, the exhaust tube test sample exhibited a lateral stiffness greater than that of the sounding tool over the same length.
- **Ultrasound Compatibility Test** – Movement of the distal end of the device was visible under ultrasound, when tested in a model representative of the clinical scenario in which the device is used.
- **Sheath Performance Test** – Testing was conducted to confirm the performance of the Sheath. The temperature of the sheath did not go below the specified temperature ( $\leq -10^{\circ}\text{C}$ ) when in contact with tissue in the test model. The Sheath did not move more than the specified distance ( $\leq 0.5\text{cm}$ ) when the specified force ( $3 \pm 0.5$  lbs.) was applied.
- **Valve Pressure Test** – The valve meets the applicable requirements from ISO 10297:2014, Gas Cylinder Valves – Specification and type testing. There was no evidence of leakage, deformation, or component damage following temperature cycling, fatigue testing, flow testing, and valve stem impact testing.
- **Maximum Liner Pressure Test** – The pressure relief valves prevent the pressure in the Liner from exceeding the specified maximum pressure (475 mmHg) at any time.
- **Cylinder Vent Test** – The manifold and cylinder subassemblies met specifications for venting (pressure reduced to  $\leq 15\text{psi}$  in  $\leq 12\text{min}$ ) the nitrous oxide cylinder following both full treatments and other scenarios.

- **Flow Rate Test** – The flow rate of the device was tested to verify that the mechanical limitations prevent delivery of more than the specified amount of nitrous oxide.
- **Manifold Pressurization Test** – The manifold (the component that experiences the forces generated by pressurized N<sub>2</sub>O) was tested to verify that it could withstand the specified excessive pressurization (1200 psi for 2.5 min).
- **Exhaust Collection Bag Functional Test** – The functionality of the exhaust collection bag was verified. Following pre-conditioning and simulated distribution testing, no visible damage was noted on the bag, the bag connected to the device and could be hung from an IV pole, and could be emptied in less than one minute following treatment. The N<sub>2</sub>O levels recorded during the treatment using the exhaust collection bag met the specified N<sub>2</sub>O exposure levels (< 25 ppm over 8 hours and < 125 ppm at any time).
- **Battery Life Test** – Battery life verification testing was conducted to demonstrate that the Cerene Cryotherapy Device is able to complete a full run through of a minimum of 1x battery test software cycle (for worst case time durations and maximum power consumption).
- **System Level Testing (Full Functional Test)** – The Cerene Cryotherapy Device underwent full functionality testing as part of distribution and accelerated aging testing, where devices in the final packaging configuration undergo the full manufacturing, packaging, and sterilization process, as well as temperature exposure, and, in the case of post-distribution functional testing, distribution simulation. The functional testing included an evaluation of the sheath functionality, battery pull tab feature, vacuum pressure pre-insertion, air inflation pressure pre-/post-deployment, pressure during N<sub>2</sub>O treatment, N<sub>2</sub>O usage (mass), peak N<sub>2</sub>O exposure level, treatment time, venting, and LCD screen visibility.

**E. Electrical Safety and Electromagnetic Compatibility (EMC/EMI + Basic Safety)**

The Cerene Cryotherapy Device complies with the following standards related to electrical safety and electromagnetic compatibility:

- IEC 60601-1:2005+A2012 Medical electrical equipment - Part 1: General Requirements for Basic Safety and Essential Performance
- IEC 60601-1-2:2014 Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Disturbances – Requirements and Tests

- IEC 60601-1-6:2010 Medical Electrical Equipment - Part 1-6: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Usability
- IEC 62366:2007 Medical Devices - Part 1: Application of Usability Engineering to Medical Devices

**F. Shelf Life**

Channel Medsystems has proposed a 6-month shelf-life for the Cerene Cryotherapy Device and the Exhaust Collection Bag accessory based on the results of an accelerated aging study. The accelerated aging study demonstrates that the Cerene Cryotherapy Device and the Exhaust Collection Bag maintain their functionality. Additionally, the study demonstrates that the packaging for the Cerene Cryotherapy Device maintains the sterility of the device for a shelf-life of six (6) months.

Channel Medsystems intends to verify the results of the accelerated aging study through a real-time aging study.

**G. Software Verification and Validation**

Channel Medsystems provided software information for the Cerene Cryotherapy Device in accordance with the FDA guidance document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” issued on May 11, 2005. In accordance with this guidance, the software used in the Cerene Cryotherapy Device has a major level of concern and the applicant provided documentation of appropriate controls and testing including:

- Level of Concern
- Software Description
- Device Hazard Analysis
- Software Requirements Specifications
- Architecture Design Chart
- Software Design Specification
- Traceability
- Software Development Environment Description
- Verification and Validation Documentation
- Revision Level History
- Unresolved Anomalies
- Run-Time Error Detection

**H. Extirpated Uteri Testing**

Channel Medsystems conducted extirpated uteri studies as part of the early development work on the Cerene Cryotherapy Device. A total of 22 extirpated uteri procedures were undertaken, with the first 12 procedures conducted to confirm the

device design. Testing was then conducted on 10 extirpated uteri using the final device configuration. The study evaluated the serosal temperature data during the treatment, histopathological analyses of the extirpated uteri, and device performance.

The device was found to operate safely in all 10 cases, with no serosal temperatures falling below the specified safe physiological temperature limit and no histopathological evidence of serosal injury. Ablation coverage was 99% overall, with 100% in the upper cavity, 98% in the lower cavity, 99% in the right cornu, and 98% in the left cornu. The maximum global maximum ablation depth was 7.3mm. No lower endocervical or exocervical ablation was noted. The closest distance of the ablation to the serosa was 8.1mm. The pathology-based criteria (e.g., no serosal thermal injury) for success were met.

Additionally, the device performed successfully in all 10 cases, as the device was inserted, deployed, conducted a complete procedure, and was withdrawn in all cases.

## **X. SUMMARY OF PRIMARY CLINICAL STUDIES**

Channel Medsystems performed four (4) clinical studies as follows:

- Peri-hysterectomy Studies (2)
- Feasibility Study
- Pivotal Clinical Study

### **1. Peri-hysterectomy Studies**

Channel Medsystems conducted two (2) peri-hysterectomy studies at one investigational site to evaluate the safety and the ablation parameters of the Cerene Cryotherapy Device. In these studies, women who were scheduled for an abdominal hysterectomy underwent endometrial ablation with the Cerene Cryotherapy Device just prior to hysterectomy. Inclusion and exclusion criteria matched those of the pivotal study protocol and most endometrial ablation studies. Study evaluations were measured by the collection of any serious adverse events, serosal temperature data during the treatment (if applicable), and post-treatment evaluation of any thermal injury to the serosa. Secondary evaluations were measured by histopathological analyses of the extirpated uteri.

The first study enrolled 10 women who underwent endometrial ablation prior to hysterectomy. This study measured the serosal surface temperature at six (6) locations on the uterus during the ablation. The device was found to operate safely in all 10 cases, with no serious device-related adverse events, no serosal temperature falling below 0 °C, and no histopathological evidence of serosal injury. Except for the ablation coverages in the right and left cornua, all pathology-based criteria for success (e.g., no serosal thermal injury) were met. Subsequent evaluation concluded that incorrect device placement attributed to suboptimal coverage in the cornual regions. Procedural changes were enacted in subsequent studies to improve and confirm device

placement.

The second study enrolled nine (9) women who underwent endometrial ablation. The device was found to operate safely in all nine (9) cases, with no serious device-related adverse events and no histopathological evidence of serosal injury. One ablation procedure was not completed due to a device malfunction during treatment (pressure sensor differential error), and that case was reported but excluded from the overall pathology analysis. For the included cavities, all pathology-based criteria for success were met.

Results from these studies show that the Cerene Cryotherapy Device performed as intended and had a safety profile that supported ongoing clinical use.

## **2. Feasibility Study**

Channel Medsystems conducted a prospective, single-arm, multi-center feasibility study at three (3) Canadian centers using a predecessor of the Cerene Cryotherapy Device (the Device for Endometrial Cryoablation [DEC]). The primary safety evaluation was based on adverse events reported during the study. The primary effectiveness evaluation was reduction in bleeding to a score of 75 or less on the Pictorial Blood Loss Assessment Chart (PBLAC) scale at 6 months post-treatment.

Forty (40) subjects underwent ablation treatments with the DEC. Thirty-seven (37) subjects completed 6 months of follow-up. The clinical protocol was amended and subjects were asked to continue their participation. Twenty-four (24) subjects consented to and completed additional follow-up visits at 9 and 12 months post-treatment. Inclusion and exclusion criteria closely followed those of other endometrial ablation studies, with the main exceptions being that subjects with larger cavities, some Type 2 fibroids, and irregular cycles were included in the study.

There were no unanticipated adverse device effects or serious adverse device events. At 6 months post-treatment, 75% of evaluable subjects (n=36) had a PBLAC score of  $\leq 75$ . For subjects who would meet the current criteria for treatment (i.e., eliminating those with fibroids and large uterine cavities) (n=26), 81% of subjects had a PBLAC score of  $\leq 75$  at 6 months post-treatment. At 12 months post-treatment, 71% of evaluable subjects (n=24) had a PBLAC score of  $\leq 75$ . For subjects who would meet the current criteria for treatment (n=18), 72% of subjects had a PBLAC score of  $\leq 75$  at 12 months post-treatment.

The results of this feasibility study provided initial support that endometrial ablation with the first iteration of the Cerene Cryotherapy Device was safe, well tolerated, and effective in reducing heavy menstrual bleeding, supporting the development of the next generation Cerene Cryotherapy Device and further clinical research.

### **3. Pivotal Clinical Trial (CLARITY Study)**

The applicant performed a pivotal clinical study to establish a reasonable assurance of safety and effectiveness of endometrial ablation with the Cerene Cryotherapy Device for its labeled indication, endometrial cryoablation in premenopausal women with heavy menstrual bleeding due to benign causes for whom childbearing is complete, in the United States. The study was conducted under IDE G160101. 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**

The study was an international, prospective, multi-center, single-arm, open label, non-randomized clinical study. The objective of the study was to evaluate the safety and effectiveness of the Cerene Cryotherapy Device in premenopausal women with heavy menstrual bleeding due to benign causes for whom childbearing was complete. There were 12 investigational sites that enrolled subjects and 11 that performed treatments, located in the United States, Mexico, and Canada. Treatments took place between June 2016 and March 2017.

Five hundred and fifty-four (554) subjects were enrolled in the study, with 242 proceeding to treatment and comprising the Intent-to-Treat (ITT) population. The primary safety and effectiveness outcomes were analyzed based on the ITT population.

During the first year after study treatment, each subject was evaluated at Day 1, Week 2, Month 3, Month 6, and Month 12. After the first year, subject follow-up is yearly at Month 24 and Month 36. The database reviewed for this PMA submission reflects data collected through Month 12 post-procedure.

The primary safety endpoint was incidence of serious adverse events and serious device-related adverse events at 12 months.

The primary effectiveness endpoint was reduction in menstrual bleeding at 12 months; success was defined as a PBLAC score of  $\leq 75$ . The PBLAC is a self-administered instrument that allows the subject to record the number of menstrual products she used during her menstrual period. A PBLAC score is calculated from the number, type, and saturation level of menstrual products recorded on the diary.

Additional evaluations included amenorrhea rate at Month 12, subject-reported peri-procedural pain experience, evaluation of dysmenorrhea at Month 12, Quality of Life outcomes at Month 3, 6, and 12 using the Menorrhagia Impact Questionnaire (MIQ) and the Premenstrual Symptoms Impact Survey (PMSIS™), evaluation of uterine access and healing at 12 months post-procedure, and additional medical or surgical interventions for continued heavy menstrual bleeding through Month 36.

The effectiveness of the Cerene Cryotherapy Device was compared to an FDA established objective performance criterion (OPC); and therefore, there was no active Control Group in the study. The OPC was developed by FDA with input from industry and members of the Obstetrics and Gynecology Devices Panel.

The OPC approach used data from the pivotal clinical trials of five (5) approved endometrial ablation systems. These five (5) studies were randomized, controlled trials that used the same active control (rollerball ablation) and had similar patient populations. The study sizes ranged from 260 patients to 322 patients with either a 1:1 randomization or a 2:1 (device:control) randomization scheme. The primary endpoint was reduction in menstrual blood loss as assessed by PBLAC. The inclusion criteria required a baseline PBLAC score of  $\geq 150$  (four (4) studies) or  $> 185$  (one study), and individual patient success was defined as a PBLAC score of  $\leq 75$  at 12 months post procedure. The ITT population consisted of all patients who presented on the day for either the endometrial ablation device or rollerball ablation. Patients with missing PBLAC scores at 12 months were treated as failures. A study was considered a success, if the proportion of successes in the Global Endometrial Ablation (GEA) group met a pre-specified non-inferiority margin compared to the proportion of success in the rollerball ablation control group.

Using a generalized linear mixed model with study as a random effect, the FDA determined that the average success rate across the five (5) GEA devices was 75.6% (65.6%, 83.5%) and 77.2% (66.5%, 85.2%) for the rollerball ablation control. The FDA performed additional analyses to evaluate the effect of baseline covariates on the primary endpoint, including (subject age above and below 40 years), baseline PBLAC score (over 150), uterine sound (6 to 12 centimeters), and presence of fibroids ( $<3$  cm). Using analysis of covariance methods, the FDA found that none of these baseline covariances had a significant impact on the study results. Based on this analysis, the FDA developed a minimum success rate for effectiveness known as an objective performance criterion (OPC). The OPC is 66% of patients achieving a PBLAC score of  $\leq 75$  based on the lower bound of the 95% confidence interval (CI) of the average success rate for the five (5) approved GEA devices.

#### 1. Clinical Inclusion and Exclusion Criteria

Enrollment in the CLARITY Clinical Study was limited to subjects who met the following inclusion criteria:

- Refractory heavy menstrual bleeding with no definable organic cause
- Female subject age 25 to 50 years, inclusive
- Endometrial cavity measurements within the following parameters:
  - Sounded length of uterine cavity (exocervix to fundus) no greater than 10 cm; AND

- Endometrial cavity length (internal os to fundus) must be between 2.5 and 6.5 cm, inclusive
- Myometrial thickness of at least 10 mm
- Menstrual blood loss with a PBLAC score of  $\geq 150$ , within 3 months of informed consent, for:
  - Two (2) baseline cycles; OR
  - One baseline cycle in a woman who has at least three (3) prior months documented failed medical therapy; or has a contraindication to medical therapy; or cannot tolerate medical therapy; and/or was offered and declined medical therapy
- Premenopausal confirmed by Follicle-stimulating hormone (FSH) measurement  $\leq 30$  IU/L when age is  $> 40$  years
- Agreed to use a reliable form of non-hormonal contraception following ablation treatment up to the 12-month follow-up visit unless the subject was using a hormonal birth control method, had been on said method for  $\geq 3$  months prior to informed consent, and agreed to remain on the same hormonal regimen up to the 12-month follow-up visit
- Provided written informed consent using a form that had been approved by the reviewing institutional review board/ethics committee (IRB/EC)
- Agreed to follow-up exams and data collection requirements
- Demonstrated an understanding of how to record menstrual blood loss using a menstrual pictogram
- Had predictable, cyclic menstrual cycles

Patients were not permitted to enroll in the CLARITY Clinical Study if they met any of the following exclusion criteria:

- Pregnant or has a desire to conceive
- Endometrial hyperplasia as confirmed by histology
- Active endometritis
- Active pelvic inflammatory disease
- Active sexually transmitted disease (STD)
- Presence of bacteremia, sepsis, or other active systemic infection
- Active infection of the genitals, vagina, cervix, or uterus
- Known/suspected abdominal, pelvic, or gynecological malignancy within the past 5 years
- Known clotting defects or bleeding disorders
- Abnormal cytology on human papillomavirus (HPV) testing not treated according to local standards
- Prior uterine surgery that interrupts the integrity of the uterine wall (e.g., transmural myomectomy or classical cesarean section)
- Previous low transverse cesarean section where the myometrial wall thickness at the thinnest section of the scar is less than 10 mm, measured by Saline Infused Sonohysterogram

- Previous endometrial ablation procedure
- Clinically significant adenomyosis indicated by subject complaints, imaging, or clinician’s judgment
- Presence of an implantable contraceptive device (e.g. Essure® or Adiana™)
- Currently on medications that could thin the myometrial muscle, such as long-term steroid use (except inhaler or nasal therapy for asthma)
- Currently on anticoagulants
- Abnormal or obstructed cavity, specifically:
  - Septate or bicornuate uterus or other congenital malformation of the uterine cavity
  - Polyps larger than 1cm (in largest dimension) or which are likely to be the cause of the subject’s heavy menstrual bleeding
  - Any submucosal myoma
  - Any myoma that distort(s) the endometrial cavity
  - Any myoma, polyp configuration, uterine position, and/or uterine anomaly that, in the opinion of the investigator,
    - obstructs or hinders treatment access to the endometrial cavity
    - prevents deployment of the device
    - and/or is contraindicated for use of the investigational device
- Currently using an intrauterine device (IUD), including Mirena™ device, and unwilling to remove the IUD
- Post-partum ≤ 6-months
- Considering participation in a research study of an investigational drug or device that would begin during the course of this investigational study
- Any general health or mental, or other situation or condition which, in the opinion of the Investigator, could represent an increased risk for the subject or impact the subject’s ability to comply with protocol requirements

## 2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at Day 1, Week 2, Month 3, Month 6, and Month 12 postoperatively. Month 24 and Month 36 data are currently being collected.

Preoperatively, each subject recorded her menstrual blood loss in a self-reported PBLAC diary. A baseline PBLAC score of  $\geq 150$  was required to qualify for treatment. Subjects also completed quality of life questionnaires (MIQ and PMSIS) at baseline.

Postoperatively, at each follow-up visit, the investigator reviewed the subject's current menstrual bleeding status (via collected monthly PBLAC diaries) and queried the subject for possible adverse events. The subject completed quality of life questionnaires (MIQ and PMSIS) at her Month 3, 6, and 12 follow-up visits. The Month 12 follow-up visit included a diagnostic hysteroscopy to evaluate the uterine cavity.

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

### 3. Clinical Endpoints

With regard to safety, the primary endpoint was incidence of adverse events. Channel Medsystems evaluated safety by determining the number and percentage of subjects who experienced one or more adverse events and the number of subjects who experienced one or more device- or procedure-related serious adverse events (SAEs).

With regard to effectiveness, the primary effectiveness endpoint was menstrual blood loss as assessed by the PBLAC method. An individual subject was considered a success if her PBLAC score was  $\leq 75$  at 12 months post-treatment. An individual subject was considered a failure if she did not meet success criteria.

With regard to success/failure criteria, to achieve study success, the lower bound of the 95% CI should exceed the 66% OPC developed by the FDA for subjects with a PBLAC score of  $\leq 75$  at 12 months.

The secondary evaluations included amenorrhea rate, subject-reported peri-procedural pain experience, evaluation of dysmenorrhea, Quality of Life outcomes using the MIQ and the PMSIS, evaluation of uterine access and healing, and additional medical or surgical interventions for continued heavy menstrual bleeding.

#### **B. Accountability of PMA Cohort**

At the time of database lock, of 242 subjects treated in the PMA study, 95% (230) were available for analysis at the 12-month post-operative visit. Table 1 below summarizes subject disposition.

**Table 1 – Subject Disposition at Month 12**

<b>Disposition Category</b>	<b>Safety N (%)</b>	<b>Effectiveness N (%)</b>
<b>ITT: Treated</b>	<b>242 (100%)</b>	<b>242 (100%)</b>
<b>Subjects not evaluable at Month 12</b>	<b>12 (5.0%)</b>	<b>12 (5%)</b>
Lost to follow-up	7 (2.9%)	7 (2.9%)
Secondary intervention for menstrual bleeding	4 (1.7%)	4 (1.7%)
Other: No menstrual diary	N/A	1 (0.4%)
Other: Safety evaluation not available	1 (0.4%)	N/A
<b>Subjects with a known Month 12 outcome</b>	<b>230 (95.0%)</b>	<b>230 (95.0%)</b>

**C. Study Population Demographics and Baseline Parameters**

The demographics of the ITT cohort are typical for an endometrial ablation study performed in the United States. Table 2 and Table 3 below provides the baseline demographic and gynecological history parameters.

One hundred and sixteen (116) subjects were 25-40 years old, and 126 patients were > 40 years old. The mean age of subjects at baseline was 40.1 years. An evaluation of these data confirmed the data could be pooled across sites and countries.

**Table 2 - Demographics and Gynecological History**

	<b>Patient number = 242</b>
<b>Age</b>	
Mean ± SD (median)	40.1 ± 5.1 (41.0)
Range (min, max)	(25, 50)
N Age 25-40	116 (47.9%)
N Age > 40	126 (52.1%)
<b>Ethnicity</b>	
Hispanic or Latino	42 (17.4%)
Not Hispanic or Latino	200 (82.6%)
<b>Race</b>	
White	190 (78.5%)
Black or African American	6 (2.5%)
Asian	0 (0.0%)
American Indian or Alaska Native	3 (1.2%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
Other	43 (17.8%)
<b>BMI, kg/m<sup>2</sup></b>	

	<b>Patient number = 242</b>
Mean ± SD (median)	29.8 ± 6.9 (28.5)
Range (min, max)	(16.7, 50.5)
<b>Gravida</b>	
Mean ± SD (median)	3.0 ± 1.5 (3.0)
Range (min, max)	(0, 8)
<b>Para</b>	
Mean ± SD (median)	2.4 ± 1.1 (2.0)
Range (min, max)	(0, 6)
<b>C-Section (Low Transverse)</b>	
Number of subjects with LTCS (%)	86 (35.5%)
Mean ± SD (median)	2.0 ± 0.8 (2.0)
Range (min, max)	(1, 4)
<b>Dysmenorrhea</b>	
No symptom	27 (11.2%)
Very Mild	16 (6.6%)
Mild	23 (9.5%)
Moderate	74 (30.6%)
Severe	69 (28.5%)
Very Severe	33 (13.6%)
<b>PBLAC Score at Baseline</b>	
Mean ± SD (median)	360.6 ± 332.1 (290.5)
Range (min, max)	(150.0, 4506.5)

**Table 3 - FSH Measurement**

<b>FSH (IU/L) (subjects &gt; 40 years of age at screening)</b>	<b>Patient number = 126</b>
Mean ± SD	7.8 ± 5.3
Median (min, max)	6.3 (0.2, 29.1)

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the ITT cohort of 242 subjects available for the 12 month evaluation. The key safety outcomes for this study are presented below in Table 4, which shows the number of device- or procedure-related adverse events and the number and percentage of subjects who experienced device- or procedure-related adverse events (one or more times) during the 12-month follow-up period.

There were no reported serious adverse device effects (SADEs) nor any reported serious adverse events (SAEs) that were procedure-related.

**Table 4 - Number of Related Adverse Events and Number and Percentage of Subjects with One or More Related Adverse Events by Time of Occurrence**

Adverse Event	Number of Events	Number and Percent of Subjects N=242			
		Day of Treatment	Day 1	Day 2 to Week 2	> Week 2 to Month 12
Emesis	1			1 (0.4%)	
Fever	1		1 (0.4%)		
Bacterial vaginosis	7			7 (2.9%)	
Endometritis	1			1 (0.4%)	
Vulvovaginitis	1				1 (0.4%)
Groin pain	1				1 (0.4%)
Presyncope	4	3* (1.2%)			
Urinary incontinence	2			2 (0.8%)	
Dyspareunia	1				1 (0.4%)
Menstrual cramps	2				2 (0.8%)
Pelvic pain	2				2 (0.8%)
Uterine cramps	8	4 (1.7%)	2 (0.8%)	1 (0.4%)	1 (0.4%)
Uterine tenderness	1				1 (0.4%)
Vaginal discharge	2			1 (0.4%)	1 (0.4%)
Hypertension	2	2 (0.8%)			

\*Subjects with more than one occurrence of same event are only counted once.

Three (3) subjects reported pregnancies, two (2) of which were uterine pregnancies and one of which was an ectopic pregnancy.

The first uterine pregnancy was reported one-year post-treatment and the subject subsequently chose to voluntarily withdraw from the study before her Month 12 follow-up visit. The second uterine pregnancy was reported 17 months post-treatment (following her Month 12 follow-up visit) and the subject subsequently chose to voluntarily withdraw from the study. Both events were recorded as adverse events not related to the study procedure or device.

The ectopic pregnancy was reported nine (9) months post-treatment. The subject contacted the site due to amenorrhea with a positive urine pregnancy test, vaginal spotting, and mild abdominal pain/cramps. Ultrasound confirmed the diagnosis of ectopic pregnancy. The subject underwent laparoscopic bilateral salpingectomy and was discharged on the same day. The subject has no further complaints and continues in the study. This event is recorded as not related to the device or procedure.

## 2. Primary Effectiveness Results

The analysis of effectiveness was based on the 242 evaluable patients (ITT cohort) at the Month 12 time point. Key effectiveness outcomes are presented in Table 5.

The observed success rate in the ITT population treated with the Cerene Cryotherapy Device is 76.9% (186/242) with a 95% CI of (70.9%, 81.9%). The lower bound of the 95% CI (70.9%) exceeds the objective performance goal of 66% success rate. The primary endpoint of effectiveness was met in the ITT population.

Table 5 below summarizes the effectiveness outcomes.

**Table 5 - Primary Endpoint Response Rate at Month 12\***

<b>Month 12 Response Rate</b>	<b>ITT analysis cohort (N=242)</b>
Number of successes (PBLAC $\leq$ 75)	186
Study success rate	76.9%

\*PBLAC outcomes represent the most recent menses within 8 weeks of the 12-month follow-up

## 3. Secondary Effectiveness Results

### **Need for Medical or Surgical Intervention**

Four (4) subjects (1.7%) had interventions for continued heavy menstrual bleeding and were exited from the study. Two (2) subjects (0.83%) elected to proceed to surgical treatment. One subject (0.41%) required medication for frequent, prolonged heavy menses. One subject (0.41%) resumed treatment with Lysteda and voluntarily withdrew at Month 3.

### **Pain Management and Peri-Procedural Pain Experience**

All treatments were performed under local anesthesia using paracervical or parametrial block (PCB) per standard of care. The investigator administered other medications to the subject, including IV sedation (including conscious sedation not requiring airway management by an anesthesiologist), oral and/or IV NSAIDs, oral anxiolytics, and narcotics per his/her discretion.

Table 6 presents the medications administered at the time of Cerene treatment. A subject is counted only once in each category, according to the highest level of medication administered. Subjects that received oral narcotics and/or anxiolytics or IV sedation may have also received an NSAID. NSAIDs at the time of treatment included ketorolac (208 subjects [86%]) and/or ibuprofen or other NSAID (64 subjects [26.4%]).

The analgesia regimen included PCB with oral narcotics and/or anxiolytics in the majority of subjects (167 subjects [69%]), PCB only in 20 subjects (8.3%), and PCB with NSAIDs in 48 subjects (19.8%). Intravenous sedation was used for seven (7) subjects (2.9%). Of the seven (7) subjects who received IV sedation, four (4) received combination fentanyl and midazolam (1.7%), one received combination fentanyl and propofol (0.4%), one (0.4%) received combination fentanyl, midazolam, and propofol, and one received fentanyl only (0.4%). No subject treated with the Cerene Device received general anesthesia and no subject required airway management by an anesthesiologist.

**Table 6 - Anesthesia and Pain Medications at Treatment (N=242)**

Anesthesia/Medications Used During Treatment	N	%
PCB only	20	8.3%
PCB with NSAIDs	48	19.8%
PCB with oral Narcotics and/or Anxiolytics	167	69.0%
PCB with IV Sedation*	7	2.9%
General Anesthesia	0	0%

\*Two (2) subjects received propofol but did not require airway management

Subjects tolerated the procedure well and reported low pain scores. Subjects may have received additional medication during recovery to manage discomfort.

At several points before, during, and after the procedure, each subject was asked to rank her pain experience, on a numeric rating scale of 0-10 with 0 designated as no pain and 10 designated as the worst pain. A rating of 1 to 3 is considered mild pain, 4 to 6 moderate pain, and 7 to 10 severe pain<sup>1</sup>.

Prior to the procedure, subjects were asked to rate their acceptable pain threshold on the scale of 0-10. For 223 subjects that rated their acceptable pain threshold, the median acceptable rating of pain was 6, a moderate level of pain.

Table 7 presents the subjects' pain scores during the Cerene treatment and at Day 1 post-treatment. Throughout the Cerene treatment, the median pain rating was 2 or less (mild). At Day 1, the median pain rating was 0. The pain ratings demonstrate that the Cerene treatment was well tolerated with mild discomfort.

**Table 7 - Subject Rating of Pain during Treatment and Day 1 Post Treatment**

<b>Time of Pain Rating during Treatment</b>	<b>N</b>	<b>Median (min, max)</b>
Before Device Insertion	241*	1.0 (0, 10)
After Device Insertion	240*	2.0 (0, 10)
After Liner Deployment (before endometrial ablation was initiated)	240*	1.0 (0, 10)
After 1 Minute of Ablation	240*	2.0 (0, 10)
End of Ablation	239*	1.0 (0, 10)
15-30 Minutes Post Procedure	242	2.0 (0, 10)
At Time of Discharge	242	2.0 (0, 8)
Day 1	241^	0.0 (0, 8)

\*Remaining subjects unable to provide pain score rating due to sedation

^One subject did not provide a pain score at her Day 1 visit

### **Quality of Life**

The Menorrhagia Impact Questionnaire (MIQ) was administered at baseline and follow-up to assess quality of life.

At Month 12, 95.7% of responding subjects (112 of 117) reported a meaningful improvement in blood loss, demonstrating a perceived improvement in quality of life.

The Premenstrual Symptoms Impact Survey (PMSIS) was administered at baseline and follow-up to assess the effect of treatment with the Cerene Cryotherapy Device on premenstrual symptoms.

Table 8 presents the combined PMSIS score at screening and Month 12. The tabulation demonstrates a reduction in the subjects' combined PMSIS score, from a mean Screening score of 53.8 to 16.9 at Month 12 (a 68.6% decrease). These scores indicate an improvement in premenstrual symptoms following treatment with the Cerene Cryotherapy Device.

**Table 8 - Combined PMSIS Score**

<b>Combined Score</b>	<b>Screening N=242</b>	<b>Month 12 N=230</b>
Mean ± SD	53.8 ± 22.3	16.9 ± 18.6
Median (min, max)	58.3 (0.0, 100.0)	8.3 (0.0, 79.2)

The subjects were queried on her experience of painful menstrual cramps (dysmenorrhea) at baseline and follow-up. At screening, over 40% of subjects reported dysmenorrhea as 'severe' or 'very severe' and at Month 12, 6% of subjects reported the same intensity of symptoms.

Table 9 presents the subjects' report of dysmenorrhea at screening and Month 12.

**Table 9 - Dysmenorrhea at Screening and Month 12**

Subject report of Dysmenorrhea	Screening N=242		Month 12 N=230	
	N	%	N	%
0-No symptom	27	11.2%	74	32.2%
1-Very Mild	16	6.6%	70	30.4%
2-Mild	23	9.5%	40	17.4%
3-Moderate	74	30.6%	33	14.3%
4-Severe	69	28.5%	10	4.3%
5-Very Severe	33	13.6%	3	1.3%
Missing	0	0%	0	0%

**Subject Satisfaction**

Of 214 subjects that reported their level of satisfaction, 192 (89.7%) were satisfied or very satisfied with their outcome following treatment with the Cerene Cryotherapy device.

Of 225 subjects that reported their level of recommendation to a friend/family, 213 subjects (94.7%) would definitely recommend or consider recommending the Cerene Cryotherapy Device procedure to a friend/family.

**Uterine Access and Intrauterine Adhesions**

The Month 12 follow-up assessment included a hysteroscopic evaluation of the uterine cavity to determine if physical access and the ability to systematically assess the post-ablation uterine cavity were preserved.

Of 230 available subjects, 223 (97%) underwent a hysteroscopy at Month 12. The remaining seven (7) subjects encountered scheduling conflicts or illness.

The uterine cavity was accessible in 220 subjects (98.7%) and was not accessible in three (3) subjects due to pain intolerance (2) and cervical stenosis (1). The uterine cavity could be fully visualized in 204 subjects (93%). The cavity was only partially visualized in the remaining 16 subjects due to: intrauterine adhesions (14), technical difficulties (1), and menstruation (1).

Table 10 presents the investigators' assessments of the uterine cavity. Based upon the hysteroscopic view, the investigator could biopsy anywhere within the cavity in 87.3% of subjects (178/204) and was satisfied that the endometrium could be visualized sufficiently to evaluate for pathologic change in 95.6% of subjects (195/204).

**Table 10 - Investigator Assessment of Cavity Findings**

Assessment (N=204)	Yes (%)
Would the Investigator be able to direct a biopsy anywhere within the uterine cavity?	178 (87.3%)
Overall, was the Investigator satisfied that he/she was able to adequately visualize the endometrium to evaluate the uterine cavity for pathologic change?	195 (95.6%)

**Additional Bleeding Outcomes at Month 12**

In addition to the primary success criterion of  $PBLAC \leq 75$ , analyses were also completed to evaluate amenorrhea ( $PBLAC=0$ )<sup>2</sup>. Table 11 below summarizes these outcomes.

**Table 11 - Amenorrhea Rates at Month 12**

Category; PBLAC Score	ITT analysis cohort (N=242) N (%)
Amenorrhea; 0	25 (10%)

PBLAC outcomes represent the most recent menses within 8 weeks of the 12-month follow-up.

4. Other Assessments at Subject Follow-Up Visits**Procedure Time**

Procedure time for each subject was determined by recording the time of device insertion and device removal. Treatment time is fixed at 2.5 minutes for each subject. Table 12 below shows average procedure and treatment times.

**Table 12 – Length of Cerene Procedure**

Length of Procedure in Minutes	N=242
Mean ± SD	6.9 ± 1.1
Median (min, max)	7.0 (4, 17)

**Subjects' Report of Their Last Menstrual Period**

Subjects were asked to describe their last menstrual period prior to the Month 12 follow-up visit. Over 90% of subjects reported that they no longer get their period or have a normal or lighter-than-normal period. Table 13 below presents subjects' reports of their last menstrual period.

**Table 13 - Subjects' Report of Last Menstrual Period**

Description of Last Menstrual Period	N=230
I no longer get my period	15 (6.5%)
My periods are lighter than normal	168 (73%)
My periods are normal	25 (10.9%)
I continue to have heavy periods	22 (9.6%)

**Return to Normal Activities**

At the Week 2 follow-up visit, the subject was queried about her return to normal activities. The mean length of time for the subject to return to her daily routine was 2 days.

Table 14 presents length of time to return to normal activities following the Cerene treatment.

**Table 14 - Return to Normal Activities**

Return to Normal Activities in days	N=242
Mean $\pm$ SD	2.0 $\pm$ 2.3
Median (min, max)	1.0 (0, 21)

At the Week 2 and Month 3 follow-up visit, the subject was queried whether the post-cryoablation watery discharge had stopped and the stop date. At Month 3, one subject did not respond to the question. Of the 241 subjects who responded, five (5) experienced no watery discharge, and one subject's watery discharge had not yet stopped by the Month 3 visit. For the remaining 235 subjects, on average, the watery discharge stopped within three (3) weeks.

Table 15 presents duration of water discharge reported at the Month 3 visit.

**Table 15 - Duration of Post Ablation Watery Discharge Reported at Month 3**

Duration of Post Ablation Watery Discharge in days	N=235*
Mean $\pm$ SD	20.7 $\pm$ 11.9
Median (min, max)	19.0 (1, 89)

5. 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 22 investigators and co-investigators who were directly involved in the treatment or evaluation of research subjects throughout the course of the study. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(2) of the Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Obstetrics and Gynecology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

In the CLARITY pivotal study, the observed success rate in the ITT population treated with the Cerene Cryotherapy Device is 76.9% (186/242) with a 95% CI of (70.9%, 81.9%). The lower bound of the 95% CI (70.9%) exceeds the objective performance goal of a 66% success rate. The primary endpoint of effectiveness was met in the ITT population.

### **B. Safety Conclusions**

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

The safety profile for the Cerene Cryotherapy Device is favorable based on the outcomes of the pivotal study. There were no serious device or procedure-related adverse events reported. Most of the adverse events occurred within two (2) weeks of the procedure and were resolved without clinical sequelae. The most common adverse events included uterine cramping, bacterial vaginosis, and presyncope (vasovagal) symptoms.

If a patient experiences a non-serious adverse event, it will most likely occur within the initial two (2) weeks of the procedure. Serious events are expected to be rare (i.e., occurring in less than 1% of patients). The most serious adverse events anticipated with any global endometrial ablation system (e.g., thermal injury to bowel and sepsis) would manifest within two (2) weeks of the procedure and would require aggressive management including possibly major surgery and/or intensive care.

### **C. Benefit-Risk Determination**

The probable benefits of the Cerene Cryotherapy Device are based on data collected in clinical studies conducted to support PMA approval as described above. The benefit of the Cerene Cryotherapy Device is a reduction in menstrual blood loss. At 12-months, 76.9% (186/242) of treated subjects met the study definition of success and experienced a reduction in menstrual blood loss from excessive to normal or less than normal. In addition, improvement in subjective quality of life scores and high patient satisfaction provide further evidence of probable benefit. Based on available clinical performance outcomes, the risks associated with the Cerene Cryotherapy Device are modest and similar to risks associated with approved global endometrial ablation systems.

Additional factors to be considered in determining probable risks and benefits for the Cerene Cryotherapy Device include: The clinical study demonstrated that treatment with the Cerene Cryotherapy Device does not necessarily require the use of IV sedation or general anesthesia and can be performed in an office setting. Following treatment with the Cerene Cryotherapy Device, it should be possible to adequately evaluate the endometrial cavity in most patients to diagnose and treat intrauterine conditions. In the Month 12 hysteroscopic evaluation, investigators reported that, in 95.6% of evaluable subjects, access and the ability to systematically assess the uterine cavity were preserved.

#### **1. Patient Perspectives**

Patient perspectives considered during the review included:

- Quality of Life (Menorrhagia Impact Questionnaire and Premenstrual Symptoms Impact Survey)
- Subject Satisfaction (level of satisfaction with their outcome following treatment and whether they would recommend the treatment to family/friends)

In conclusion, given the available information above, the data support that for ablation of the endometrial lining of the uterus in pre-menopausal women with heavy menstrual bleeding due to benign causes for whom childbearing is complete, the probable benefits of treatment with the Cerene Cryotherapy Device outweigh the probable risks.

### **D. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use and also support that the probable benefits outweigh the probable risks for the Cerene device.

Additionally, the applicant intends to obtain long-term (two- and three-year) safety and effectiveness data from subjects in the ITT cohort of the CLARITY Clinical Study

who received a complete ablation procedure, completed 24 and/or 36 month follow-up and have no major protocol deviations that would render the subject data unevaluable. The labeling for the Cerene Cryotherapy Device will be revised with this information when it becomes available.

The reported clinical outcomes from these studies and long-term follow-up plan are adequate for premarket approval.

### **XIII. CDRH DECISION**

CDRH issued an approval order on March 28, 2019. The final conditions of approval cited in the approval order are described below.

The applicant must complete a post-approval study (PAS) within two (2) years of approval. At least 85% of the current patient cohort must be followed out to 36 months post procedure. The applicant must provide the following data in PAS reports. A PAS Progress Report must be submitted every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA.

The purpose of the CLARITY Clinical Study is to provide long term safety and effectiveness data for the Cerene Cryotherapy Device. The CLARITY Clinical Study is a prospective, single-arm, non-randomized, multicenter, open label study conducted at nine (9) sites in the United States and three (3) sites outside the United States to evaluate the safety and effectiveness of the Cerene Cryotherapy Device. The study includes 242 pre-menopausal women with menorrhagia (excessive uterine bleeding) due to benign causes for whom childbearing is complete. The one-year outcome data from this study were reviewed during this PMA review. The two- and three-year outcomes from this study will be provided post-market and will consist of the following:

- Need for surgical or medical intervention to treat abnormal bleeding
- Subject self-report of pregnancy
- Contraception status (data to be collected at 3 years only)
- Menstrual status
- Gynecologic adverse events
- Quality of Life Questionnaire
- Patient Satisfaction

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

### **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

**XV. REFERENCES**

1. McCaffery, M. and A. Beebe (1993). Pain: Clinical Manual for Nursing Practice. Baltimore, V.V. Mosby Company.
2. Higham, J. M., P. M. O'Brien and R. W. Shaw (1990). "Assessment of menstrual blood loss using a pictorial chart." Br J Obstet Gynaecol **97**(8): 734-739.