

**SUMMARY OF SAFETY AND EFFECTIVENESS DATA:
Her Option™ Uterine Cryoblation Therapy™ System**

I. GENERAL INFORMATION

DEVICE GENERIC NAME: Thermal (Cryosurgical) Endometrial Ablation Device

DEVICE TRADE NAME: Her Option™ Uterine Cryoblation Therapy™ System

APPLICANT'S NAME AND ADDRESS: **CryoGen, Inc.**
11065 Sorrento Valley Court
San Diego, CA 92121

PREMARKET APPROVAL APPLICATION (PMA) NUMBER: P000032

DATE OF PANEL RECOMMENDATION: January 29, 2001

DATE OF NOTICE OF APPROVAL TO THE APPLICANT: April 20, 2001

II. INDICATIONS FOR USE

The **Her Option™ Uterine Cryoblation Therapy™** System is a closed-cycle cryosurgical device intended to ablate the endometrial lining of the uterus in premenopausal women with menorrhagia (excessive bleeding) due to benign causes for whom childbearing is complete.

III. CONTRAINDICATIONS

Use of the Her Option™ System is contraindicated for patients with the following conditions:

- ✓ A patient who is pregnant or who desires to become pregnant in the future. (Pregnancies following ablation can be dangerous for both mother and fetus.)
- ✓ A patient with a known or suspected endometrial carcinoma (uterine cancer) or premalignant change of the endometrium such as unresolved adenomatous hyperplasia.

- ✓ A patient with an active genital or urinary tract infection at the time of the procedure (e.g., cervicitis, vaginitis, endometritis, salpingitis or cystitis).
 - ✓ A patient with active pelvic inflammatory disease (PID).
 - ✓ A patient with an intrauterine device (IUD) currently in place.
 - ✓ A patient with any anatomic or pathologic condition in which weakness of the myometrium could exist, such as history of previous classical cesarean sections or transmural myomectomy.
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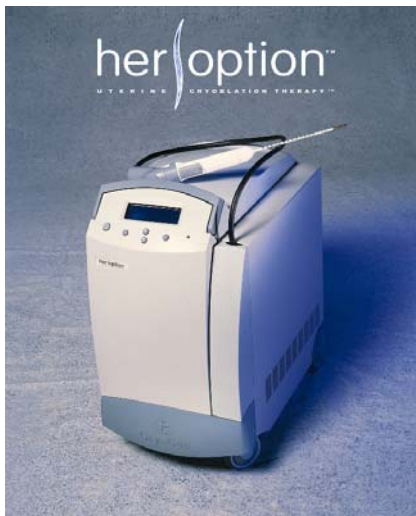
IV. WARNINGS AND PRECAUTIONS

A listing of Warnings and Precautions can be found in the device labeling.

V. DEVICE DESCRIPTION

The following includes a pictorial representation of the Her Option™ System and a brief description of the device including the functional components and the properties of the device relevant to the treatment of menorrhagia.

Figure 1 - Her Option™ Uterine Cryoblation Therapy™ System



Console



Cryoprobe and Disposable Control Unit

The Her Option™ System ablates tissue by the application of extreme cold. Its operation is based on the Joule-Thomson principle in which pressurized gas is expanded through a small orifice to produce cooling. Temperatures of -100 to -120 °C are developed at the tip producing an iceball. As this iceball grows, its leading edge advances through tissue. Tissue that comes into contact with the portion of the iceball that is ≤ -20 °C is destroyed.

The Her Option™ System consists of a console (consisting of the compressor system, user interface, and microprocessor), cryoprobe and single-use disposable Control Unit which covers the cryoprobe during use.

Console

The console contains the compressor system that, during operation, continuously circulates a pressurized gas mixture consisting of a mixture of common refrigerants during operation. The mixture is non-flammable, non-corrosive and non-toxic. The compressor system has an operating pressure of 350 to 400 psi. A pressure control feedback loop controls the stroke of the compressor and limits the pressure to less than 400 psi.

The controls and displays are mounted on the front panel of the console. There is an on/off button as well as other information for commands and user interface. The user interface will display the cycle, temperature, mode (heating or thawing) and total time in each mode.

Cryoprobe

The Cryoprobe consists of a handle and a probe shaft. Flexible plastic transport hoses connect the Cryoprobe to the compressor system housed within the Console. The Cryoprobe shaft is comprised of concentrically oriented stainless steel tubes and a metal tip. Two of the stainless steel tubes form the walls of the dewar. The dewar provides insulation to prevent freezing along its length by evacuation of the space between the outer and middle tubes to a pressure less than 1 microtorr. The remaining tubes deliver the high-pressure gas to the metal tip. Pressurized inflow gas is carried through the lumen of the innermost tube and the expanded effluent gas is returned through the annular space between the inner and middle tubes. The tip at the distal end of the shaft is the site of freezing.

Disposable Control Unit

The disposable Control Unit fits snugly over the cryoprobe. It is provided sterile, for single use only. A fuse located in the disposable CU prevents function of the system if re-use is attempted. The “Freeze” and “Heat” buttons are located on this CU. The portion of the CU which contacts the patient is fabricated from USP Class IV polymers. A metal tip at the distal end provides a conductive surface for efficient heat transfer. This tip contains the heater wire and thermocouple. The heater is used at the completion of a freeze cycle to ease removal of the tip from the iceball.

Active freezing is initiated by pressing the Freeze button on the CU. Freezing continues until the user presses the freeze button to pause freezing (freeze time will stop counting and resume when the user presses the freeze button again), presses the heat button to begin heating or until the safety time limit of 10 minutes is reached. The user presses the heat button to cease the freeze. The heater cycles automatically to maintain temperatures on the probe surface of 37° C until the user pushes the freeze button to start a second freeze cycle.

VI. ALTERNATE PRACTICES OR PROCEDURES

The following alternate practices and procedures are currently available to treat excessive uterine bleeding due to benign causes:

- **Drug Therapy**

Drug therapy using estrogen-progestogen combinations, (such as those found in oral contraceptives) or progestogens (progesterone) by themselves are most often employed for the treatment of menorrhagia. Other classes of drugs used include androgens such as danocrine, GnRH agonists, non-steroidal anti-inflammatory drugs (NSAIDs). Drug therapy is typically the first order treatment to alleviate menstrual symptoms. Drug therapies usually require long term treatment. They are successful for some patients but for others they are ineffective and often introduce unpleasant side effects. This treatment, however, does allow the woman to maintain her fertility.

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

D&C is typically the first surgical step if drug therapy is unsuccessful in eliminating excessive bleeding. The uterine contents are either scraped away by an instrument or removed through vacuum aspiration. This may reduce bleeding for a few cycles. If a polyp is present and removed, the bleeding may stop. In most cases, it does not provide the patient with long-term definitive results but it is useful for those women who desire to maintain their fertility. D&C is also useful as a diagnostic technique to rule out endometrial cancer.

- **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 inner lining of the uterus, the endometrium. The procedure is typically performed under general or epidural anesthesia. Dilation of the cervix must accommodate the hysteroscopic instrument, usually to a minimum of 9 mm and the uterus must be properly distended. The most common risks associated with hysteroscopic endometrial ablation are fluid overload, and perforation. This treatment is intended for women who no longer desire to maintain their fertility.

- **Thermal Balloon Ablation**

The ThermaChoice™ Uterine Balloon Therapy™ (UBT) System is a software controlled device designed to ablate endometrial tissue by thermal energy heating of sterile injectable fluid (5% dextrose in water) within a silicone balloon. The ThermaChoice™ UBT System consists of a controller with power cord, single-use sterile catheter, and umbilical cable. During the treatment, the fluid within the balloon is circulated via an impeller to maintain a temperature of 87°C for a period of 8 minutes. This treatment is intended for women who no longer desire to maintain their fertility.

- **Hysteroscopic Thermal Ablation**

The Hydro ThermAblator® is a software-controlled, hysteroscopic, thermal endometrial ablation system that consists of an operational unit, a heater canister, and a sterile procedural set. The procedure set consists of a sterile patient sheath assembly, a sterile cassette, a fluid level measurement reservoir, and a fluid collection bag. The system also requires the use of USP 0.9% saline, a standard hysteroscope, and a cervical-sealing tenaculum. The system is designed to ablate the endometrial lining of the uterus by heating saline to a temperature of 90°C, by means of a heating element located in the external heater canister, and by recirculating this heated fluid through the uterus for a period of 10 minutes. The system includes various alarms and sensors to monitor the safe and effective delivery of the treatment therapy. This treatment is intended for women who no longer desire to maintain their fertility.

- **Hysterectomy**

The most common surgical procedure, hysterectomy, is a definitive treatment for excessive menstrual bleeding. It is, however, a major surgical procedure performed in the hospital under general anesthesia that is associated with risks and complications and generally a lengthy recovery period.

VII. MARKETING HISTORY

The Her Option™ System has been marketed under a 510(k), K972662, since May of 1999 for use as a general cryosurgical tool. This device is currently available in Canada. The Her Option™ System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The Her Option™ device was evaluated in a randomized, prospective, multi-center clinical study, comparing the Her Option™ (Cryo) to a control arm of rollerball endometrial ablation (REA). There were no reported incidents of serious device-related

adverse events in the cryoblation group. Tables 1a - c summarize the adverse events for the 272 patients treated in this study:

Table 1a - Adverse Events During Procedure and within 24 hours Post-Procedure

Adverse Event	Cryo n=186	REA n=86
Uterine cramping	15 (8%)	4 (5%)
Other abdominal or pelvic pain/cramping	27 (15%)	10 (12%)
Nausea and vomiting	4 (2%)	4 (5%)
Hot flashes	2 (1%)	0 (0%)
Hyponatremia/Fluid Overload	0 (0%)	3 (3%)
Perforation*	1 (.5%)	1 (1%)
Cervical/vaginal laceration	0 (0%)	1 (1%)

*Cryo perforation occurred during sounding prior to treatment. REA perforation occurred during treatment.

Table 1b - Adverse Events at 2 week Post-Procedure

Adverse Event	Cryo n=186	REA n=86
Uterine cramping	5 (3%)	0 (0%)
Other abdominal or pelvic pain/cramping	7 (4%)	8 (9%)
Urinary tract infection (UTI)	5 (3%)	3 (3%)
Hot flashes	6 (3%)	3 (3%)
Vaginal infection	2 (1%)	1 (1%)
Nausea/vomiting	2 (1%)	2 (2%)

Table 1c - Adverse Events at 3, 6, and 12 months Post-Procedure*

Adverse Event	Cryo n=186	REA n=86
Uterine cramping	7 (4%)	5 (6%)
Other abdominal or pelvic pain/cramping	26 (14%)	16 (19%)
Vaginal infection	7 (4%)	1 (1%)
Hot flashes	3 (2%)	7 (8%)
Urinary tract infection	2 (1%)	3 (3%)
Nausea/vomiting	1 (1%)	1 (1%)

Below is a more detailed description of the Adverse Events reported above:

- **Pelvic Pain/Cramping** – Peri-operative cramping typically lasted a few hours and rarely continued beyond the first day following ablation. Some of the mild cramping was reported as resolved without medication. The use of non-steroidal anti-

inflammatory drugs (NSAIDs) was reported to typically manage the cramping and pain.

- **Nausea and Vomiting** – Nausea and vomiting were managed with medication.
- **Bladder Infection/Vaginal Infection** – The infections were managed with oral antibiotics.
- **Other Events** – Other Adverse Events reported which occurred in no greater than 1% of the patients treated with Her Option™ include: severe bleeding (more than 2 weeks following the procedure); difficulty recovering from anesthesia and pregnancy (1 patient).

Other Potential Adverse Effects

The following adverse effects might be expected (potential), but have not yet been observed in the ongoing clinical study of the **Her Option™** System:

- Endometritis
- Difficulty with defecation or micturition
- Hematometra
- Hemorrhage
- Thermal injury to adjacent tissue
- Post-ablation tubal sterilization syndrome

IX. SUMMARY OF PRECLINICAL STUDIES

A. PERFORMANCE TESTING - DESIGN VERIFICATION

- 1) Clinical Evaluation Build Test – Six (6) lots of sterile Control Units were manufactured to evaluate test results to stated acceptance criteria. All lots were built according to approved documentation and sterilized per internal procedures. Testing of sterile Build #1 (3 lots) indicated a few minor issues that did not affect the safety of the device. Testing of sterile Build #2 (1 lot) indicated minor issues that did not affect the safety of the device. Testing of Build #3 (1 lot) also indicated minor issues, which did not affect the safety of the device. Testing of Build #4 (1 lot) demonstrated product that passed all visual and functional requirements. All lots were found acceptable with minor miscellaneous issues. All issues have been addressed and corrected.
- 2) CryoProbe Flow Test – Cryoprobes (cryostat, dewar, flexline) were subjected to flow testing to verify that the mechanical design of the units permit adequate mixed gas flow such that the probe is capable of cooling to the required temperature while producing sufficient refrigeration. Test results show that the system achieves the specified operating temperatures in the required time.
- 3) Cryosurgical System Cycle Testing – Preliminary cycle testing was completed to evaluate the continuity and consistency of the performance of the system. A total of 30 runs, 10 per day for 3 consecutive days were conducted. Each run included 5

- minutes of cooling and a 5 minute thaw cycle. Test results indicated that the clinical configuration of the system met preliminary cycle and reliability performance criteria.
- 4) Gelatin Ice Ball Test – Gelatin is commonly used to provide a reproducible heat load for testing of cryosurgical systems. This test was done to determine the temperature distribution within gelatin. With and without the disposable Control Unit in place, the cryoprobe achieved temperature specifications within 5 minutes. Both the temperatures achieved and the ice ball sizes meet specifications.
 - 5) Design Verification: Revised Cryoprobe Handle and Control Unit - This test protocol included the design verification for the revised Cryoprobe Handle and Control Unit (CU). Electrical and mechanical testing was repeatedly performed using 10 different CU's and a prototype Cryoprobe with two different handle sets. Test results indicated that the revised handle and CU passed verification testing.
 - 6) Cryoprobe Gas Mixture Verification - The purpose of this test was to verify the performance of the cryoprobe design and identify the optimal gas mixture. The following parameters were examined: cool down rate; surface temperature; and the size of the gelatin ice ball at specified freeze times.
 - 7) Thermal Grease Application Characterization Test - The purpose of this test was to verify the grease applicators and application method for attaching a disposable to the cryosurgical system. The grease helps eliminate the air gaps between the inner surface of the Control Unit and the outer surface of the cryoprobe tip. This grease also serves as a heat transfer medium. It was noted that there is a large temperature variation along the tip; however, the temperature specification is met in at least one location along the tip and the specification for ice ball diameter is met. The manufacturer concludes that the observed variation in tip temperatures may be due to variations in the thermal grease applications and the large gap at the end between the Control Unit and the cryoprobe. To help improve the temperature profile along the tip, the method for grease application has been improved.
 - 8) Charge Pressure Characterization Test - The purpose was to establish the optimal working pressure that will increase the performance of the cryosurgical system. During this test it was noted that there was poor heat transfer at the very end of the cold tip and that multiple cycles conducted at each set pressure yielded decays in performance. These deficiencies were attributed to thermal grease application and to system plugging due to moisture contamination. Further changes to the gas mixture are described below in CG-1 Gas Mixture Verification.
 - 9) CG-1 Gas Mixture Verification – Testing was performed to assess performance of the System with a modified gas mixture to determine if the new gas mixture meets performance criteria. Results demonstrated that the modified gas mixture is optimized to allow ongoing system reliability and maintenance of desired tip temperatures and heat transfer rate performance.
 - 10) Flex Line Testing – Flex Line assemblies, which provide a flexible pathway for the gas mixture and precooling fluid to flow from the compressor to the cryoprobe, were assessed for mechanical integrity at 1 ½ times the normal working pressure and colder than normal temperatures. There were no failures.
 - 11) Dewar Burst Test – Dewars were stressed to assess the dewar wall strength. Results indicate that all components of the dewar exceed the stress values even at 8 times the compressors maximum operational pressure.

- 12) Dewar Thermal Insulation Test – Testing was done to verify that the Dewar meets the thermal insulation requirement during normal operating conditions. Results indicate that the Dewar provides sufficient thermal insulation along the shaft and handle of the cryoprobe.
- 13) Control Unit Verification – Testing was completed on 15 samples to ensure that the design of the CryoGen Control Unit met specifications with regard to function and mechanical integrity. Tests included in the protocol include but are not limited to: Bond Strength, Bond Integrity, Leak Test, Pressure/Flow Relationship and Abrasion Test. All testing performed met the acceptance criteria outlined in the protocol.
- 14) Cryoprobe Thermal Switch Operational Test – This test was designed to ensure that the thermal switch operates per CryoGen specifications to prevent excess heating. The thermal switch activated according to specifications for a 100% success rate.
- 15) GMC and PCC High Pressure Verification – Testing was done to verify that the GMC and PCC operate within the specified high pressure limits and to verify that the maximum pressure of the system is below the specified safety pressure. The compressor unit was able to maintain an operational high pressure below the system maximum operational pressure.

B. PERFORMANCE TESTING - ELECTROMAGNETIC COMPABILITY

Electromagnetic Compatibility (EMC) testing was performed in accordance with IEC 60601-1-2 by an accredited independent test house for: 1) Electrostatic Discharge (ESD), 2) Radiated Electromagnetic Fields, 3) Fast Transients (Burst), 4) Surge Transients, 5) Conducted Disturbance, 6) RF Frequency Magnetic Fields, and 7) Voltage Dips, Interruptions & Variations. The unit successfully passed all testing.

C. PERFORMANCE TESTING - ELECTRICAL SAFETY

Electrical safety testing was performed in accordance with IEC 60601-1 by an accredited independent test house for: 1) Chassis Current Leakage, and 2) Ground Resistance. The unit successfully passed all testing.

D. SOFTWARE VALIDATION

In accordance with the definitions set forth in the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 28, 1998, the software represents a “moderate” concern. The software primarily controls the display of the various treatment delivery parameters. The software validation is conducted according to internal procedures. It addresses the following items:

- ❖ Device hazard analysis and Failure Modes Effects and Criticality Analysis (FMECA)
- ❖ Software requirements documents
- ❖ Software validation traceability analysis
- ❖ Software test protocols and validation procedures

The software contained in the Her Option™ System should function safely and effectively per the specified software requirements.

E. MATERIAL SAFETY (TOXICOLOGY)

The Disposable Control Unit (CU) is the only device component that contacts the patient. The materials of the CU were evaluated for their safety and sterility.

1) Biocompatibility/Toxicity Testing

Biocompatibility testing was conducted on the sterilized Control Unit assembly to provide assurance that the materials were safe for use in a medical device. The testing was conducted in accordance with ISO 10993. All testing was performed in accordance with Good Laboratory Practices (GLP).

Components of the Control Unit passed the following biocompatibility testing: Cytotoxicity using ISO Elution Method, ISO sensitization in the Guinea Pig, Acute Systemic Toxicity in the Mouse, Vaginal Irritation Study in the Rabbit Pyrogen Study, Hemolysis Study – *in vitro* – (extraction method), C3a Complement Activation Assay, Coagulation – Plasma Recalcification Time. In addition, the following tests were conducted on the fluid path: Cytotoxicity using ISO Elution Method, Hemolysis – *in vitro* – (extraction method).

2) Sterility

The CryoGen disposable Control Unit is gamma sterilized according to AAMI Guidelines. The sterility assurance level is 10^{-6} . LAL and pyrogen testing in completed on each manufacturing lot prior to final release. A 2-year shelf-life for the CU has been demonstrated through both accelerated and real time aging.

X. ANIMAL STUDIES

A. *Ex Vivo* Beef Liver Study

Bench testing in tissue was completed to verify the performance specifications of the System. The tests included verification of CryoZone temperature gradients in beef liver warmed to 37 °C following a 10-minute freeze cycle. A multi-probe thermocouple array with 3mm spacing between each probe was utilized to confirm the isothermal gradients within the frozen tissue. Ten minute freeze cycles in the beef liver produced similar sized CryoZones as the earlier tests in gelatin.

B. Goat Study

In a second study, the medial and lateral lobes of the liver of an anesthetized goat were frozen with a double freeze for a total of 10 minutes. Five minutes of thawing took place between each freeze. The heater on the probe was activated at full power until the thermocouple for the surface temperature reach 0 °C. The size of the CryoZone was measured using calipers. The results of the goat study were comparable to both the tests in gelatin and beef liver.

XI. EXTIRPATED UTERI STUDY

Pre-clinical testing of the Her Option™ System was completed in extirpated uteri. The objective of the study was to examine the thermophysical and histologic characteristics of tissue freezing in freshly harvested extirpated human uteri. The study findings were to be used to assist in the definition of a protocol for later clinical studies. Determinations were made of the maximum growth of the iceball, CryoZone, following 10 – 15 minutes of maximum total freeze duration. Eight uterine specimens were obtained. All uteri were parous. Five of them had fibroid disease and three contained submucous fibroids. The uterine specimens were subjected to either a single midline freeze, two midline freezes or two angled freezes. Average freeze times per cycle were 6 minutes. The average CryoZone diameter for the 2 angled freezes was 42.3 mm at the fundus, with the amount of injury lagging behind by 3-5 mm. This diameter was larger in comparison to the midline freeze group by 9.2 mm. In specimens with similar uterine width measurements, tissue at the cornu was destroyed in the angled freeze group but not in the midline freeze groups. There was no added advantage to the double midline freeze. The presence of fibroids did not significantly alter these findings. The study showed that the probe could be used to freeze a uterine cavity with a depth of 5 cm without injuring the cervical canal.

When examining the treated specimens histologically, it was noted that the specimen subjected to a single midline freeze did not show any gross visual differences in stain distribution on non-viable tissue within the cavity when compared to those subjected to a double midline freeze. The two angled freezes maximized the tissue destruction in the transverse (lateral) direction while maintaining a diameter similar to the single freeze in the anterior/posterior dimension which is the dimension with the smaller safety margin or the thinnest total dimension of the uterus.

The CryoZone was noted to grow both incrementally and symmetrically. There was no evidence by palpation, ultrasound visualization or direct visualization of penetration of the CryoZone through the serosal surface. Ultrasound demonstrated clear visualization of the hyperechoic CryoZone and post acoustic shadowing. It was concluded that the depth of thermal injury following cryoablation was sufficient to produce thermal necrosis without risking injury to surrounding tissue. The pre-hysterectomy study was planned with the two angled freezes to provide maximum endometrial coverage during treatment.

XII. SUMMARY OF CLINICAL STUDIES

A. FEASIBILITY CLINICAL STUDY

CryoGen conducted a pre-hysterectomy safety study to support IDE G970302. The purpose of this study was to evaluate the extent of myometrial freeze and subsequent tissue destruction during cryoablation of the endometrium. This was evaluated grossly using ultrasound, as well as histologically using tetrazolium red staining and Electron Microscopy.

Both abdominal and laparoscopically assisted vaginal hysterectomy (LAVH) procedures were included in this study. The abdominal procedures allowed for serosal temperature monitoring to provide evidence that there is minimal danger of freezing surrounding organ structures during endometrial cryoablation and the LAVH procedures allowed for ultrasound visualization.

Two angled freezes, one toward each cornu, were performed on 10 uteri, with complete data available for 8 specimens. The freeze cycle times ranged from 3-6 minutes. A summary table is provided below:

Table 2 – Pre-Hysterectomy Study Summary

Patient #	Uterine Size (gms)	Uterine Sound (cm)	Freeze time Cycle 1 (min)	Iceball diameter Cycle 1 (mm)	Freeze time Cycle 2 (min)	Iceball diameter Cycle 2 (mm)	Max. Diam. Of Thermal Injury (mm)
201	119	8	6	34.0	6	28.0	22
104	140	ND	6	25.8	6	34.0	25
202	121	8	5	26.0	5	ND	21
103	137	8.5	4	27.0	6	35.0	25
102	605	10	6	30.5	6	34.1	ND
203	365	ND	4	29.0	6	37.0	30
204	1459	14	4	27.0	6	31.0	23
205	383	8	3	39.0	3	24.0	28
105	130	ND	4	24.0	6	29.8	25
106	174	9.5	4	24.3	6	38.0	25

**ND denotes those measurements not determined*

The results from the extirpated uteri study suggested that 2 angled freezes provided adequate lateral coverage and depth of tissue ablation, while providing an acceptable safety margin in the A/P dimension. Thus, the initial patients in the pre-hysterectomy study were treated with two angled 6 minute freezes. The histology from patients 201 and 104 suggested that the cryosurgery probe was not reaching the opposite cornu during the second freeze cycle. Probe placement to the opposite cornu prior to the second freeze had been difficult in these patients due to the larger size of the CryoZone from the first freeze.

A shorter 5 minute first and second freeze were attempted on patient 102 where better ablation was achieved, however one side of the uterine cavity was still incompletely ablated. A 4 minute first freeze was performed on patient 103 with more favorable depth and coverage of tissue ablation. Patient 104 was treated with 2 six minute freezes in an attempt to determine whether instillation of 20 cc of saline into the cavity between freezes would facilitate probe placement to the opposite cornu for the second freeze. As demonstrated by histology, one cornu was not entirely covered.

Based on the histology from these patients (201, 104, 102, and 103) the remainder of the patients were treated with 2 freezes, the first was 4 minutes and the second was 6 minutes. Instillation of 20 cc saline between freezes was also added to the protocol to facilitate melting of the CryoZone and repositioning of the probe to the opposite cornu. The only exception was patient 205 where the distance from the outer edge of the CryoZone as imaged on ultrasound was only 3 mm from the serosal surface and subsequently the freeze time was shortened to 3 minutes for both freezes.

This study demonstrated the safety of the device in vivo, while providing the opportunity to refine the cryoablation technique. The data confirmed that the CryoZone grows incrementally and uniformly. The growth of the ice front can be visualized and monitored via ultrasound. The serosal temperature measurements suggest that the risk of freezing into adjacent organs is very low.

B. UNITED STATES MULTI-CENTER CLINICAL INVESTIGATION

A Phase III trial of the Her Option™ System was undertaken after successful completion of the preclinical testing, animal studies and the pre-hysterectomy study. This trial was designed as a multi-center, randomized, concurrently-controlled evaluation of the Her Option™ System for the treatment of women with menorrhagia.

◆ Study Objectives

The primary study objective was to evaluate the safety and effectiveness of the CryoGen Her Option™ System as compared to hysteroscopic rollerball ablation in the elimination or reduction of excessive uterine bleeding from benign causes in women who no longer wished to bear children. Additional objectives included the identification of complications or adverse effects that may occur in using the CryoGen Her Option™ System.

◆ Study Hypothesis

The study hypothesis proposed a statistical difference of less than 20% in patient success rates between the CryoGen Her Option™ System and the control procedure of hysteroscopic rollerball ablation in treating excessive uterine bleeding.

◆ Study Design

The study was designed as a 2:1 randomized, prospective, multi-center clinical investigation to evaluate a minimum of 222 women with excessive uterine bleeding at a total of 10 sites. The primary study endpoint was uterine bleeding at 12 months with a score of ≤ 75 as documented by the validated menstrual diary scoring system developed by Higham (Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *British Journal of Obstetrics and Gynecology*, 1990;97:734-9)).

◆ Study Procedure Methods

Patient bleeding, the primary study endpoint, was documented by the subject in menstrual diaries and scored by the clinical investigator or his/her designee to determine amount of blood loss before and after treatment. The blood loss was scored using the validated scoring system. All patients were instructed to maintain menstrual diaries for 12-months post-procedure. All complications and adverse events were documented and reported. Protocol deviations and failures of the device to meet minimum performance criteria were also recorded. Quality of Life Questionnaires were completed prior to treatment and at 6 and 12 months post-treatment. As part of the study approval, questionnaires are to be completed at 24 and 36 month's post-procedure as well.

Following determination of patient eligibility and obtaining Informed Consent, each women was stratified by age (≤ 40 or > 40 years of age) and randomized into either the cryoablation treatment group or the control group of rollerball ablation with a 2:1 ratio. Patients were subjected to the following inclusion/exclusion criteria:

Inclusion Criteria:

- Pre-menopausal female, between 30 and 50 years of age, and in good general health, for example able to tolerate procedure and anesthesia
- Documented history of excessive uterine bleeding for a minimum of 3 months pre-procedure with failed traditional medical therapy, such as birth control pills, non-steroidal anti-inflammatories (NSAIDs), failed D&C within 6 months or Depo-Provera and has a completed pictorial blood assessment chart (PBAC) menstrual diary score > 150 recorded for at least one menstrual cycle
- Patients with a pre-op PBAC score of ≥ 150 who refuse hormonal treatment, NSAIDs medications or D&C may be included if they demonstrate a PBAC score > 150 for 3 consecutive months
- Patient agrees to follow-up exams and data collection
- Patient signed the Informed Consent
- Uterine cavity sound measurement ≤ 10 cm

- Uterine volumetric measurement ≤ 300 cc
- Patient does not desire to maintain fertility

Exclusion Criteria:

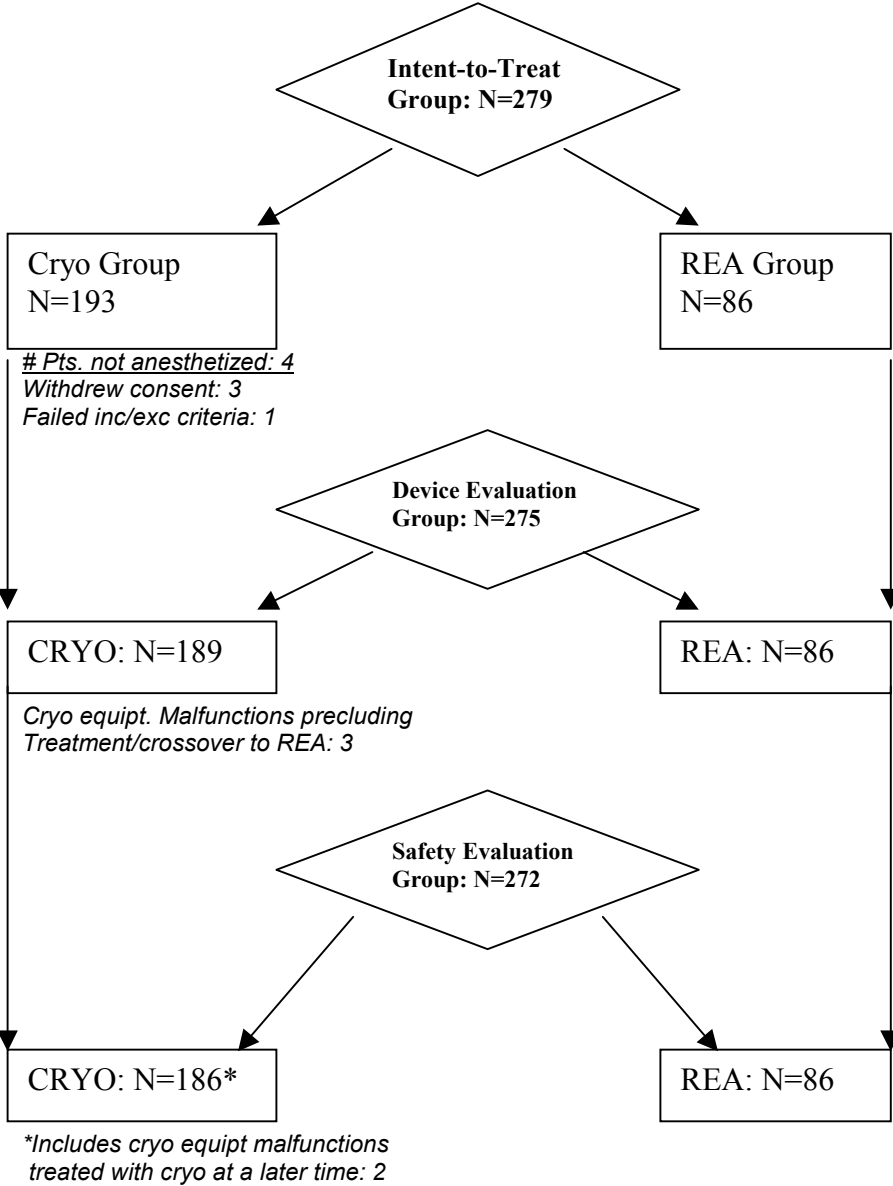
- Clotting defects or bleeding disorders
- Active pelvic inflammatory disease
- Abnormal pap smear within the previous year, unless appropriately evaluated
- History of gynecologic malignancy within the past 5 years
- Intramural myomas >2 cm diameter
- Intrauterine polyps
- Pedunculated fibroids
- Septate uterus
- Previous endometrial ablation procedure or previous uterine surgeries in which thinning of the uterine musculature occurs
- Malignant pathology or hyperplasia within the previous 6 months, as documented by endometrial biopsy
- Pregnancy

◆ **Study Period and Population**

The first patient was treated in May 1998 at Columbia Rose Medical Center in Denver, Colorado. All patients were treated by November 30, 1999. One year follow-up on all enrolled patients was completed.

A total of 279 women were randomly enrolled in the study in a 2:1 ratio (193 Cryoablation, 86 Rollerball).

Patient flow diagram:



◆ **Demographics and Gynecological History**

Pre-procedure baseline demographics and gynecological history are summarized in Table 3.

Table 3 – PRETREATMENT DEMOGRAPHICS

Demographic Characteristics	Cryo	REA	p*
Age (years)	41.2 ± 5.1	41.1 ± 4.8	0.8278
Body Mass Index	29.3 ± 8.4	28.6 ± 6.7	0.7777
PBAC Diary Scores (average)	570 ± 441	474 ± 374	0.0223
PBAC Diary Scores (median)	453	356.5	0.0106
Gravidity	3.2 ± 1.6	3.2 ± 1.9	0.4763
Parity	2.5 ± 1.2	2.2 ± 1.3	0.1119
Full-term Deliveries	2.4 ± 1.2	2.2 ± 1.4	0.2416
Previous Cesarean Section	30.2%	25.6%	0.437
Previous D & C	36.5%	47.7%	0.080
Previous Tubal Ligation	54.5%	48.8%	0.383
Presence of Fibroids/Myomas	20.1%	25.6%	0.308
Cavity Sounding Length (cm)	8.0 ± 1.1	7.9 ± 1.1	0.3517
Severe Menstrual Pain and Cramping ^ϕ	47.4%	43.8%	0.585
Severe PMS Symptoms ^ϕ	36.2%	32.5%	0.565
Medication Therapy for Menorrhagia	86.2%	86.1%	1.0000
Hematocrit (%)	38.3 ± 4.2	38.3 ± 3.7	0.7911
FSH (IU/L)	6.7 ± 7.0	8.0 ± 9.0	0.3697

* *Wilcoxon 2-sample test for continuous variables; Fisher Exact test for discrete variables*

In analyzing the demographic and gynecological history variables, it was determined that the baseline variables are equivalent between both the treatment and control groups, except for the baseline PBAC or diary scores. There is a

statistically significant difference in baseline PBAC scores when comparing the cryoablation group to the rollerball group. The effect of the higher pre-operative baseline PBAC scores on outcome is unknown.

◆ **Device Procedural Incidents**

A total of 305 sterile Control Units were shipped for use during the multi-center clinical study, 221 were returned used and 84 were returned unused and unopened. Eleven (11) consoles were used during the study. User feedback on the system was tracked, including device malfunctions and user errors. The malfunctions reported were related primarily to reliability and did not compromise patient safety. The following table summarizes the device malfunctions reported during the study:

Table 4 – Device Reports

Number of patients in Device Evaluation Group	N=189
Total number of Device Malfunctions	N= 49(25.9%)
Resolvable device issues*	13
Disposable Control Unit attachment/detachment	5
Console malfunction – plugging of System and device not meeting target temperatures	31

**Resolvable device issues refers to those device malfunctions that did not preclude completing treatment. Examples include excess thermal conductive media on tip of probe and low level system plugging.*

Of those 49 reported device malfunctions, 5 (3%) resulted in acute treatment failure. In two (2) patients there were system malfunctions that delayed treatment and in three (3) patients the treatment could not be initiated and the patients were treated with REA.

Where appropriate, corrective actions were implemented to address the reliability issues. A post-market study is underway to verify that the corrections made to the latest generation Her Option™ System have addressed the reliability issues reported during the multi-center clinical study.

◆ **Anesthesia**

The clinical protocol did not specify the type of anesthesia to be used for either treatment group. This decision was left to the discretion of the physician and anesthesiologist. General anesthesia was administered to 92% (79/86) of the REA patients and 46% (85/186) of the Cryo patients. In the Cryo group, 39% (72/186) of the patients received a paracervical block with conscious sedation as compared to 1% (1/86) of the REA group.

◆ **Efficacy at One Year: Diary Scores**

Patient success was based on a reduction in diary score from ≥ 150 pre-treatment to ≤ 75 at one year. Effectiveness rates are based on the intent-to-treat population.

Table 5 – Effectiveness*: Diary Scores at 1 year

	CRYO n=193	REA n=86
Number of successful patients (diary score ≤ 75)	130	63
Study success rate (% patients with diary score ≤ 75)	67.4%	73.3%
Number of patients with amenorrhea (diary score = 0)	43	40
Amenorrhea rate (% patients with diary score = 0)	22.2%	46.5%

**Fifteen (15) Cryo patients and 9 REA patients were lost to follow-up. All of these patients were considered treatment failures in calculating the intent-to-treat effectiveness rates.*

Table 5a- 12-Month Success Rates by Investigational Site –Evaluable Patients*

SITE	CRYO N=174	REA N=77	TOTAL
Scripps	83% (19/23)	80% (8/10)	33
LDS	80% (31/39)	93% (14/15)	54
Columbia Rose	88% (14/16)	78% (7/9)	25
USC	71% (10/14)	60% (3/5)	19
Yale	60% (6/10)	86% (6/7)	17
Swedish	90% (19/21)	92% (11/12)	33
Denver Health	73% (8/11)	100% (2/2)	13
Los Gatos	80% (8/10)	100% (5/5)	15
Alabama	57% (8/14)	40% (2/5)	19
B&W/Mass General	44% (7/16)	71% (5/7)	23

**Evaluable population does not include those patients lost to follow-up (15 Cryo/9 REA).*

◆ **Efficacy at One Year: Quality-of-Life Improvements**

Quality of Life (QOL) data was obtained using the SF-36 Health Survey as well as a version of the validated Dartmouth COOP assessment tool. Because there are no QOL questions pertaining to menorrhagia, approval from the Dartmouth Committee was granted to use the same style of questions and format them according to the study design. Parameters included SF-36 PMS symptoms and menstrual pain indices.

Table 6 – Effectiveness - Quality of Life (QoL) at 1 year (Scale 1-5)

	<u>CRYO</u>	<u>REA</u>
Number of patients who responded to QOL questionnaire (n=230)	157	73
QOL Pre-op (mean ± SD)	3.4 ± 1.0	3.5 ± 0.9
Improvement in QOL (mean ± SD)	1.3 ± 0.7	1.3 ± 0.9
% patients very/extremely satisfied	86%	88%
% patients recommend to a friend	98%	95%
% patients reported time lost from work/other activities:		
Pre-operatively	74%	71%
Post-operatively	6%	7%

◆ **Hysterectomy**

There were 9 patients enrolled in the study who underwent hysterectomy prior to the 12-month follow-up. The reasons are included in the table below:

REASON FOR HYSTERECTOMY	CRYO	REA
Cramping/PMS	1	
Cramping/bleeding	3	1
Bleeding	2	1
Pain		1
Totals	6	3

**6 of the hysterectomies were in women <40 years (4 Cryo/2REA) and 3 were > 40 years (2Cryo/1REA)*

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

The pre-clinical and clinical data provide reasonable assurance that the Her Option™ System is safe and effective when used in accordance with the directions for use.

XIV. PANEL RECOMMENDATIONS

At a January 29, 2001 meeting of the Obstetrics and Gynecology Devices Advisory Panel Meeting, the Panel discussed the PMA (P000032) for the Her Option™ Uterine Cryoblation Therapy™ System. The Panel discussed the variability in success rates across investigational sites in an attempt to understand this study observation. In addition, they spent time discussing the treatment technique including the placement of

the probe, the lack of adherence to the treatment regimen provided in the protocol (i.e., 4 minute first freeze followed by a 6 minute second freeze) and the level of competence necessary for the required adjunctive ultrasound. The Panel also examined the adverse events observed in the study and provided feedback on the device labeling including some Panel member's objection to the name: First Option.

At the conclusion of the deliberations, the Panel voted 9-0 to recommend approval of the Her Option™ System subject to the following conditions:

- 1) The sponsor should conduct a prospective premarket study to demonstrate that the device malfunction rate observed in the pivotal trial has been reduced to an acceptable level for the commercial Her Option™ System.
- 2) The sponsor should standardize and carefully document the procedure in their labeling.
- 3) The sponsor should conduct a post-market analysis of this standardized technique using six months follow-up to further evaluate the inter-site variability encountered in the pivotal clinical trial.
- 4) The sponsor should revise the indication to specifically state that this device is for the reduction of bleeding.
- 5) The sponsor should revise the physician and patient labeling.

XV. FDA DECISION

CDRH concurred with the Panel's recommendation, except for the need to evaluate device malfunction rates prior to approval. CDRH recommended and CryoGen has agreed to conduct a post-approval study to evaluate device reliability (acute technical failure rate). In making the decision to examine device reliability in the post-market setting instead of the pre-market study recommended by the Panel, FDA considered several factors, the most significant of which was the fact that the device malfunctions did not affect patient safety. Few of the malfunctions observed in the pivotal study precluded patient treatment. (The acute failure rate was 3%.) Instead, the majority of the malfunctions resulted in the user modifying the treatment technique in an attempt to compensate for suboptimal device performance. FDA also considered how CryoGen handled the complaints received during the trial and how they identified the causes. The corrective actions developed to address the malfunctions included changes to device software, design, specification, and manufacturing. The device modifications have been adequately validated on the bench. CryoGen has also made changes to the lot release criteria and labeling. All of these changes should reduce the observed malfunction rate. Finally, since the general cryosurgical use of this device was cleared via 510(k), there is some information on modified versions of this system in the field. While the information obtained on these system through CryoGen's Complaint Handling System is limited, it is suggestive of an improvement in device reliability. A careful examination of the device reliability will be conducted through the approved post-market study protocol and MDR and MEDWATCH.

CryoGen agreed to conduct a second post-approval study to examine technique

standardization to determine whether there are variations in surgical technique that may contribute to the effectiveness of the treatment with the Her Option™ System. CryoGen also agreed to continue to follow the cryoblation subjects from the multi-center study for a period of three years from the time of treatment (two years post-market) in order to gather long-term safety and effectiveness data on the HerOption™ Uterine Cryoblation Therapy™ System.

Finally, CryoGen revised the patient and professional labeling, in keeping with the recommendations of the Panel, e.g., the change in device name from First Option to Her Option.

An FDA inspection of the CryoGen, Inc. manufacturing facility was completed on July 21, 2000, and the sterilization facility's inspection was completed on June 7, 2001. It was determined that the manufacturer was in compliance with Quality Systems Regulation.

XVI. APPROVAL SPECIFICATIONS

Directions for use: See the Device Labeling.

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

Post-approval Requirements and Restrictions: See approval order.