Device:	**Cerene™** Cryotherapy Device
Study Number & Rev.:	CIP-0101, Rev. K
Protocol Date:	2018-Oct-12
Study Title:	A **CL**inical Study to Evaluate the Safety **A**nd Effectiveness of the Ce**R**ene Dev**I**ce to **T**reat Heav**Y** Menstrual Bleeding (**CLARITY**)
Study Design:	This is a prospective, multi-center, single-arm, open-label, non-randomized pivotal study. The **Cerene Device** will be used in women with heavy menstrual bleeding, due to benign causes, for whom childbearing is complete.
Sponsor Name:	Channel Medsystems, Inc.
Sponsor Address:	5858 Horton Street, Suite 200 Emeryville, CA 94608 USA
Authorized Representative:	[redacted]
Study Coordination:	Channel Medsystems, Inc.
Data Analysis:	Berry Consultants

The study will be conducted in compliance with the protocol, FDA 21 CFR 812, 21 CRF 50, 21 CFR 56, ISO 14155, and applicable local regulatory requirements.

STATEMENT OF CONFIDENTIALITY

The information contained herein is confidential, the sole and exclusive property of Channel Medsystems, and may not be divulged to any person (except as required by law) without the prior written consent of Channel Medsystems.

STUDY ACKNOWLEDGMENT

Investigator's Statement
I have read and understand the foregoing protocol entitled: **"**A **CL**inical Study to Evaluate the Safety **A**nd Effectiveness of the Ce**R**ene Dev**I**ce to **T**reat Heav**Y** Menstrual Bleeding (**CLARITY**)" and all corresponding amendments and agree to conduct the study as outlined herein.

Confidentiality
I understand that all information not previously published concerning this study and Channel Medsystems devices is confidential. The confidential information includes, but is not limited to, the study protocol, case report forms, and study data. I agree not to publically disclose such confidential information without first acquiring written permission from Channel Medsystems.

Ethics Committee / Investigational Review Board Approval
I acknowledge that I will not begin enrolling subjects into this study before obtaining approval from my local ethics committee or investigational review board.

Deviations
I understand my obligation to complete this study with full adherence to the written protocol, informed consent, and Instructions for Use. I understand that deviations from the protocol impair the ability to interpret the study data. Unless required to protect the health and/or safety of the individual subject, I will not knowingly deviate from the protocol without first obtaining written permission from the study sponsor.

_____
Investigator's Name (please print)

_____ _____
Investigator's Signature Date

SIGNATURE OF THE SPONSOR'S MEDICALLY RESPONSIBLE PERSON

The Study Medical Expert agrees to the content of the clinical study protocol as presented.

_____
Name (please print)

_____ _____
Signature Date

SIGNATURE OF STUDY PRINCIPAL INVESTIGATOR

The Study Principal Investigator agrees to the content of the final clinical study protocol as presented.

NOT APPLICABLE; THERE IS NO STUDY PRINCIPAL INVESTIGATOR

_____, MD
Name (please print)

NOT APPLICABLE

_____ _____
Signature Date

Hospital or Medical Center Affiliation and Address:

NOT APPLICABLE

Table of Contents

STUDY SYNOPSIS

INTENDED USE	The Cerene Cryotherapy Device (Cerene) is intended to ablate the endometrial lining of the uterus in premenopausal women with heavy menstrual bleeding due to benign causes for whom child bearing is complete.
STUDY PURPOSE	The purpose of this study is to evaluate the safety and effectiveness of the Cerene Device.
STUDY DESIGN	This is a prospective, multi-center, single-arm, open-label, non-randomized pivotal study. The Cerene Device will be used to treat heavy menstrual bleeding due to benign causes in women who meet the inclusion and exclusion criteria. Subjects will be assessed following ablation treatment through Month 12 for all study endpoints and at Month 24 and 36 for any additional medical or surgical interventions needed to manage continued heavy menstrual bleeding.
NUMBER OF SUBJECTS	242 subjects will undergo Cerene cryoablation treatments.
STUDY CENTERS	Up to 20 centers in 3 countries
STUDY EVALUATIONS	**Primary safety endpoint:** • Incidence of serious adverse events and serious device-related adverse events at 12 months **Primary effectiveness endpoint:** • Reduction in menstrual bleeding at 12 months; success is defined as a score of ≤ 75 measured using a pictorial blood loss assessment chart (PBLAC) **Additional evaluations:** • Amenorrhea rate at Month 12 • Subject-reported peri-procedural pain experience • Evaluation of dysmenorrhea at Month 12 • Quality of Life outcome at Month 3, 6, and 12: using the Menorrhagia Impact Questionnaire (MIQ) and the Premenstrual Symptoms Impact Survey (PMSIS) • Month 24 and 36 telephone contact or office visit to include an assessment of gynecologic adverse events, additional medical or surgical interventions for continued heavy menstrual bleeding, QoL measurements by MIQ and PMSIS, type of contraception and compliance, and pregnancy query • Evaluation of uterine access and healing at Month 12

STUDY SYNOPSIS

STUDY DURATION	Total Duration: 3 years after last subject treated
STUDY POPULATION	Adult pre-menopausal female subjects with heavy menstrual bleeding who meet the inclusion and exclusion criteria
INCLUSION CRITERIA	1. Refractory heavy menstrual bleeding with no definable organic cause 2. Female subject age 25 to 50 years, inclusive 3. 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 4. Myometrial thickness of at least 10 mm 5. Menstrual blood loss with a PBLAC score of ≥ 150, within 3 months of informed consent, for: Two baseline cycles; OR One baseline cycle in a woman who has at least 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 6. Premenopausal confirmed by FSH measurement ≤ 30 IU/L when age is > 40 years 7. Agrees to use a reliable form of non-hormonal contraception following ablation treatment up to the 12-month follow-up visit unless the subject is currently using a hormonal birth control method, has been on said method for ≥ 3 months prior to informed consent, and agrees to remain on the same hormonal regimen up to the 12-month follow-up visit. 8. Provides written informed consent using a form that has been approved by the reviewing IRB/EC 9. Agrees to follow-up exams and data collection requirements 10. Demonstrates an understanding of how to record menstrual blood loss using a menstrual pictogram 11. Has predictable, cyclic menstrual cycles
EXCLUSION CRITERIA	1. Pregnant or has a desire to conceive 2. Endometrial hyperplasia as confirmed by histology 3. Active endometritis 4. Active pelvic inflammatory disease 5. Active sexually transmitted disease (STD) 6. Presence of bacteremia, sepsis, or other active systemic infection 7. Active infection of the genitals, vagina, cervix, or uterus

STUDY SYNOPSIS

	8. Known/suspected abdominal, pelvic, or gynecological malignancy within the past 5 years 9. Known clotting defects or bleeding disorders 10. Abnormal cytology on Human papillomavirus (HPV) testing not treated according to local standards. 11. Prior uterine surgery that interrupts the integrity of the uterine wall (e.g., transmural myomectomy or classical cesarean section). 12. 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 13. Previous endometrial ablation procedure 14. Clinically significant adenomyosis indicated by subject complaints, imaging, or clinician's judgment 15. Presence of an implantable contraceptive device (e.g. Essure™ or Adiana™) 16. Currently on medications that could thin the myometrial muscle, such as long-term steroid use (except inhaler or nasal therapy for asthma) 17. Currently on anticoagulants 18. Abnormal or obstructed cavity, specifically: *a)* Septate or bicornuate uterus or other congenital malformation of the uterine cavity *b)* Polyps larger than 1 cm (in largest dimension) or which are likely to be the cause of the subject's heavy menstrual bleeding *c)* Any submucosal myoma *d)* Any myoma that distort(s) the endometrial cavity *e)* Any myoma, polyp configuration, uterine position, and/or uterine anomaly that, in the opinion of the investigator, *i.* obstructs or hinders treatment access to the endometrial cavity *ii.* prevents deployment of the device *iii.* and/or is contraindicated for use of the investigational device 19. Currently using an intrauterine device (IUD), including Mirena™ device, and unwilling to remove the IUD 20. Post-partum ≤ 6-months 21. Considering participation in a research study of an investigational drug or device that would begin during the course of this investigational study 22. 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

LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
EA	Endometrial Ablation
EC	Ethics Committee
EEC	Endometrial Echo Complex
FDA	Food and Drug Administration
GCP	Good Clinical Practice
FSH	Follicle-Stimulating Hormone
GLP	Good Laboratory Practices
HMB	Heavy Menstrual Bleeding
IC	Informed Consent
IFU	Instructions for Use
IRB	Institutional Review Board
MIQ	Menorrhagia Impact Questionnaire
NREA	Non-Resectoscopic Endometrial Ablation
PBLAC	Pictorial Blood Loss Assessment Chart
QOL	Quality of Life
REA	Resectoscopic Endometrial Ablation
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
STD	Sexually transmitted disease
SIS	Saline Infused Sonohysterography
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

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1 Introduction

1.1 Background on Ablation Techniques

Historically, therapy with hormonal or non-hormonal medications and surgical procedures, including supracervical or total hysterectomy, have been the mainstay of treatment for the spectrum of disorders that manifest in heavy menstrual bleeding (HMB). Although the minimally invasive procedures that are collectively known as endometrial ablation (EA) were originally developed more than 100 years ago (Fritsch 1898), and further evolved in the early and mid-20th century (Bardenheuer 1937, Cahan and Brockunier 1967, Droegemueller, Greer et al. 1970, Droegemueller, Greer et al. 1971), it is only in the past 25 years that they have been practicably available to at least selected women experiencing the symptom of HMB.

Endometrial ablation has been classified as “first generation” and “second generation,” but confusion regarding just what was “first” and what was “second” has led to a more descriptively accurate classification of resectoscopic and non-resectoscopic technique. Whereas the earliest non-resectoscopic techniques were introduced in the late 19th (Fritsch 1898) and early 20th century (Bardenheuer 1937), intrauterine application of the urological resectoscope introduced in the late 1980s was responsible for the widespread adoption of endometrial ablation as a viable therapeutic procedure (Vancaillie 1989). Resectoscopic endometrial ablation (REA) requires the use of a modified urological resectoscope that includes an endoscope (a hysteroscope), a mechanism for instilling and removing fluid distending media, and a radiofrequency electrode shaped as a barrel, ball ("rollerball") or wire loop that is used to remove or destroy the endometrial lining. These techniques typically require an anesthesiologist to administer general or regional anesthesia in the context of an institutional operating room. Potential risks of these procedures include cervical laceration, uterine perforation and subsequent sequelae, and fluid overload that may result in heart failure and pulmonary edema, and, if electrolyte-poor solutions are used, hyponatremia and related encephalopathy, an event that contributes to the mortality associated with these procedures (Ayus, Wheeler et al. 1992, Istre, Skajaa et al. 1992, Baggish, Brill et al. 1993, Corson 1994, Overton, Hargreaves et al. 1997, Munro 2010). Furthermore, it is evident that both the clinical outcome and the incidence of these complications are directly related to the training and skill of the surgeon (Overton, Hargreaves et al. 1997, Pooley, Ewen et al. 1998).

Non-resectoscopic endometrial ablation (NREA) techniques use one of a number of approaches to destroy the endometrium but do not require the use of a resectoscope and the accompanying large volumes of fluid, thereby eliminating the risks of fluid overload and resulting fluid and electrolyte imbalances. In addition, NREA techniques typically are automated and/or provide surgeon feedback to at least some degree and, while they can’t be perceived to be “global” in impact, the clinical outcome is less dependent upon the skill and training of the surgeon. Furthermore, and to some degree, depending on the technique, they can be performed in the context of an office procedure room, potentially using local anesthesia.

In 1997, the United States Food and Drug Administration approved the first global endometrial ablation (GEA) device (Meyer, Walsh et al. 1998) designed to treat heavy menstrual bleeding, in selected women with normal endometrial cavities. The GYNECARE THERMACHOICE® Uterine

Balloon Therapy System (Ethicon, Inc., Somerville, NJ) comprises a 5.5 mm outside diameter (OD) balloon-tipped catheter that is blindly positioned in the endometrial cavity and then filled with fluid that is subsequently heated by a remotely located controller "box" to 188°F (87°C) for eight minutes. In 2001, the FDA approved the other devices. The Hydro ThermAblator® System (Boston Scientific Corp., Natick, MA) is a 7.8 mm OD sheath that is used to deliver saline into the endometrial cavity under hysteroscopic guidance (Corson 2001). Upon confirmation of proper positioning, the remotely located controller system heats the saline solution until it reaches the target temperature of 93°C, which it holds for 10 minutes before the system is cooled. The NovaSure® Impedance Controlled Endometrial Ablation System (Hologic, Inc., Bedford, MA) is a 7.2 mm probe that, following blind positioning in the endometrial cavity, deploys a triangular bipolar mesh electrode (Cooper, Gimpelson et al. 2002). Following passage of a gas-based confirmation test, the system is activated by the remotely located controller system. When the combination of coagulation and desiccation results in a threshold local impedance of 50 ohms, the machine turns off, generally following about 90 seconds of therapy. The Her Option® Office Cryoablation Therapy (CooperSurgical, Inc., Trumbull, CT) uses a 5.5 mm OD cryoprobe that is blindly positioned in the endometrial cavity, but which can, in many instances, be confirmed by ultrasound (Duleba, Heppard et al. 2003). When activated by the remotely located controller unit, the system is capable of producing temperatures of negative 148°F (minus 100°C) to freeze the uterine lining. This device is used with ultrasound guidance to monitor the ablation procedure with treatment times typically ranging from 10 – 20 minutes. In 2015, the FDA approved the Minerva Endometrial Ablation System (Minerva Surgical, Inc., Redwood City, CA) which uses a bipolar 480 kHz RF power generator and controller for endometrial ablation. The handpiece contains circulating argon gas and is blindly positioned in the endometrial cavity. Treatment is achieved during a two minute procedure from heat conduction through the distal end of the handpiece and a small amount of bi-polar RF current travelling through the target tissue (U. S. Food and Drug Administration, Minerva™ SSED, 2015). (U. S. Food and Drug Administration, Minerva™ SSED, 2015). Collectively and individually, these NREA techniques have been associated with fewer severe adverse events than was the experience with REA (Lethaby, Hickey et al. 2009).

Channel Medsystems, Inc. (California, USA) has developed the Cerene Cryotherapy Device (Cerene Device) to address the unmet clinical need for a totally handheld device with a narrow diameter probe and fast treatment time that could also be used in the office setting with limited requirements for sedation or anesthesia (deep sedation). The distally-located cavity-conforming liner is filled with nitrous oxide from the device handle, which freezes and ablates the adjacent endometrium. The ablation procedure should be less painful than those performed with the hyperthermic (heat-based) ablation techniques due to the anesthetic effect of the cryogenic fluid on nerves in the uterine tissue (Evans 1981). As well, the tissue healing response to cryoablation is favorable, has been well documented (Droegemueller, Makowski et al. 1971, Schantz and Thormann 1984, Chua, Chou et al. 2007, Baust, Gage et al. 2009), and may preserve access to the endometrial cavity in subsequent years. By minimizing the development of synechiae, or adhesions, that make sampling of the endometrium difficult (Sharp 2012), treatment with the Cerene Device may reduce the risk of impaired cavity access.

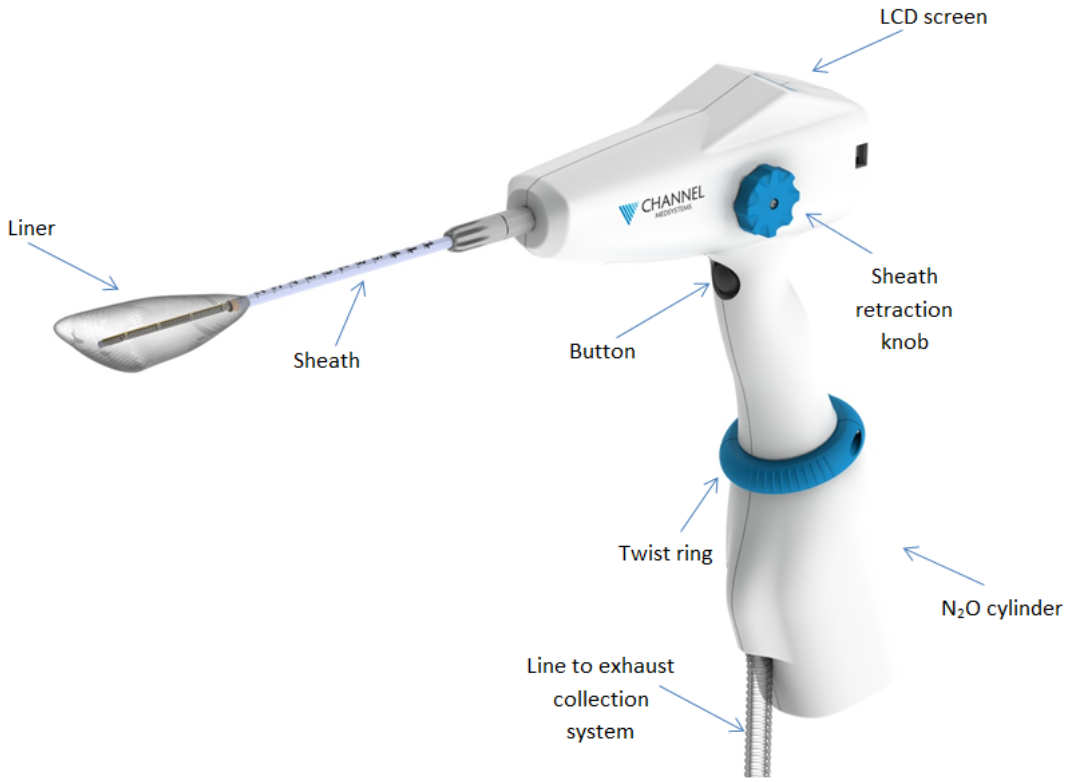
The Cerene Device is intended to reduce treatment time and to deliver consistent results that are less dependent on physician skill levels. The Cerene Device is also designed to tailor the ablation to the endometrial cavity being treated, while delivering consistent ablation depths throughout the cavity and simultaneously reducing ablation depth in thinner areas of the myometrium, particularly the cornual regions and the lower segment. The device is designed as an alternative to hysterectomy, aiming to achieve the desired reduction in heavy menstrual bleeding while reducing the risks associated with major surgery, such as illness or death. This device requires no incision and, therefore, is minimally invasive.

This multi-center, international, single arm pivotal study will be conducted under all applicable local and country regulatory requirements and guidance. The objective of the study is to demonstrate the safety and effectiveness of the Cerene Device in a population of subjects with heavy menstrual bleeding due to benign causes.

1.2 Description of the Cerene Device

Channel Medsystems' Cerene Device (**Figure 1**) is handheld and designed to safely treat heavy menstrual bleeding (HMB). [redacted] The device uses cryothermic energy to achieve uniform ablation depths [redacted] throughout the uterine cavity [redacted] The cryothermic energy is provided by a liquid-to-gas phase change of nitrous oxide (N_2O) [redacted] During the 2½ minute treatment cycle, liquid N_2O (originating from a small cylinder located in the device handle) flows through a Nitinol tube and into an infusion lumen with multiple jets. This liquid N_2O is infused into an ultra-thin [redacted] polyurethane liner (balloon) and phase changes into gas. The gaseous N_2O is exhausted through a flexible tube exiting the bottom of the handle. [redacted] s a result, the Cerene Device is able to treat uterine cavities ranging in length between 2.5 and 6.5 cm. [redacted]

Figure 1: Cerene Device



The status and sequential operating instructions are displayed on the device's LCD screen. After removal from sterile packaging, a twist ring is rotated to open the N_2O valve and turn on the device. The user is then prompted to press the button and insert the device to the fundus. The small diameter of the device [redacted] is designed to facilitate insertion and minimize the need for dilation. 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 cavity length (shown on the LCD). A third button press initiates treatment. The uterine cavity is gently pressurized [redacted] with filtered air, deflated and re-pressurized a second time. A final liner leak detection test is completed and then the N_2O flow is automatically initiated. At any time, the user can pause or stop the procedure. After 2½ minutes, N_2O flow is stopped and the user is prompted to vent the remaining N_2O. Vacuum is initiated within the liner to expedite device removal. After use, the entire device is disposed per local practice.

Numerous features ensure the safety of the Cerene Device. [redacted]

[redacted]

1.3 Report of Prior Investigations

Channel Medsystems conducted multiple studies during the development of the Cerene Cryotherapy Device. These included extirpated, peri-hysterectomy, pre-hysterectomy trials. In addition, a feasibility study was conducted that included the intended population of subjects for a pivotal trial. These trials were designed to establish the final device configuration and assure that the device would deliver the intended energy in a safe and effective manner in a clinical setting.

The feasibility study was a prospective, single-arm, multi-center study to evaluate the safety and potential effectiveness of the cryotherapy device in reducing heavy menstrual bleeding and to define parameters for a future pivotal clinical trial that would support a pre-market approval application to the U.S. Food and Drug Administration (FDA). Three (3) Canadian clinical sites participated [redacted] forty (40) subjects underwent endometrial cryotherapy treatment. Thirty seven (37) evaluable subjects completed six (6) months of follow-up. Twenty-four (24) of the 37 subjects consented to and completed additional follow up visits at nine (9) months and twelve (12) months post treatment.

The primary safety endpoint was the incidence and severity of adverse events at 6 months. The primary efficacy endpoint was the reduction in menstrual bleeding at 6 months defined as a score of $\leq$ 75 using a Pictorial Blood Loss Assessment Chart (PBLAC).

The feasibility protocol included subjects with a broad range of uterine cavity measurements: uterine sound measurement of $\leq$ 14 cm and endometrial cavity length (internal os to fundus) between ≥ 2.5 cm and ≤ 8.0 cm. A reduction in menstrual bleeding was demonstrated in the majority of evaluable subjects treated. At baseline, all subjects had a PBLAC score of ≥ 150 and at the 6 month visit, 75% of evaluable subjects had a PBLAC score of ≤ 75.

In the proposed CLARITY pivotal study, the effectiveness of the Channel Medsystems Cryotherapy device will be compared to an FDA established objective performance criterion (OPC). The OPC approach utilizes data from the pivotal clinical trials of five approved endometrial ablation systems that included similar patient populations. In general, the endometrial ablation systems that comprise the OPC are indicated for a uterine sound measurement of ≤10 cm. Therefore, Channel Medsystems tabulated the PBLAC data from the feasibility study for subjects with a uterine sound measurement between 6 and 10 cm, inclusive, and endometrial cavity length ≥ 2.5 cm to ≤ 6.5 cm. At the 6 month visit, 81% of this group of subjects had a PBLAC score of ≤

75. The proposed pivotal study of the Channel Medsystems cryotherapy device will include only subjects with a uterine sound measurement of ≤ 10 cm, consistent with currently marketed endometrial ablation systems.

The incidence of adverse events and serious adverse events in the feasibility study was very low. [redacted] There were no unanticipated adverse device effects or unanticipated adverse events.

[redacted]

[redacted]

[redacted]

The results of this feasibility study provide reasonable assurance that endometrial ablation with the Channel Medsystems cryotherapy device is safe, well tolerated, and effective in reducing heavy menstrual bleeding, establish tentative effectiveness rates for use in sample size calculations, and support initiation of this pivotal clinical study.

2 Study Design

This is a multi-center, international, single arm study to evaluate the safety and effectiveness of the Cerene Device. Subjects must satisfy all eligibility criteria. Approximately 242 women with heavy menstrual bleeding, with no definable organic cause, will be treated.

Post ablation treatment, subject follow-up will include assessments at day 1, week 2, months 3, 6, 12, 24, and 36. Subjects will be assessed through month 12 post ablation treatment for all safety and effectiveness endpoints and at months 24 and 36 for any additional medical or surgical interventions that were needed to manage continued heavy menstrual bleeding.

2.1 Study Objectives

The purpose of this study is to evaluate the safety and effectiveness of the Cerene Device.

2.2 Primary safety endpoint

The incidence of serious adverse events and serious device-related adverse events at twelve (12) months will be evaluated.

2.3 Primary effectiveness endpoint

The reduction in heavy menstrual bleeding will be evaluated. Success is defined as a reduction in menstrual bleeding at 12 months to ≤ 75 as measured by a Pictorial Blood Loss Assessment Chart (PBLAC).

2.4 Additional evaluations following Ablation treatment

- Amenorrhea rate at Month 12
- Subject-reported peri-procedural pain experience
- Evaluation of dysmenorrhea at Month12
- Quality of Life outcomes at Month 3, 6, and 12: using the Menorrhagia Impact Questionnaire (MIQ) and the Premenstrual Symptoms Impact Survey (PMSIS)
- Month 24 and 36 telephone contact or office visit to include an assessment of gynecologic adverse events, additional medical or surgical interventions for continued heavy menstrual bleeding, QoL measurements by MIQ and PMSIS, contraception type and compliance, and pregnancy query

- Evaluation of uterine access and healing at Month 12

3 Subject Eligibility

Subjects who meet all inclusion and exclusion eligibility criteria and agree to participate in the study will be treated.

3.1 Inclusion Criteria

A subject must meet **all** of the following inclusion criteria prior to ablation treatment:

1. Refractory heavy menstrual bleeding with no definable organic cause
2. Female subject age 25 to 50 years, inclusive
3. 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
4. Myometrial thickness of at least 10 mm
5. Menstrual blood loss with a PBLAC score of ≥ 150, within 3 months of informed consent, for:

   Two baseline cycles; OR

   One baseline cycle in a woman who has at least 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
6. Premenopausal confirmed by FSH measurement ≤ 30 IU/L when age is > 40 years
7. Agrees to use a reliable form of non-hormonal contraception following ablation treatment up to the 12-month follow-up visit unless the subject is currently using a hormonal birth control method, has been on said method for ≥ 3 months prior to informed consent, and agrees to remain on the same hormonal regimen up to the 12-month follow-up visit.
8. Provides written informed consent using a form that has been approved by the reviewing IRB/EC
9. Agrees to follow-up exams and data collection requirements
10. Demonstrates an understanding of how to record menstrual blood loss using a menstrual pictogram
11. Has predictable, cyclic menstrual cycles

3.2 Exclusion Criteria

A subject must NOT meet **any** of the following exclusion criteria prior to ablation treatment:

1. Pregnant or has a desire to conceive
2. Endometrial hyperplasia as confirmed by histology
3. Active endometritis

4. Active pelvic inflammatory disease
5. Active sexually transmitted disease (STD)
6. Presence of bacteremia, sepsis, or other active systemic infection
7. Active infection of the genitals, vagina, cervix, uterus
8. Known/suspected abdominal, pelvic, or gynecological malignancy within the past 5 years
9. Known clotting defects or bleeding disorders
10. Abnormal cytology on HPV testing not treated according to local standards
11. Prior uterine surgery that interrupts the integrity of the uterine wall (e.g., transmural myomectomy or classical cesarean section).
12. 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
13. Previous endometrial ablation procedure
14. Clinically significant adenomyosis indicated by subject complaints, imaging, or clinician's judgment
15. Presence of an implantable contraceptive device (e.g. Essure™ or Adiana™)
16. Currently on medications that could thin the myometrial muscle, such as long-term steroid use (except inhaler or nasal therapy for asthma)
17. Currently on anticoagulants
18. Abnormal or obstructed cavity, specifically:
    a. Septate or bicornuate uterus or other congenital malformation of the uterine cavity
    b. Polyps larger than 1 cm (in largest dimension) or which are likely to be the cause of the subject's heavy menstrual bleeding
    c. Any submucosal myoma
    d. Any myoma that distort(s) the endometrial cavity
    e. Any myoma, polyp configuration, uterine position, and/or uterine anomaly that, in the opinion of the investigator,
        i. obstructs or hinders treatment access to the endometrial cavity
        ii. prevents deployment of the device
        iii. and/or is contraindicated for use of the investigational device
19. Currently using an intrauterine device (IUD), including Mirena™ device, and unwilling to remove the IUD
20. Post-partum ≤ 6-months
21. Considering participation in a research study of an investigational drug or device that would begin during the course of this investigational study
22. 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

4 Success Criteria

This study is designed to demonstrate statistical success in effectiveness relative to a clinical performance goal (PG). The primary effectiveness endpoint for the study is 12-month success where success is defined as a reduction in menstrual bleeding to ≤ 75 as measured by a PBLAC.

The null and alternative hypotheses for the primary endpoint are as follows:
H0: PE < PG
H1: PE ≥ PG

where PE is the 12-month success rate for the Cerene Device and PG is a Performance Goal based on results from the pivotal trials of the five approved global endometrial ablation (GEA) devices. The performance goal was selected based on the outcomes achieved in the PMA trials of the approved GEA devices as a class, using a mixed model with each approved GEA modeled as a random effect. Based on the Summaries of Safety and Effectiveness for these five approved GEAs, the estimated mean effectiveness and 95% confidence interval adjusted for the random effect of individual studies are as follows:

Least square means of success rate (PBLAC ≤75) at 12mo based on SSED data		
	Investigational devices	Rollerball therapy
Mean (95% CI)	75.6 % (65.6%, 83.5%)	77.2% (66.5%, 85.2%)

When the variability in performance among the five devices is taken into consideration, the 95% lower confidence bound of mean approved device effectiveness is approximately 66%, based on the results from the GEA devices as well as the control (rollerball therapy) therapy. Therefore, the performance goal for this study has been chosen to be 66%. This study will be deemed successful if the 12-month Cerene Device success rate is found to be significantly greater than this threshold value of 66%.

4.1 Statistical Analysis Plan Summary

A detailed statistical analysis plan will be developed prior to database lock for the final analysis or prior to any interim analysis. Following are the critical parameters controlling this study.

4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this single arm study is that the proportion of women with menstrual bleeding at 12 months less than or equal to 75 as assessed by the PBLAC scale. The null and alternative hypotheses for the primary endpoint are as follows:

H0: PE < 0.66 versus H1: PE ≥ 0.66

where PE is the 12-month success rate for the Cerene Device. Success is determined by obtaining a PBLAC score of less than or equal to 75.

4.1.2 Primary Safety Endpoint

The primary safety endpoint is the proportion of women in the study who experience a serious adverse event or serious device-related adverse event. The analysis of this endpoint will be descriptive. The number of women experiencing a serious adverse event or serious device-related adverse event, the number evaluated, the percentage and the 95% exact confidence interval will be presented. In addition, these items will be provided for specific individual events.

4.1.3 Sample Size

Assuming the success rate of the Cerene device in the ITT population is 75%, then 242 subjects will provide at least 85% power to show Cerene is superior to an OPC of 66% with an overall Type I error rate < 2.5%. If 5% of patients drop-out, then the Cerene device must have a success rate among patients with complete 12-month follow-up of at least 79% in order to achieve a success rate in the ITT population of 75%. If 10% of patients drop-out, then the Cerene device much achieve a success rate of approximately 84% among patients with complete 12-months follow-up in order to achieve a success rate in the ITT population of 75%.

4.1.4 Study Populations

All women for whom a treatment with the device is placed in the cavity and treatment is attempted comprise the intention-to- treat (ITT) population. The primary effectiveness analysis will be done in the ITT population. [redacted]

4.1.5 Poolability

Pooling of data across study sites involves two concepts. The first is whether the data from the sites can be combined for analysis. This concept is confirmed if the sites all used a common protocol, the sites were monitored for protocol compliance, and the data gathering instruments used at each site are identical.

The second concept is whether the data from all sites can be sufficiently similar that it can be combined to estimate a common effect size for the endpoints. The primary efficacy analysis will

pool data across all sites. Secondary analyses will test the homogeneity of success proportions across sites. This will be done by the Fisher-Freeman-Halton test. If the P-value for this test of homogeneity has a P-value of 0.10 or less, the sites will be considered heterogeneous with respect to the primary endpoint analysis. If that occurs, an estimate of the effect will be presented with Bayesian hierarchical modeling across sites.

4.1.6 Adaptive Design Interim Analysis

Interim analyses are planned when 100 and 175 patients have been treated and in the trial for 12 months, i.e. when the first 100 and 175 patients have had the opportunity to complete follow-up for the 12-month primary endpoint. The trial may declare an early success at each interim analysis. Specifically, the trial may declare success early if there is at least a 97.9% probability that PE ≥ 0.66.

Even if early success is declared, final trial success will be evaluated when all 242 patients have the opportunity to complete follow-up for the 12-month primary endpoint. Final trial success is also defined as at least a 97.9% probability that PE > 0.66. If an early success is declared, Channel Medsystems will approach FDA with an early request for market approval (i.e. PMA) of the Cerene device should there be at least a 97.9% probability that PE ≥ 0.66. Note that the final clinical report's success rate will still be based on the evaluation when all 242 patients have the opportunity to complete follow-up for the 12-month primary endpoint.

4.1.7 Patient Accountability and Missing Data

Subjects that exit the study for any reason will be tabulated and the reason will be recorded. Also an accountability analysis will be presented to show compliance with planned study visits. The number and percentage of subjects with study visits will be presented based on the number that are eligible for each visit.

4.1.8 Statistical Method

4.1.8.1 Character of Study Variables

A routine assessment is done to assure that the data of the study complies with the assumptions of the tests to be used.

4.1.8.2 Analysis of Baseline Characteristics of the Study Population

A descriptive analysis of the subjects enrolled in the study will be presented. For continuous variables the mean, standard deviation (SD), number evaluated, median, minimum, and maximum will be provided. For categorical variables, the number with the characteristic, the number evaluated, the percentage, and the exact 95% confidence limits will be provided.

4.1.8.3 Primary effectiveness analysis

Y_{i12} be the 12 month PBLAC score for subject i. Let I_{i12} be the success indicator for the i^{th} patient at 12 month. I_{i12} will be 1 where Y_{i12} is less than or equal to 75 and will be 0 where Y_{i12} is greater than 75. Let $\pi = \Pr(I_{i12} = 1)$ be the probability of success at 12 months. We model the log odds of success,

$$\theta = \log(\pi/1\text{-}\pi)$$

as having a normal distribution. The prior distributions for the log-odds of success is

$$\theta \sim N(0, 2^2),$$

When converted from the log-odds scale back to the original probability scale, the resulting prior distribution for the log odds of success has a median of 50% and a 95% probability that the success rate is between 2% and 98%. At each interim and at the final analysis we calculate the posterior probability that $\pi > 66\%$.

4.1.8.4 Longitudinal Modeling

Patients will be assessed at 3, 6, and 12 months following enrollment. We use a longitudinal model of the primary endpoint to allow these earlier observations to predict the final 12-month status. At each interim analysis, some patients will have completed follow-up and we will have observed their 12-months endpoint. These patients may also have earlier measures of the primary endpoint, such as at 3 and 6 months. There will be patients with earlier observations of the primary endpoint who have not yet reached 12 months of follow-up. We utilize the information from patients with incomplete follow-up to the extent that these earlier observations are correlated with the final 12-month value. A Bayesian model is built to learn how the early endpoints are correlated with the final 12-month endpoint and patients with complete follow-up information this model.

A linear regression model is created to model the association between the baseline, 3-, and 6-month values with the 12-month value. Therefore, there are three instances of the model. Each model instance is identical.

4.1.8.5 Operating Characteristics

In order to determine the performance of this trial design, we simulated it 5000 times across various assumptions for the PBLAC over time. Under the null hypothesis, that response rate is the same as the OPC, 66%, this trial will declare success with 2.5% probability. This is the simulated one-sided Type I error rate in this scenario. Under an alternative hypothesis, that the response rate is 75%, this trial will declare early success with approximately 30% probability. The total probability of trial success in this scenario is 87%. This is the power of the trial in this scenario. There is less than a 1% probability that a trial that qualifies an early success would not still be successful at the final analysis with complete data.

4.1.8.6 Primary safety analysis

The primary safety analysis will be a descriptive presentation of the proportion of subjects with any serious adverse event and/or serious device-related adverse event. The number with an event, the number evaluated, the percent, and the exact 95% confidence interval will be provided. The total number of events will also be provided. A secondary analysis will be done for all adverse events and the same information will be provided.

4.1.8.7 Additional Analyses (if any)

1. Amenorrhea rates will be recorded and presented descriptively at Month 12.
2. Subject-reported procedure pain experience will be recorded and presented descriptively.
3. Evaluation of dysmenorrhea at Month12
4. Quality of Life (QOL) outcomes at six months and twelve months post-procedure compared to baseline (measured using MIQ and PMSIS) will be presented descriptively.
5. Evaluation of uterine access and healing at twelve months post-procedure will be assessed and reported descriptively.
6. Additional medical or surgical interventions to address excessive bleeding will be reported descriptively.

4.1.8.8 Detailed Statistical Analysis Plan

Prior to database lock for the interim analysis, a detailed statistical analysis plan will be drafted and approved.

5 Study Methods

5.1 Institutional Review Board / Ethics Committee Approval

The Sponsor will obtain national regulatory authority approvals prior to initiating the study at a clinical site. The study will be conducted in accordance with the applicable local law(s) and regulations in the country in which it is conducted, all requirements set forth in the clinical protocol, Good Clinical Practices (GCP), the provisions of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2000), and the Sponsor's Clinical Department Standard Operating Procedures .

The investigator will obtain prospective approval of the study protocol, protocol amendments/changes, Informed Consent Form, and other relevant documents (e.g.

advertisements) from the IRB/EC prior to study start at his or her site. All correspondence with the IRB/EC should be retained in the site study file.

5.2 Informed Consent

The complete study and its required visits and assessments will be carefully discussed with the study subjects using an IRB/EC approved informed consent from (ICF).

The Investigator or designee will explain all relevant aspects of the study to each subject to facilitate her understanding of the information. Topics to be discussed include and are not limited to: study purpose, screening procedures, study procedures, follow-up visits, risks and discomforts, alternative treatments. Each subject will be provided ample time and opportunity to ask questions, have questions answered, and, without coercion or undue influence, to consider whether to voluntarily participate. The subject will be informed about the right to withdraw from the study at any time without prejudice. The subject will sign the ICF before any study specific examinations and/or procedures are performed to confirm subject eligibility. The clinical site will retain the original signed ICF in the subject's study file or medical record or per institutional requirement and provide the subject with a copy of the signed and dated ICF.

The ICF to be used should be the IRB/EC approved version. The ICF and any other written information provided to a subject will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written ICF. Any revision to the ICF must be approved by the IRB/EC prior to use. The Investigator will inform the subject of changes to the ICF, ask the subject to confirm her agreement to continue participate in the study by signing the revised ICF, and provide the subject with the revised copy. The signed ICF for each subject will be available for inspection by the Sponsor (or designee), FDA, IRB/EC, or other regulatory agency at the clinical site.

5.3 Study Identification Number

The subject will be assigned a unique study identification number (Study ID number) after signing the ICF. The subject number will be sequential in the order in which a subject signs the ICF. The study ID number, used to identify the subject throughout the study, will include a unique country number, site number, and subject number.

5.4 Investigational Device Training

Investigators will be fully trained in the proper use and operation of the Cerene Device before the initiation of subject treatments. [redacted]

5.5 Safety Data Review

Channel Medsystems, Inc., or its designee, will review the clinical study progress and safety data periodically and as needed with a Medical Advisory Board (MAB) and/or a Clinical Events Committee (CEC). [redacted] All records of event review will be documented and maintained in the sponsor's master study file.

5.6 Subject Exit

Subjects are considered to have completed the study when follow-up through month 36 post treatment has been achieved. Subject participation is voluntary. The subject may discontinue her participation in the study without prejudice or may be withdrawn from the study. If a subject exits the study, a subject exit CRF will be completed with the reason for exit.

[redacted]

[redacted]

5.7 Premature Study Termination

The Sponsor has the right to close or suspend this study at any time due to a change in the risk-benefit ratio, interim analysis, study conduct, or other. The Sponsor may terminate an Investigator and site from participation if there is evidence of an Investigator's failure to maintain adequate clinical standards or evidence of continued serious protocol deviations.

If the study or a specific site is closed prematurely, regulatory bodies, IRBs/ECs, and study subjects will be promptly notified. Site investigators will discuss with subjects any standard of care for future medical follow-up. The Sponsor will provide the site with details regarding archiving of study data and retention, return, or destruction of other study materials.

6 Schedule of Study Procedures and Assessments

[redacted]

6.1 Subject Recruitment and Screening

6.1.1 Subject Recruitment

Study subjects may be recruited from the pool of subjects attending clinics at the study site. Referrals may be sought from local physicians/general practitioners in the community who see and treat subjects. In addition, internet, radio, newspaper, and other clinical site defined advertising methods that have been approved by the EC/IRB, may be utilized.

6.1.2 Screening Evaluations

Subject screening for study specific examinations may begin after the subject signs the IRB/EC approved informed consent form.

[redacted]

The investigator will determine a subject's eligibility for treatment when all screening requirements have been completed. Screening may include immediate pre-procedure assessments that are performed on the same day as the scheduled ablation treatment (e.g. urine pregnancy). The evaluations listed below will be performed to assess for anomalies and pathology to confirm the subject's eligibility for treatment. All documentation supporting that the subject has completed assessments and the accuracy of those assessments, including images from TVU and SIS, should be retained in the subject study file.

Screening Examination	Window for examination
• Detailed medical history [redacted]	During screening
• Height and weight for BMI calculation	≤ 6 months prior to informed consent
• Blood testing [redacted]	≤ 6 months prior to informed consent unless previously performed and results are available
• Blood testing [redacted]	≤ 6 months prior to informed consent
• Blood testing: follicular stimulating hormone (FSH) if subject age is > 40 years	≤ 6 months prior to informed consent
• Pelvic Exam	≤ 6 months prior to informed consent

Screening Examination	Window for examination
• Uterine sound measurements	During screening at the time of pelvic exam, endometrial biopsy or other
• Diagnostic hysteroscopy	≤ 6 months prior to informed consent
• Transvaginal ultrasound [redacted]	≤ 6 months prior to informed consent
• Saline Infused Sonohysterography [redacted]	≤ 6 months prior to informed consent
• Endometrial biopsy	≤ 12 months prior to informed consent
• Papanicolaou test and HPV testing	Per current ASCCP guidelines with appropriate documentation (no > 5 years prior to informed consent if age ≥ 30 years; no > 3 years prior to informed consent if age < 30 years)
• Sexually transmitted disease (STD) testing	During screening
• Subject baseline assessment of pain rated on scale of 0 (no pain) to 10 (worst possible pain)	≤ 24 hours of scheduled treatment
• Menorrhagia Impact Questionnaire Quality of Life Assessment	During screening
• Premenstrual Symptoms Impact Survey	During screening
• PBLAC Diary	Per eligibility requirements for at least one menstrual cycle within 3 months of informed consent
• Transvaginal ultrasound [redacted]	[redacted]
• Urine Pregnancy test	≤ 24 hours of scheduled treatment

6.2 PBLAC Diary: Screening and Follow-up Reporting

The validated menstrual pictogram instrument [redacted] will be used [redacted] A subject must maintain a PBLAC diary during screening and if treated, through the 12 month follow-up visit. Each subject will be provided with a supply of sanitary products, menstrual towels (pads) and tampons, to use during her menstrual bleeding cycle. The subject will be instructed to use only the specific sanitary products provided to her as the fluid absorption of sanitary products varies considerably and the use of non-specific study products can affect study results.

To qualify for treatment, the subject must record her menstrual blood loss using a PBLAC diary to confirm a PBLAC menstrual blood loss score of ≥ 150, within 3 months of informed consent, as follows:

- For two baseline cycles; OR
- For one baseline cycle if the subject has at least 3 prior months documented failed medical therapy, or a contraindication to medical therapy, or cannot tolerate medical therapy, and/or was offered and declined medical therapy.

Sites will collect and review subject screening PBLAC diaries. The screening PBLAC diary(s) will be scored to confirm the subject meets the PBLAC inclusion criteria. If the investigator determines that the screening PBLAC diary was not recorded correctly, the subject may be asked to complete another diary for an additional menstrual cycle.

Subjects treated with the Cerene device will be required to maintain a monthly PBLAC diary to track their blood loss after ablation treatment. [redacted]

[redacted]

[redacted]

If the subject becomes amenorrheic following ablation treatment, the investigator will determine whether a urine and/or blood test for pregnancy is indicated, based upon subject symptoms.

6.3 Endometrial Thinning

Endometrial thinning prior to ablation is recommended and can be achieved through medication or timing of the menstrual cycle to the early proliferative phase, per Investigator discretion.

6.4 Cerene Ablation Treatment

6.4.1 Subject Preparation for Treatment

- Urine for pregnancy
- Confirm subject eligibility
- Uterine sound measurements
- Endometrial thickness measurement: [redacted]
- Administer pre-procedure medications for anesthesia and/or analgesia

6.4.2 Ablation Treatment

NOTE: Introduction of air and/or bubbles via saline hysteroscopy immediately prior to the ablation could interfere with the subsequent ablation. Use of CO_2 hysteroscopy is not indicated immediately prior to ablation. Hysteroscopy, of any kind, immediately post ablation treatment is not indicated.

- Prepare subject for ablation procedure per standard practice
- Administer local analgesics, paracervical block, and anesthesia per investigator discretion
- Record all analgesia/anesthetics administered
- Initiate the ablation treatment with the Cerene Device per the Instructions for Use and physician training materials
- Assess and record subject's pain intensity (0-10):
    1. After subject preparation and cervical dilation, but before device insertion
    2. After device insertion (before liner deployment)
    3. After liner deployment (before ablation)
    4. After 1 minute of ablation
    5. At end of ablation
    6. Post ablation: one additional pain measurement between >15 and 30 minutes, inclusive.
- Ultrasound monitoring during device placement and ablation may be used, but is not mandatory

- Dispose of Nitrous oxide per standard hospital procedure and/or according to Instructions for Use and physician training materials

6.5 Post-Treatment through Discharge

- Allow the subject to recover following treatment and monitor her per standard practice
- Record medication administered post-procedure
- Record adverse events
- Assess and record subject's pain intensity at discharge/dischargeability
- Record the subject's time and date of discharge

- Record time and date the subject is eligible for discharge

6.6 Day 1 Post treatment (+3 days)

- Contact subject next day after Cerene Device treatment procedure to assess status (telephone or office visit)
- Record subject's adverse events
- Assess subject's pain intensity (0-10)

6.7 Week 2 Post treatment (+ 2 weeks)

- Perform pelvic exam
- Query subject on return to activities of daily living
- Record Adverse Events
- Review PBLAC diary recording and instructions. Remind subject to submit monthly PBLAC diary.
- Query subject regarding the use of additional medications or surgical procedures to manage heavy menstrual bleeding

6.8 Month 3 Post treatment (± 4 weeks)

- Perform pelvic exam, if needed
- Administer MIQ and PMSIS questionnaires
- Collect and review PBLAC
- Query subject regarding the use of additional medications or surgical procedures to manage heavy menstrual bleeding
- Record Adverse Events since last follow-up

6.9 Month 6 Post treatment (± 4 weeks)

- Perform pelvic exam, if needed
- Administer MIQ and PMSIS questionnaires
- Collect and Review PBLAC
- Query subject regarding the use of additional medications or surgical procedures as intervention to manage heavy menstrual bleeding
- Record Adverse Events since last follow-up

6.10 Month 12 Post treatment (± 4 weeks)

- Perform pelvic exam
- Collect FSH when age is > 40 years
- Administer MIQ and PMSIS questionnaires
- Assess uterine cavity access and healing via hysteroscopy
- Collect and Review PBLAC
- Query subject regarding the use of additional medications or surgical procedures as intervention to manage heavy menstrual bleeding
- Record Subject satisfaction and recommendation
- Record Adverse Events since last follow-up

[redacted]

6.11 Month 24 Post Treatment (± 4 weeks)

Collect the information listed below during the subject's office or telephone contact visit.

- Query the subject regarding:

1. Any medication that she is taking or any surgical procedure or other treatment that she has undergone for uterine bleeding
2. Gynecologic adverse events
3. Type of contraception, compliance with contraception, and if she is pregnant or had a pregnancy
4. Menstrual status
5. Satisfaction with the results of the Cerene treatment and willingness to recommend the procedure to a friend or relative

- Administer the MIQ and PMSIS questionnaires during the contact

6.12 Month 36 Post Treatment (± 4 weeks) / Subject Exit

Collect the information listed below during the subject's office or telephone contact visit.

- Query the subject regarding:
  1. Any medication that she is taking or any surgical procedure or other treatment that she has undergone for uterine bleeding
  2. Gynecologic adverse events
  3. Type of contraception, compliance with contraception, and if she is pregnant or had a pregnancy
  4. Menstrual status
  5. Satisfaction with the results of the Cerene treatment and willingness to recommend the procedure to a friend or relative
- Administer the MIQ and PMSIS questionnaires during the contact
- Exit subject at this visit per protocol

7 Adverse Event Reports

An adverse event is any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event that appears or worsens in a subject during a clinical study, regardless of whether or not it is considered related to the procedure / investigational device.

Anticipated signs and symptoms (e.g. nausea, cramping) which occur in the recovery room will not be considered adverse events unless they occur with greater severity or intensity than anticipated.

It is the responsibility of the investigator to report all adverse events as required by this protocol. Adverse event information will be collected throughout the study at each subject contact as defined in the table below. Adverse events will be recorded on the Adverse Event CRF by the investigator or study coordinator and include start and stop date, anticipated or unanticipated,

outcome, severity, seriousness, and relatedness to the procedure, device, and/or pre-existing condition.

Table 3: Adverse Event Reporting at Subject Follow-up Contacts

Type of Adverse Event	Follow-up Visit for Subject Query / Assessment
Any non-serious AE or SAE	Any contact through the Month 12 follow-up visit
Gynecologic non-serious AE or SAE	After Month 12, any contact through subject exit
Pregnancy	Any contact through subject exit

The number and percent of subjects experiencing an adverse event will be summarized by site, severity, relatedness, and seriousness. The number and percent of subjects who withdraw or discontinue from the study due to an adverse event will also be tabulated.

Serious adverse events and unanticipated adverse device effects must be reported to the Sponsor immediately or within 24 hours (one working day) by telephone (+1-510-338-9301), fax (+1-510-338-9303), or e-mail (clinreg@channelmedsystems.com). To maintain subject confidentiality, the subject will be identified only by the subject study identification number. A written report must follow the initial notification within five working days and include a full description of the event and sequelae, in the format detailed by the serious adverse event reporting form. After the Month 12 follow-up visit, events that are not gynecologic SAEs or device related are not required to be reported. A subject's death must always be reported regardless of cause.

A serious adverse event must be followed until it has subsided or, in case of permanent impairment or residual effects, until the event stabilizes, and the overall clinical outcome has been ascertained.

Severity of Adverse Events: The definitions below will be used to rate the severity of adverse events for this study.

- **Mild:** Awareness of signs or symptoms, but easily tolerated and transient; causing no loss of time from normal activities; symptoms would not require medication or a medical treatment; signs and symptoms are transient.
- **Moderate:** Marked symptoms and discomfort severe enough to cause moderate interference with the subject's usual activities. Symptomatic treatment is possible.
- **Severe:** Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical intervention and/or treatment. Hospitalization may be required or prolonged.

Serious Adverse Events (SAE): An Adverse event is categorized as an SAE if it meets any of the criteria listed below. SAE categorization is independent of the severity rating applied above.

- Death
- Life-threatening: the subject was at substantial risk of dying at the time of the adverse event, or if use or continued use of the device or other medical product might have result in the death of the subject
- Hospitalization (initial or prolonged) due to an adverse event

  Emergency room visits that do not result in admission to the hospital will be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

  A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
  - The admission results in a hospital stay of less than 12 hours
  - The admission is pre-planned (such as elective or scheduled surgery arranged prior to the start of the study)
  - The admission is not associated with an AE (such as hospitalization for purposes of respite care)
- Disability or permanent damage
  - Disability means a substantial disruption of a person's ability to conduct normal life's functions
- Requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
- Congenital anomaly / birth defect caused by exposure to a medical product prior to conception or during pregnancy

- Any medically important serious adverse event as judged by the investigator
  This includes an adverse event that does not fit the other outcomes, but it may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Serious Deterioration in the State of Health, per Health Canada SOR/98-282:

- Serious Deterioration in the State of Health, as defined in the Health Canada Regulations, involves: life-threatening disease, disorder or abnormal physical state,
- The permanent impairment of a body function or permanent damage to a body structure, or
- A condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or investigator's brochure), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Near incident: Any malfunction or deterioration in the characteristics and/or performance of the device which might have led to death or serious deterioration in health; incident occurred and is such that if it occurred again, it might lead to death or serious deterioration in health.

Adverse Event Relationship: The relationship of an Adverse Event to a pre-existing condition, underlying disease, screening procedure, ablation procedure or treatment, or the device will be attributed as not related or related.

Adverse Event Status (outcome): The outcome of an adverse event should be assessed at every subject contact to determine if it has resolved or stabilized, or is ongoing. It can be updated if new information is received. The status should be recorded as follows:

- Resolved: the AE has stopped and the stop date should be recorded.
  NOTE: The severity of an AE may change. If the severity changes, the AE with the existing severity should be recorded as resolved and the stop date when the severity changed should be entered. A new AE with the updated severity should be recorded with a start date that the severity changed.
- Resolved with residual side effects: this outcome would be recorded if the AE has stabilized but a pathological or residual condition continues. Therefore, the AE

symptom(s) has not completely resolved and a new baseline for the subject/ patient is established since full recovery is not expected (the AE is expected to continue for an undetermined amount of time). A stop date for the AE should be recorded as the approximate date of AE stabilization.

- Not resolved: this outcome would be recorded at subject exit if the adverse event has not stopped or stabilized. A stop date for the AE should NOT be recorded.
- Fatal: this outcome would be recorded if the subject expired. The stop date for the AE is recorded as the date of death.
- Other: this outcome would be recorded if any of the outcomes listed above do not apply. The reason for other should be specified. A stop date for the AE may or may not be recorded.

8 Risks and Benefits

8.1 Potential Risks to the Subject

Participation in this clinical study may expose the subject to potential risks associated with the device or the procedure. Safety events will be collected and reviewed throughout the study. Investigators will be notified of any additional risks identified during the study that could affect the health, safety, or welfare of the study subjects.

Risks associated with the use of the **Cerene Device** are anticipated to be similar to risks associated with other endometrial cryoablation products. The list of potential risks, provided below, is based on a review of scientific literature, animal studies, product risk and clinical risk analyses performed by the Sponsor.

- Abdominal bloating
- Abdominal pain
- Additional intervention for bleeding
- Anesthesia-related, adverse reaction or over-medication
- Cervical stenosis
- Cervical tear/injury
- Damage to adjacent organs (e.g. bowel burn or bladder injury) (Note: a severe bowel injury could potentially lead to death)
- Dysmenorrhea
- Dyspareunia
- Embolism
- Endometritis
- Fever
- Hematometra
- Infection, sepsis, or death due to sepsis
- Nausea

- Nitrous oxide impairment (dizziness)
- Pelvic cramping
- Pelvic or abdominal injury resulting from excessive uterine pressures
- Possible missed diagnosis of uterine cavity pathology post-endometrial ablation
- Post-ablation tubal sterilization syndrome
- Pregnancy (Note: Pregnancy following ablation may be life threatening to both mother and fetus)
- Urinary tract infections
- Uterine perforation
- Uterine synechiae (Asherman's syndrome)
- Vaginal bleeding
- Vaginal discharge
- Vomiting
- Some or all of these risks may require a need for reoperation or subsequent treatment and/or may lead to permanent disability or death.

Note: Vaginal discharge usually happens during the first few days following treatment and may last as long as six weeks. It is generally described as bloody during the first few days, a mixture of blood and fluid for another week, then followed by a watery discharge that can be substantial at times. This is an anticipated symptom of the cryotherapy treatment and is not considered an adverse event unless the vaginal discharge suggests infection.

There is also the possibility of an unanticipated reaction to the study device and/or medications used during the procedure that could require emergency intervention. Subjects with known sensitivity to drugs that may be used during the procedure are excluded from study participation. Should a subject experience a significant side effect for which there is concern, she will be managed per investigator standard of care and institutional requirements.

If sedation is used, potential risks from the agents and/or gases used include postoperative pain, nausea and vomiting, dizziness, drowsiness, shivering, liver toxicity, and/or cardiovascular events. Trained professionals with extensive experience and expertise who routinely administer anesthesia to subjects will be responsible for the induction and associated monitoring required for this type of procedure. Study subjects will be monitored throughout treatment, recovery, and discharge per investigator and institution requirements. In addition, the risks of blood draws include temporary pain and discomfort from the needle stick, and/or tenderness, redness or bruising at the site, bleeding, fainting and lightheadedness.

This list of risks may not be complete and it is possible that unforeseen risks could occur. There is also the risk that the procedure may not be effective or the subject may not be able to be treated because of obstructions within the cavity, an unusual cavity shape, or inadequate uterine dimensions that are determined at completion of screening on the day of study treatment.

8.2 Insurance Coverage

Channel Medsystems, Inc. maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study it is being performed. Documentation will be provided upon request.

8.3 Potential Benefits to the Subject

It is possible that Subject will not receive any benefits from treatment with the Cerene Device. Potential benefits of treatment that may be realized by study participants include overall fewer symptoms related to heavy menstrual bleeding and improved quality of life. In addition, subjects participating in the study is the ability to learn more about their heavy menstrual bleeding, based on the assessments that will be performed throughout the course of the study. In addition, the subjects will receive education about the monitoring of their disease, as will be required for study participation.

9 Study Monitoring

In accordance with applicable regulations, GCP, and Sponsor procedures, when subject enrollment is initiated, study monitors will meet with clinical site staff to review the protocol, subject eligibility criteria, study requirements, data collection and reporting requirements, and the investigator's responsibilities to satisfy regulatory, ethical, and Sponsor's requirements. The study monitor will identify the types and location of source documentation in use at the site.

The study monitor will monitor study data to verify that the subject's rights and well-being are protected, the study investigator is conducting the study in compliance with the protocol and the investigator's agreement, and to ensure reported data are authentic, accurate and complete. Remote and on-site data monitoring will be utilized. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF.

The Investigator will allow direct access to subject files and source documents for the purpose of verifying CRF entries and assist with the study monitor's activities as required. Clinical site staff will provide adequate time, office accommodations, and resources (including copy machine, phone, and/or internet access) to the study monitor for monitoring visits. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status. Source documents must be signed and dated by the investigator or designee for each visit.

A third-party monitor has been appointed as the data management CRO for this study.

Study Monitor: [redacted]

9.1 Responsibilities of the Sponsor

Sponsor responsibilities include but are not limited to:

- Conducting this clinical study in compliance with all applicable regulatory requirements and guidelines, specifically in accordance with FDA regulations as described in 21 CFR 50 and 56 and 812, ISO 14155:2011(E) Clinical investigation of medical devices for human subjects – Good clinical practice, IRB/EC requirements, and the Informed Consent provisions of the Declaration of Helsinki.
- Ensuring study oversight.
- Monitoring study data to verify that the subject's rights and well-being are protected.
- Informing the clinical investigator of any new information about the study that may affect the health, safety or welfare of the subjects, or which may influence her decision to continue participating in the study.
- Providing the clinical investigator with the study protocol and the CRFs on which to document the study evaluation variables for each subject.
- Selecting qualified investigators to conduct this clinical study. Each Investigator will sign an Investigator Agreement prior to the study start. Financial Disclosure Statements will be completed, as required.
- Maintaining copies of correspondence, records of shipment and disposition of devices, adverse device effects, records related to the signed investigator agreements, and other records related to the clinical study.

9.2 Responsibilities of the Investigator

Each clinical investigator that will perform treatments with the investigational device in this clinical study must be licensed a physician in his/her country of employment. The investigator will affirm by his/her signature on the Investigator's Agreement that he/she will fulfill his/her responsibilities to this clinical study.

Investigator responsibilities include but are not limited to:

- Protecting the rights, safety, and welfare of subjects under his/her care
- Ensuring that all subjects meet eligibility criteria prior to treatment
- Obtaining initial and ongoing IRB/EC Approval of the protocol
- Obtaining subject informed consent using an IRB/EC approved informed consent form
- Performing subject evaluations and reporting data as specified in the protocol
- Documenting and reporting protocol deviations
- Retaining original records for the timeframe required by local regulation or longer per Sponsor instruction
- Ensuring investigational devices are dispensed only to study subjects and under the direct supervision of the investigator or co-investigators
- Maintaining records of investigational device disposition

10 Record Keeping and Report Requirements

10.1 Subject Confidentiality

Subject confidentiality shall be maintained at all times throughout the conduct of the study, and all subject data shall be maintained secure against unauthorized access. Whenever possible, subject names will not be provided to the Sponsor. Only the study ID number will be recorded on the CRF. During the informed consent process, the subject will be informed that representatives of the Sponsor, IRB/EC, or regulatory authorities may inspect, review, and photocopying of the subject records and that all personal information will be maintained in strict confidence and in accordance with local data protection requirements and/or laws. In the event a subject's data are used for educational, presentation, and/or publication purposes, subject identity will be masked to protect the subject's confidentiality.

10.2 Protocol Deviations

The investigator must adhere to all specifications defined in this protocol. The study investigator should not deviate from the protocol, unless the study plan poses unacceptable risks to the health or welfare of the involved individual subject. The investigator shall notify Channel Medsystems Inc. and the reviewing ethics committee of any deviation from the protocol intended to protect the life or physical wellbeing of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five working days after the emergency occurred. Except in such an emergency, prior approval of Channel Medsystems Inc. is required for any deviation from the protocol. Approval from the IRB/EC also is required if these changes or deviations are expected to affect the rights, safety or welfare of human subjects.

10.3 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate and timely reports on this investigation (See Table below)

Table 4: Responsibilities for Submitting Reports and Other Data

Type of Report	Prepared by Investigator For	Time of Notification
Informed Consent Not Obtained From Subject	Sponsor, IRB/EC	Within 5 working days
Device Malfunction	Sponsor Return device to Sponsor	Within 5 working days of malfunction
Device Malfunction associated with an SAE	Sponsor, Health Canada*	In Canada: Within 72 hours of occurrence
Serious Adverse Event (Including death) Notification	Sponsor, IRB/EC**	Within 24 hours of knowledge of event**
Unanticipated Adverse Device Events (UADE) Notification	Sponsor	Within 24 hours of knowledge of event
Unanticipated Adverse Device Event (UADE) Report	Sponsor, IRB/EC	Within 10 working days of knowledge of event
Serious Adverse Event Written Report	Sponsor, IRB/EC**	Within 5 working days of knowledge of event to the Sponsor and according to IRB/EC policy to the IRB/EC
Subject Withdrawal	Sponsor	Within 5 working days of withdrawal
Withdrawal of IRB/EC approval	Sponsor	Within 5 working days of withdrawal
Major deviation from the Investigational Plan, protecting life or physical wellbeing of subject	Sponsor, IRB/EC	Within 5 working days of deviation
Progress Report	Sponsor, IRB/EC	At a minimum, annually
Final Report	Sponsor, IRB/EC	Within 3 months of study completion

* Reporting requirement specific to Canadian study centers
** Notification to be made according to local and/or central IRB/EC policy.

10.4 Record Retention

For clinical sites in the United States, the investigator should retain all study records and reports for a minimum of six (6) years. For clinical sites in Canada, the investigator should retain all study records and reports for a minimum of twenty five (25) years. For other countries, the clinical site should retain records for a minimum of two (2) years or according to local requirements or regulations if longer. To avoid error, the Investigator should contact the Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the investigator should contact the sponsor if he/she plans to leave the investigational site so that arrangements can be made for transfer of records.

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