SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Thermal (Radiofrequency Ionized Argon Gas) Endometrial Ablation Device
Device Trade Name:	Minerva™ Endometrial Ablation System
Device Procode:	MNB
Applicant's Name and Address:	Minerva Surgical, Inc. 101 Saginaw Drive Redwood City, CA 94063
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140013
Date of FDA Notice of Approval:	July 27, 2105
Priority Review:	No

II. INDICATIONS FOR USE

The Minerva Endometrial Ablation System is indicated to ablate the endometrial lining of the uterus in pre-menopausal women with menorrhagia (excessive menstrual bleeding) due to benign causes for whom childbearing is complete.

III. CONTRAINDICATIONS

The Minerva Endometrial Ablation System is contraindicated for use in the following:

- A patient who is pregnant or who wants to become pregnant in the future. PREGNANCIES FOLLOWING ABLATION CAN BE DANGEROUS FOR BOTH MOTHER AND FETUS.
- A patient with known or suspected (uterine cancer) or pre-malignant conditions of the endometrium, such as unresolved adenomatous hyperplasia.
- A patient with any anatomic condition (e.g., history of previous classical cesarean section or transmural myomectomy, including hysteroscopic and/or laparoscopic myomectomy performed immediately prior to the Minerva procedure) or pathologic condition (e.g., requiring long-term medical therapy) that could lead to weakening of the myometrium.

- A patient with a history of prior endometrial ablation and/or resection (including endometrial ablation/resection performed immediately prior to Minerva procedure and regardless of the modality by which it was performed).
  REPEAT ABLATION MAY RESULT IN SERIOUS PATIENT INJURY.
- A patient with active genital or urinary tract infection at the time of the procedure (e.g., cervicitis, vaginitis, endometritis, salpingitis or cystitis).
- A patient with an intrauterine device (IUD) currently in place and which is not removed prior to the Minerva procedure.
- A patient with a uterine cavity length less than 4 cm. The minimum Plasma Formation Array (PFA) length is 4 cm. Treatment of a uterine cavity with a length less than 4 cm will result in thermal injury to the endocervical canal.
- A patient with a narrow uterine cavity.
- A patient where the Array Opening Indicator is in the Red Zone following deployment of the Minerva Disposable Handpiece.
- A patient with active pelvic inflammatory disease.
- A patient with undiagnosed vaginal bleeding.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Minerva Endometrial Ablation System labeling.

V. DEVICE DESCRIPTION

The Minerva Endometrial Ablation System is designed to treat abnormal uterine bleeding due to benign causes in pre-menopausal women for whom childbearing is complete. The purpose of this procedure is to ablate the endometrium, thereby reducing future uterine bleeding. The procedure involves the physician inserting a disposable, hand-held device into the patient's uterus via the cervical canal to allow assessment of the cavity and to enable the delivery of energy to the endometrial tissue. This delivered energy facilitates destruction of the endometrium.

The Minerva Endometrial Ablation System consists of two major components, the Minerva Radio Frequency (RF) Controller and the Disposable Handpiece. **Figure 1** is an image of the Minerva Endometrial Ablation System.

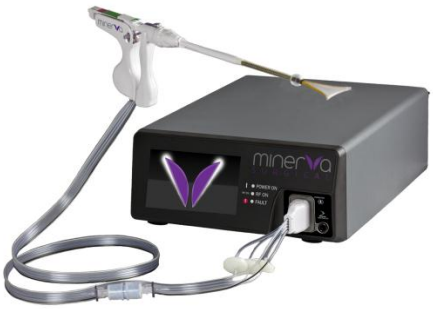


Figure 1 Minerva Endometrial Ablation System

The Minerva RF Controller is a bipolar 480 kHz RF power generator and controller. It generates, monitors, and manages this energy delivery to the patient. The user interface of the Minerva RF Controller consists of a touch screen display, a connector for a pneumatic footswitch to actuate the system, an audio feedback mechanism to inform the physician of system status, and a custom connection port for connection of the Disposable Handpiece. The rear of the Minerva RF Controller has a connection for the power cord and threaded ports for user installation of argon and CO_2 canisters.

The Disposable Handpiece is a sterile, single-use only component that connects to the Minerva RF Controller and delivers energy to the endometrial lining of the uterus. At the distal end of the Disposable Handpiece is the Plasma Formation Array (PFA). The PFA is the portion of the Disposable Handpiece that contains the circulating argon gas and is in contact with the endometrial tissue. The PFA is deployed in the uterus and approximates the size and shape of the uterus in which it is placed. When the system is energized, the argon gas within the PFA is ionized, turning it in to plasma. The argon plasma heats the interior surface of the silicone membrane, and this energy, in the form of heat, is conducted through the silicone membrane and into the tissue in contact with the membrane. The combination of the heat conducted through the membrane wall from the plasma to the adjacent endometrial tissue and resultant heat from a small amount of bi-polar RF current travelling through the target tissue results in the ablation of endometrial tissue.

To initiate the Minerva procedure, the operator prepares and plugs the Minerva RF Controller into a 110 volt power outlet using the supplied power cord. The operator installs the argon and CO_2 canisters into their respective ports on the back of the Minerva RF Controller. The two canister threads are different sizes so that the two canisters cannot be interchanged. The operator connects the pneumatic footswitch tube to the footswitch port on the front of the Minerva RF Controller and turns on the Minerva RF Controller. The Minerva RF Controller boots up automatically and completes all necessary self-tests. After the self-tests are completed, the Minerva RF Controller enters a standby mode while waiting for the operator to connect the Disposable Handpiece. The Minerva RF Controller communicates this activity to the user via the touch screen display.

After the surgical team prepares the patient for the Minerva procedure, including the completion of anesthesia, bimanual exam, all uterine measurements, and optional hysteroscopy, the operator removes the Disposable Handpiece from its sterile package. Using the uterine cavity length measurement derived from sounding the uterus, the operator sets the operating length of the PFA and plugs the Disposable Handpiece into the Minerva RF Controller. The Minerva RF Controller automatically performs the necessary self-tests of the Disposable Handpiece. After the self-tests are complete, the Minerva RF Controller communicates to the operator that the system is ready for use.

The operator initiates the ablation procedure by inserting the tip of the Disposable Handpiece into the uterine cavity via the cervical canal. (The patient's cervix should be dilated to 7.0 mm.) Once the operator properly positions the Disposable Handpiece, he or she deploys the PFA. The operator seals the uterine cavity at the internal cervical os by inflating the silicone Cervical Sealing Balloon using the 3 cc syringe. (The Cervical Sealing

Balloon is situated immediately below the PFA on the Disposable Handpiece.) The operator presses and releases the footswitch to initiate the Uterine Integrity Test. The Uterine Integrity Test verifies that there are no perforations or holes in the uterine wall or silicone membrane of the PFA using CO_2 gas. Upon completion of the Uterine Integrity Test, the Minerva RF Controller automatically initiates the treatment cycle by delivering RF energy to the Disposable Handpiece for exactly 120 seconds.

The Minerva RF Controller automatically terminates energy delivery after the 120 second treatment cycle is complete. The operator deflates the Cervical Sealing Balloon, collapses the PFA, and removes the Disposable Handpiece from the patient. The operator turns off the Minerva RF Controller.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of excessive uterine bleeding due to benign causes. Each alternative has advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets her expectations and lifestyle.

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

- **Dilatation and Curettage (D&C)**
  D&C is typically the first step in eliminating excessive bleeding if drug therapy is unsuccessful, or if the patient is intolerant to drug treatment. First the cervix is dilated, and then the endometrial lining of the uterine cavity is either scraped by an instrument or removed/evacuated through vacuum aspiration. D&C may reduce bleeding for a few cycles. If a polyp is present and removed, the bleeding may stop. In most cases, D&C does not provide the patient with long-term definitive results. It is useful, however, for women who desire to maintain their fertility.

- **Hysteroscopic Endometrial Ablation**
  Hysteroscopic endometrial ablation is a surgical procedure which utilizes a resectoscope or operating hysteroscope, a video monitor, a fluid distention medium such as Glycine or Sorbitol, and a surgical ablation device such as an electrode loop, rollerball, or laser to destroy the inner lining of the uterus, the

endometrium. The procedure is typically performed under general or epidural anesthesia. The cervix must be dilated to accommodate the hysteroscopic instrument, and the uterine cavity must be properly distended. The most common risks associated with hysteroscopic endometrial ablation are hyponatremia from fluid overload, which is a life-threatening condition, and uterine perforation. This treatment is intended for women who no longer desire to maintain their fertility.

- **Second Generation "Global" Endometrial Ablation (GEA)**
  Second Generation Global Endometrial Ablation technologies are faster, less complex and, in most cases, allow for a significant reduction in the incidence of complications associated with endometrial ablation, when compared to hysteroscopic endometrial ablation.

  There are currently five endometrial ablation systems approved by FDA:

  - The ThermaChoice Balloon Endometrial Ablation System (Gynecare, P970021) uses thermal energy from heated sterile fluid (5% dextrose in water) contained within a silastic balloon.
  - The HTA System (Boston Scientific, P000040) uses free flowing USP 0.9% saline heated externally and injected into the uterine cavity.
  - The Her Option Cyroablation System (Cooper Surgical, P000032) uses extreme cold at the tip.
  - The NovaSure RF Endometrial Ablation System (Hologic, P010013) uses bi-polar RF energy to create heat
  - The Microsulis Microwave Endometrial Ablation System (Microsulis Medical, P020031) uses microwave energy to heat the endometrial layer of the uterus.

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

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

VII. MARKETING HISTORY

The Minerva Endometrial Ablation System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Minerva Endometrial Ablation System.

- Pelvic cramping
- Vaginal discharge and/or unpleasant vaginal smell or burning or other abnormal sensation
- Bleeding or spotting
- Nausea and/or vomiting
- Abdominal pain and/or bloating
- Weakness, fatigue, sleepiness, lack of concentration, dizziness
- Circulatory symptoms
- Backache
- Headache
- Fever
- Skin rash and/or itching or burning sensation
- Constipation
- Endo- or Endomyometritis
- Pelvic inflammatory disease
- Agitation
- Vulvar pruritus
- Urinary disturbance

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

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

The following adverse events could occur or have been reported in association with the use of other endometrial ablation systems and may occur when the Minerva Endometrial Ablation System is used:

- Post-ablation tubal sterilization syndrome
- Pregnancy-related complications
  NOTE: pregnancy following endometrial ablation is very dangerous for both the mother and the fetus.
- Thermal injury to adjacent tissue, including bowl, bladder, cervix, vagina, vulva and/or perineum

- Perforation of the uterine wall
- Hemorrhage
- Hematometra
- Difficulty with defecation or micturition
- Uterine necrosis
- Air or gas embolism
- Infection or sepsis
- Complications leading to serious injury or death

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility

The patient contacting components of the Minerva Endometrial Ablation System include the Cervical Sheath Assembly and the Plasma Formation Array of the Disposable Handpiece. The Cervical Sheath assembly and Plasma Formation Array assembly contact mucosal membranes for a limited (<24 hour) contact duration. Therefore, per ISO 10993-1:2009, assessment of the cytotoxicity, sensitization, and irritation potential of these components are required.

The applicant completed the following biocompatibility testing on the final, finished version of the Cervical Sheath Assembly and Plasma Formation Array:

- Cytotoxicity - ISO Elution Method (ISO 10993-5:2009)
- Sensitization – Guinea Pig Maximization Test (ISO 10993-10:2010)
- Irritation – Vaginal Irritation Test (ISO 10993-10:2010)

The protocol and results of the above biocompatibility tests are acceptable and demonstrate that the patient contacting components of the Minerva Endometrial Ablation System are non-cytotoxic, non-sensitizing, and non-irritating.

B. Sterilization Validation

The Disposable Handpiece is terminally sterilized using gamma radiation to sterility assurance level of 10^{-6} using a minimum dose of 25 kGy. The sterilization process was validated in accordance with the applicable sections of ISO 11137-1:2006 and ISO 11137-2:2006. The sterilization validation substantiated that a minimum 25 kGy (via VD_{max} 25) production dose provides a sterility assurance level of 10^{-6}. The validated production dose is 25 to 40 kGy.

C. Shelf Life

The Disposable Handpiece has a shelf life of six months based on the results of an accelerated aging study. The accelerating study demonstrates that the Disposable Handpiece maintains its functionality, and its packaging maintains the sterility of the Disposable Handpiece for a shelf life of six months.

The applicant intends to verify the results of the accelerated aging study through a real-time aging study.

D. Mechanical Safety and Performance

Minerva Surgical, Inc. completed design verification testing on the Minerva Endometrial Ablation System.

Disposable Handpiece

- Verification of Dimensions – The PFA width, exposed PFA length, PFA insertion profile, sheath working length, cord length, and cervical sealing balloon diameter were measured and found to be within specifications following the specified number of frame expansions at maximum width and length and after maximum bending and torque cycling.

- Gas Flow Tests – The required gas flow rates at the specified pressures and settings met specifications, and the gas leak rates were below the maximum allowable leak rate specifications.

- Plasma Formation Tests – The power and voltage required to generate and maintain argon plasma were within specified levels, and the argon plasma was contained within the PFA. The PFA membrane met the specified pressure requirements to ensure the specified circulation rate of argon.

- Cervical Sealing Balloon Tests – The cervical sealing balloon was able to maintain a specified diameter for the required time following inflation and could be deflated reliably. The burst volume of the cervical sealing balloon exceeded a specified minimum.

- PFA Opening Indicator Tests – The PFA opening indicator met specifications following the specified number of frame expansions at maximum width and length after maximum bending and torque cycling. It also displayed the appropriate red/green designations based on specified frame widths. (Red and green designate insufficient and sufficient deployment, respectively.)

- PFA Deployment – The PFA remained locked after three expansions at maximum width and length settings, and when rotated and angulated per test specification

parameters. The PFA could be locked and unlocked per specification. The PFA deployment force did not exceed a specified maximum.

- Joint Strength – The sheath to handle joint met the minimum tensile force. The shaft lock to internal housing joint met a minimum tensile force. The shaft lock lever met a minimum compression force.

- Impedance – When measured at the operating frequency, the impedance did not exceed a specified maximum.

Minerva RF Controller

- Uterine Integrity Test Procedure – The evaluation of the uterine integrity test determined if the Minerva RF Controller completed the following actions:
    - Minerva RF Controller did not deliver RF energy without first completing the Uterine Integrity Test.
    - The uterine integrity test animation displayed on the touch screen display and was accompanied by an audible tone. When the uterine integrity test was complete, the touch screen display notified the user.
    - The Minerva RF controller proceeded to the treatment phase following the uterine integrity test.
    - The maximum CO_2 flow rate and pressure was within allowable limits during the uterine integrity test.

- Disposable Handpiece Integrity Tests – The Disposable Handpiece integrity test determined if the Minerva RF Controller completed the following actions:
    - Initial free CO_2 flow test reported the status of CO_2 circuit integrity.
    - Touch screen display notified user of pass or fail and replace Disposable Handpiece.
    - Initial integrity check of argon circuit prompted user if a leak was present in circuit.

- Power Output Tests – The power output tests verified that the appropriate output power was delivered at specified loads. The Minerva Endometrial Ablation System was able to generate and maintain plasma when the Disposable Handpiece was connected to the RF Controller, and the RF Controller supplied the specified voltage and power.

- Treatment Complete Test – The applicant confirmed that the Minerva RF Controller stopped treatment after 120 seconds and that the Touch Screen Display indicated "Treatment Complete."

- PFA Membrane Defect Detection Test – The applicant confirmed that defects in PFA membrane were effectively detected and that the Minerva RF Controller responded with termination of energy delivery.

- Fault Condition Tests – The applicant verified that all pre-specified fault conditions were properly functioning to ensure that the Minerva RF Controller properly terminates the treatment cycle in the case of a system fault.

E. Electrical Safety and Electromagnetic Compatibility

The Minerva Endometrial Ablation System conforms with the following standards related to electrical safety and electromagnetic compatibility:

- IEC 60601-1: Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-2: Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic Compatibility - Requirements and Tests
- IEC 60601-2-2: Medical Electrical Equipment - Part 2-2: Particular Requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories
- IEC 60601-1-6: Medical electrical equipment - Part 1-6: General requirements for safety - Collateral Standard: Usability

F. Software Validation

The applicant provided software information for the Minerva Endometrial Ablation System in accordance with the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" issued on May 11, 2005. The Minerva Endometrial Ablation System has a major level of concern.

G. Thermal Modeling

Minerva Surgical, Inc. reported the results of finite element simulation of the heating of the Minerva™ Endometrial Ablation System. The applicant completed this testing as part of the initial development of the Minerva™ Endometrial Ablation System and compared the results of the simulation to the porcine liver study results described in Section H.

H. Porcine Liver Study

Minerva Surgical, Inc. completed ex vivo porcine liver studies in which thermocouples were used to record temperature versus time data at different locations relative to the Plasma Formation Array. They conducted 10 ablations for the 120 second treatment duration of the Minerva™ Endometrial Ablation System and evaluated ablation depths for three Plasma Formation Array size configurations.

The average ablation depth for all locations ranged from 2.5 mm to 6.0 mm in depth, and the average of all ablation locations for each sample fell within the range of 4.0 mm to 5.0 mm. The peak temperatures reached during the course of the full ablation cycle were consistent across the three size configurations.

I. Extirpated Uteri Study

The applicant completed an extirpated uteri study as part of their early development work on the Minerva Endometrial Ablation System. The applicant initially conducted a "range finding" series of thirty procedures to assess the device design and to assist in protocol development for future clinical studies. They then conducted ten additional procedures on a final device configuration based on the initial "range-finding" study. During these procedures, the applicant evaluated the Minerva Endometrial Ablation System for uterine integrity, deployment, cervical seal integrity, and ablation parameters. Specifically, they measured uterine serosal temperatures during ablation and conducted gross histological examinations to evaluate thermal tissue effects.

The test devices were able to deploy and conform to the uterus in all 10 specimens, the ease of device positioning and removal was acceptable in all procedures, and uterine serosal temperatures were found to be within a safe physiological range.

The applicant excluded three cases from pathology and histological examination due to uterine size (>10cm) or cavity distorting fibroids. Pathology and histological examination on the remaining seven specimens demonstrated a mean depth of thermal ablation of 3.6 mm (2.4-4.7 mm). The mean closest depth of thermal penetration to the serosa was 11.4 mm (3.2-16.7 mm) from the serosa and was noted in either the anterior lower uterine segment or cornual regions. The applicant did not identify any perforations or signs of serosal thermal injuries. The Fallopian tubes, lower endocervix, and exocervix did not display any thermal histologic changes.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed three clinical studies as follows:

- Peri-hysterectomy study
- Single arm study (12-month safety and effectiveness outcomes)
- Randomized, controlled trial (30-day safety outcomes)

The peri-hysterectomy study was used to evaluate the safety and ablation parameters of the Minerva Endometrial Ablation System.

The applicant provided 12-month safety and effectiveness outcomes from the single-arm study conducted in Canada, Hungary and Mexico and 30-day safety outcomes from the randomized, controlled trial conducted under IDE G110215 in the United States, Canada, and Mexico to establish reasonable assurance of safety and effectiveness of the Minerva Endometrial Ablation System for ablation of the endometrial lining of the uterus in pre-menopausal women with menorrhagia (excessive menstrual bleeding) due to benign causes for whom childbearing is complete. Data from these studies were the basis for the PMA approval decision. A summary of the three studies is provided below.

1. Peri-Hysterectomy Study

Eleven (11) women who were scheduled for an abdominal hysterectomy underwent an *in-vivo* endometrial ablation with the Minerva Endometrial Ablation System, just prior to hysterectomy at three investigational sites. This study was designed to evaluate the safety and ablation parameters of the Minerva Endometrial Ablation System.

The applicant measured serosal temperatures during and immediately after the endometrial ablation procedure with five thermocouples positioned on the serosal surface. The highest serosal temperature recorded was 38.2°C. Gross pathology and histology examinations revealed no evidence of transmural myometrial perforation or serosal thermal injury in any uteri.

Complete endometrial ablation was present in five uteri, and focally absent to partial/incomplete thickness endometrial ablation without myometrial extension was macroscopically and/or microscopically identified in three uteri. One uterus had a histologic hyperthermic lower endocervical injury. The fallopian tubes and exocervix were without thermal histologic changes.

The uterine serosa temperatures maintained a safe physiological range, and the thermal depth of tissue injury was sufficient to support feasibility of the device for treatment of menorrhagia.

2. Single Arm Study

Minerva Endometrial Ablation System Single-Arm, Multi-Center Safety and Effectiveness Clinical Study

A. Study Design

Patients were treated between May 2011 and October 2011. The database for this PMA reflected data collected through one-year post procedure and included 110 subjects. There were 7 investigational sites in Canada, Hungary, and Mexico.

The study was a prospective, multicenter, single arm clinical study. The purpose of the study was to evaluate the safety and effectiveness of the use of the Minerva Endometrial Ablation System in premenopausal women suffering from menorrhagia secondary to benign causes.

The subjects received no endometrial pretreatment (e.g., hormone, dilation and curettage, or cycle timing) and underwent hysteroscopy immediately prior to the Minerva procedure.

Follow-up visits occurred at 2-4 weeks, 3 months, 6 months and 12 months post-procedure. Two- and three-year safety and effectiveness outcomes are also being collected for this study. Device labeling will be updated when these data become available.

The primary safety endpoint was occurrence of adverse events. The applicant evaluated safety by determining the number and percentage of subjects who experienced one or more adverse events and the number of subjects who experienced device-related serious adverse events (SAEs) during the study.

The primary effectiveness endpoint was menstrual blood loss as assessed by the Pictorial Blood Loss Assessment Chart (PBLAC) method. This is a validated menstrual diary scoring system developed by Higham (Higham JM, O'Brien PMS, Shaw RW Br J Obstet Gynaecol 1990; 97:734-9). An individual patient was considered a success if her PBLAC score was ≤ 75 at 12 months post-treatment without incidence of acute treatment failure or additional therapy during follow-up to control menorrhagia.

The secondary endpoints included treatment time, anesthesia type, amenorrhea rates, and patient satisfaction.

The analysis population was the Intent-to-Treat (ITT) population, (i.e., all subjects who presented on the day of the Minerva Endometrial Ablation procedure).

The effectiveness of the Minerva Endometrial Ablation System was compared to an FDA established objective performance criterion (OPC). The OPC was developed with input from industry and members of the Obstetrics and Gynecology Devices Panel. The OPC approach utilized data from the pivotal clinical trials of the five approved endometrial ablation systems. These fives studies were randomized, controlled trials that used the same active control (rollerball ablation) and had similar patient populations. The study sizes ranged from 260 patients to 322 patients with either a 1:1 randomization or a 2:1 (device:control) randomization scheme. The primary endpoint was reduction in menstrual blood loss as assessed by PBLAC. The inclusion criteria required either a baseline PBLAC score of ≥ 150 (four studies) or > 185 (one study), and individual patient success was defined as a PBLAC score of ≤ 75 at 12 months post procedure. The ITT population consisted of all patients who presented on the day for either the endometrial ablation device or rollerball ablation. Patients with missing PBLAC scores at 12 month were treated as failures. A study was considered a success, if the proportion of successes in the GEA group met a pre-specified non-inferiority margin compared to the proportion of successes in the rollerball ablation control group.

Using a generalized linear mixed model with study as a random effect, the FDA determined that the average success rate across the five GEA devices was 75.6% (65.6%, 83.5%) and 77.2% (66.5%, 85.2%) for the rollerball ablation control. The FDA performed additional analyses to evaluate the effect of baseline covariates on the primary endpoint, including age (above and below 40), baseline PBLAC score (over 150), uterine sound (6 to 12 centimeters), and presence of fibroids (< 3 cm). Using analysis of covariance methods, the FDA found that none of these baseline covariates had a significant impact on the study results. Based on this analysis, the

FDA developed a minimum success rate for effectiveness known as an objective performance criterion (OPC). The OPC is 66% based on the lower bound of the 95% confidence interval of the average success rate for the five approved GEA devices.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the single arm study was limited to patients who met the following inclusion criteria:

   - Refractory menorrhagia with no definable organic cause
   - Female subject from age 25 to 50 years
   - Uterine sound measurement of 6.0cm to 10.0cm (external os to internal fundus)
   - One of the following criteria:
     - Documented history of menorrhagia secondary to dysfunctional uterine bleeding (DUB)
     - Using a Pictorial Blood Loss Assessment Chart (PBLAC) scoring system a minimum PBLAC score of ≥ 150 for 1 month prior to enrollment
   - Premenopausal at enrollment as determined by FSH measurement ≤ 40 mIU/mL
   - Not pregnant and no desire to be pregnant in the future
   - Patient agrees not to use a hormonal contraception or any other medical intervention for bleeding during the study
   - Able to provide written informed consent using a form that has been approved by the reviewing IRB/EC
   - Subject agrees to follow-up exams and data collection, and has the ability to accurately use menstrual diaries for PBLAC analysis
   - Subject who is literate or demonstrates an understanding on how to use menstrual diaries, or how to collect and provide used sanitary products for analysis

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

   - Pregnancy or subject with a desire to conceive
   - Endometrial hyperplasia as confirmed by histology
   - Presence of active endometritis
   - Active pelvic inflammatory disease
   - Active sexually transmitted disease (STD), at the time of ablation
     Note: Treatment of STD documented in the chart serves as sufficient evidence of infection resolution. Patient may be considered for study enrollment.
   - Presence of bacteremia, sepsis, or other active systemic infection

- Active infection of the genitals, vagina, cervix, uterus or urinary tract at the time of the procedure
- Known/suspected abdominal pelvic or gynecological malignancy within the past 5 years
- Known clotting defects or bleeding disorders
- Untreated/unevaluated cervical dysplasia (except CIN I)
- Known/suspected abdominal/pelvic cancer
- Prior uterine surgery (except low segment cesarean section) that interrupts the integrity of the uterine wall (e.g., transmural myomectomy or classical cesarean section)
- Previous endometrial ablation procedure
- Currently on medications that could thin the myometrial muscle, such as long-term steroid use (except inhaler or nasal therapy for asthma)
- Currently on anticoagulants
- Abnormal or obstructed cavity as confirmed by hysteroscopy, SIS, specifically:
    - Septate or bicornuate uterus or other congenital malformation of the uterine cavity
    - Pedunculated or submucosal myomas distorting the uterine cavity
    - Polyps likely to be the cause of the subject's menorrhagia
    - Intramural or subserosal myomas that distort the uterine cavity
- Presence of an intrauterine device (IUD) which the patient is unwilling to have removed at the time of the operative visit
- Presence of an implantable contraceptive device (e.g., Essure or Adiana)
- Subject currently on hormonal birth control therapy or unwilling to use a non-hormonal birth control post-ablation (including Mirena)
- Subject who is within 6-weeks post partum
- Any general health condition which, in the opinion of the investigator, could represent an increased risk for the subject
- Any subject who is currently participating or considering participation in any other research of an investigational drug or device

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at 2-4 weeks, 3 months, 6 months and 12 months post-procedure. Two- and three-year safety and effectiveness outcomes are currently being collected for this study.

   Preoperatively, each subject completed a self-reported diary to record menstrual bleeding. These diaries were scored by a clinical research organization to ensure the subject had a minimum PBLAC score of ≥ 150 for study inclusion. The subjects enrolled at sites in Canada and Mexico completed the validated Menstrual Impact Questionnaire (MIQ) at baseline. In Hungary, the subjects completed the European Quality of Life Health Questionnaire at baseline, instead of the MIQ.

   Postoperatively, each subject maintained monthly self-reported diaries from

months two to twelve. Adverse events and complications were recorded at all visits.

The subjects enrolled at sites in Canada and Mexico completed the MIQ at all follow-up visits. In Hungary, the subjects completed the European Quality of Life Health Questionnaire at each follow-up visit.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was occurrence of adverse events. The applicant evaluated safety by determining the number and percentage of subjects who experienced one or more adverse events and the number of subjects who experienced device-related serious adverse events (SAEs).

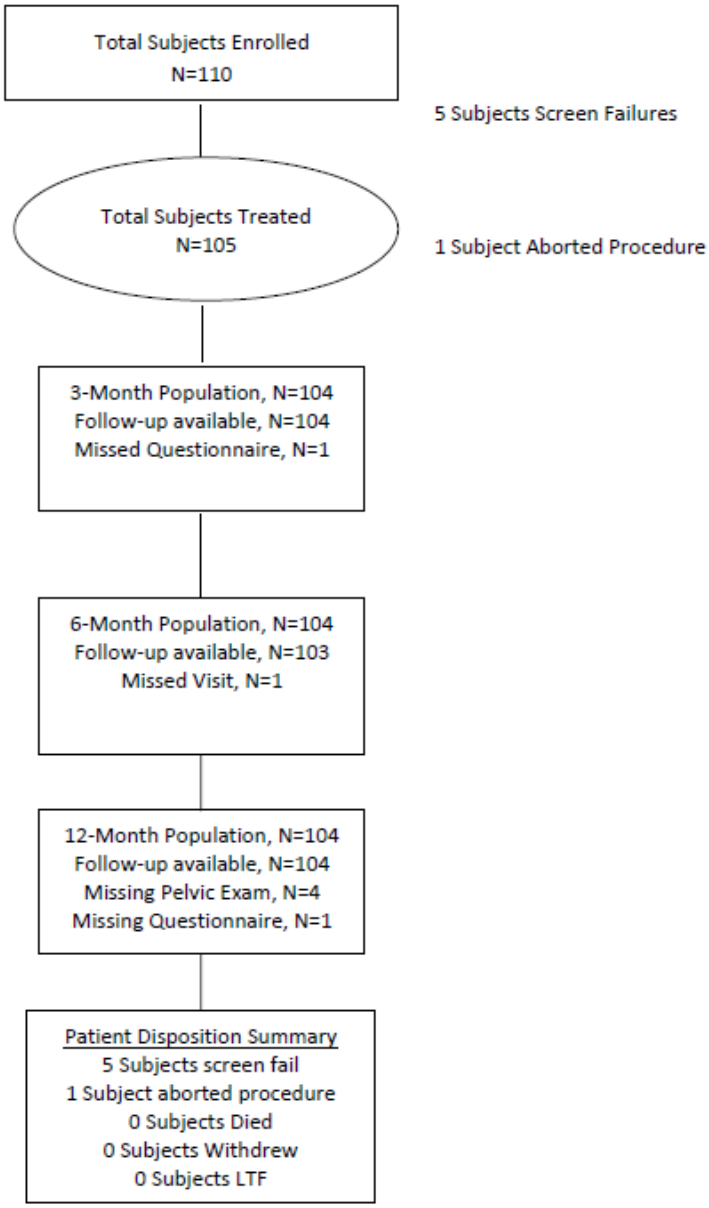
With regards to effectiveness, the primary effectiveness endpoint was menstrual blood loss as assessed by the Pictorial Blood Loss Assessment Chart (PBLAC) method. An individual patient was considered a success if her PBLAC score was ≤ 75 at 12 months post-treatment without incidence of acute treatment failure or additional therapy during follow-up to control menorrhagia.

With regard to success/failure criteria, to achieve study success, the lower bound of the 95% confidence interval should exceed the 66% OPC developed by the FDA.

The secondary endpoints included treatment time, anesthesia type, amenorrhea rates, and patient satisfaction.

B. Accountability of PMA Cohort

At the time of database lock, of 110 patients enrolled in the single arm study, 94.5% (104) patients were available for analysis at the 12 month post-operative visit.



C. Study Population Demographics and Baseline Parameters

The demographics of the study population may not reflect the US patient population. African American women are not represented in this study, which was conducted outside of the United States. African American women have a higher prevalence of uterine fibroids compared to other groups. The Minerva Endometrial Ablation System is not indicated for treating uterine fibroids.

Table 1 provides the baseline demographic and gynecological history parameters. An evaluation of these data confirmed the data could be pooled across sites and countries (protocols). Thirty-eight patients were 25 to 40 years old, and 67 women were 41 to 50 years old.

Table 1 Baseline demographic and gynecological history parameters

Subject Characteristic	Total Subjects (N=110)
Age (yrs)	
Mean ± SD (Median)	42.0 ± 5.3 (43.2)
Range (min, max)	(29.3, 49.7)
Race/Ethnicity	
Hispanic**	23.6% (26)
Asian	0.9% (1)
Caucasian	75.5% (83)
African American	0% (0)
Body Mass Index (BMI) (Kg/m^2)	
Mean ± SD (Median)	28.2 ± 5.8 (27.3)
Range (min, max)	(18.0, 57.3)
Reproductive History	
Gravida	
Mean ± SD (Median)	2.8 ± 1.4 (3.0)
Range (min, max)	(0, 6)
Para	
Mean ± SD (Median)	2.3 ± 1.0 (2.0)
Range (min, max)	(0, 5)
Menstrual History	
Regular Cycle Pattern	86.4% (95)
Dysmenorrhea	59.1% (65)
PMS	72.7% (80)
PBLAC Score at baseline	
Mean ±SD (Median)	469.4 ± 337.2 (381.4)
Range (min, max)	(151.1, 2048.0)
Laboratory Testing	
FSH (IU/L)	
Mean ±SD (Median)	8.0 ± 7.2 (6.0)
Range (min, max)	(0.4, 38.0)

[1]Hispanic is not a race; however, it is listed as such in the database to provide information on ethnicity of this subject population.

D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on all 110 enrolled patients. The key safety outcomes for this study are presented below in **Table 2** and **Table 3**.

   Table 2 shows the number and percent of patients in each study who reported specific endometrial ablation-related adverse events and symptoms (one or more times) during the 12-month follow-up period.

Table 2 Number and Percent of Patients with One or More Related* Adverse Events and Symptoms by Time of Occurrence

Adverse Event/Symptom	Minerva Single-Arm Study
	Minerva (n=110)
Intra-operative Adverse Events	
Skin Rash and/or Itching or Burning Sensation	0 (0.0%)**
Post-operative Adverse Events (< 24 hours) * **	
Pelvic Cramping	64 (58.2%)
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	15 (13.6%)
Bleeding or Spotting	8 (7.3%)
Nausea and/or Vomiting	17 (15.5%)
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	6 (5.5%)
Abdominal Pain and/or Bloating	10 (9.1%)
Circulatory Symptoms	4 (3.6%)
Headache	4 (3.6%)
Backache	3 (2.7%)
Fever	0 (0.0%)
Agitation	0 (0.0%)
Vulvar Pruritus	0 (0.0%)
Urinary Disturbance	0 (0.0%)
Post-operative Adverse Events (≥ 24 hours – 2 Weeks) * **	
Pelvic Cramping	12 (10.9%)
Abdominal Pain and/or Bloating	1 (0.9%)
Nausea and/or Vomiting	1 (0.9%)
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	0 (0.0%)
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	0 (0.0%)
Circulatory Symptoms	1 (0.9%)
Constipation	1 (0.9%)
Pelvic Inflammatory Disease	1 (0.9%)
Fever	1 (0.9%)
Endometritis or Endomyometritis	0 (0.0%)
Skin Rash and/or Itching or Burning Sensation	0 (0.0%)
Post-operative Adverse Events (>2 Weeks – 1 Year)	
Abdominal Pain and/or Bloating	0 (0.0%)

* Possibly, probably, or highly probably related to Device or Procedure
** Percent of patients who reported related adverse events and symptoms
*** Ten patients reported the same AE at the < 24 hours and the 24 hours – 2 Weeks visits

Table 3 shows the frequency (number of occurrences) of endometrial ablation-related adverse events and symptoms reported during the 12-month follow-up period.

Table 3 Number of Occurrences of Related* Adverse Events and Symptoms

Adverse Event/Symptom	Minerva Single-Arm Study
	Minerva (n=110)
Intra-operative Adverse Events	
Skin Rash and/or Itching or Burning Sensation	0
Post-operative Adverse Events (< 24 hours)	
Pelvic Cramping	64
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	16
Bleeding or Spotting	8
Nausea and/or Vomiting	21
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	7
Abdominal Pain and/or Bloating	10
Circulatory Symptoms	4
Backache	3
Headache	4
Fever	0
Agitation	0
Vulvar Pruritus	0
Urinary Disturbance	0
Post-operative Adverse Events (≥ 24 hours – 2 Weeks)	
Pelvic Cramping	12
Abdominal Pain and/or Bloating	1
Nausea and/or Vomiting	1
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	0
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	0
Circulatory Symptoms	1
Constipation	1
Pelvic Inflammatory Disease	1
Fever	1
Endometritis or Endomyometritis	0
Skin Rash and/or Itching or Burning Sensation	0
Post-operative Adverse Events (>2 Weeks – 1 Year)	
Abdominal Pain and/or Bloating	0

* Possibly, probably, or highly probably related to Device or Procedure

There was a report of pregnancy in one subject eleven months after the Minerva endometrial ablation procedure was performed. The subject was scheduled for a dilatation & curettage (D&C) to terminate the pregnancy. At the time of the D&C, she was diagnosed with a non-viable pregnancy (empty sac). The D&C was uneventful and the subject was discharged the same day with no adverse events.

2. Effectiveness Results

The analysis of effectiveness was based on the 110 evaluable subjects at the 12-month time point. Key effectiveness outcomes are presented in **Table 4** and **Table 5**.

Based on the success rate of 91.8% with a 95% confidence interval (CI) of (85.0%, 96.2%) observed in the Minerva ITT population, the null hypothesis was rejected at the significance level of 5%, and the 12-month follow-up success rate observed with the Minerva Endometrial Ablation System was demonstrated to be statistically significantly greater than the OPC of 66% (p-value <0.0001).

This analysis did not compare the success rate of the Minerva Endometrial Ablation Device to the individual success rates of the five approved endometrial ablation devices used to set the OPC.

Table 2 summarizes the effectiveness outcomes from the single arm study.

Table 2 Effectiveness outcomes from single arm study

	MINERVA™ N (% OF 110)
Number of successful patients (diary score ≤ 75)	101
Study success rate (% patients with PBLAC score ≤ 75) – Non-Proportional (Traditional) Method[1]	91.8%
Study success rate (% patients with PBLAC score ≤ 75) – Proportional Method	87.3%
Number of patients reporting amenorrhea (PBLAC score=0)	73
Amenorrhea rate (% patients with PBLC score=0)	66.4%

[1]The success rate compared to the OPC. See discussion of non-proportion (traditional) versus proportional method below

When using the PBLAC scoring method, subjects in the single arm study compared the appearances of their catamenial products (pads and tampons) to a set of pictures/icons. To calibrate these icons with the blood volume absorbed by catamenial products used in this study, expired diluted human blood was applied in 0.5 ml increments to the catamenial products to determine the minimum and maximum amount of blood needed to produce each icon on the PBLAC (i.e., heavy, moderate and light staining). This yielded a range of volumes for each icon. The process was repeated five times by the same investigator, yielding 15 scores for each pad/tampon. The mean volume was determined for each icon for each pad/tampon. The applicant used the mean volumes for the icons for one brand of pads as the baseline for the PBLAC scores. The scores for the icons for the other brands of pads were then calibrated using an "adjustment factor." The purpose of this adjustment factor is to account for the variability across pads. This method is referred to as the non-proportional or traditional method.

To evaluate whether the PBLAC instrument could be appropriately applied in the study, two investigators and ten female observers were randomly assigned catamenial products with known amounts of expired diluted blood applied. The

agreement among investigators/observers was high which demonstrated the validity of the PBLAC instrument.

When using an adjustment factor, the adjusted PBLAC scores may not score blood loss proportionally (i.e., same PBLAC scores may imply different amount of blood loss) across different products. To correct for this, an alternative method may be used called the "proportional method." Using the proportional method, a universal proportional coefficient can be applied to each mean volume. This method directly estimates the total blood loss regardless of the product types and amount of staining, because the same PBLAC score corresponds to the same amount of blood loss.

Both the non-proportional (traditional) and proportional method are included in **Table 4**. The non-proportional (traditional) method was used to determine study success based on comparison with the OPC. The pivotal studies used to support the approved PMAs for global endometrial ablation devices utilized the non-proportional (traditional) method.

Table 5 summarizes the quality of life outcomes from the single arm study. The subjects were asked at study entry if they experienced pre-menstrual symptoms and dysmenorrhea. The subjects who reported symptoms at baseline saw a reduction of symptoms at 12-months. The subjects in Canada and Mexico also completed the Menstrual Impact Questionnaire (MIQ) or other quality of life questionnaires before treatment, and then again at 3, 6, and 12-months post-treatment. **Table 5** includes presence of pre-menstrual symptoms and dysmenorrhea in the analysis population and patient satisfaction responses for the subset of subjects who completed the MIQ at 12 months (n=83).

Table 5 Quality of life outcomes from single arm study

	12 Month Results
Decrease in pre-menstrual symptoms (PMS)	80.8% (84/104)
Decrease in Dysmenorrhea	54.8%(57/104)
Satisfied or very satisfied with procedure	97.6% (81/83)
Definitely or maybe would recommend procedure to friend or relative	98.8% (82/83)

The secondary endpoint of procedure time was determined for each subject by recording the time from device insertion to the time of device removal. The mean procedure time was 3.9 ± 1.5 minutes.

The clinical protocol did not specify the type of anesthesia to be used. This decision was left to the discretion of each patient, the physician, and

anesthesiologist. **Table 6** summarizes the anesthesia regimens used in the single arm study.

Table 6 Anesthesia Regimen

Anesthesia Type	Total Subjects (n=110) % (n)
General	9.1% (10)
IV Sedation	11.8% (13)
Paracervical Block	9.1% (10)
IV Sedation/Paracervical Block	57.3% (63)
IV Sedation/Paracervical Block/ Other	12.7% (14)

During the 12-month follow-up period, there were no reported hysterectomies and/or any other medical/surgical interventions to control bleeding.

3. Subgroup Analyses
   The following preoperative characteristics were evaluated for potential association with outcomes: subject age, baseline PBLAC value, gravida (number of times a woman is pregnant), para (number of times a woman has given birth), baseline PMS, BMI, baseline dysmenorrhea, cycle, race, and baseline cavity length. A multivariate logistic regression analysis of the primary endpoint was done using the completed case population (all subjects who completed the 12-month evaluation) to determine whether any baseline or study site characteristics affected the study outcome. No baseline or study site characteristics were statistically significantly associated with the primary endpoint (all p-values > 0.10).

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included seven investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

3. Randomized Controlled Trial

A. Study Design

Patients were treated between March 2012 and November 2013. The database for this PMA reflected data collected through 30-days post treatment and included 153 patients. There were 13 US and OUS investigational sites.

The study was a prospective, multi-center, randomized (2:1), controlled clinical study comparing the subject device to rollerball ablation, with 102 subjects undergoing treatment with the Minerva Endometrial Ablation Device and 51 subjects undergoing rollerball ablation. The subjects were stratified by age.

The subjects received no endometrial pretreatment (e.g., hormone, dilation and curettage, or cycle timing) and underwent hysteroscopy immediately prior to the Minerva procedure.

Follow-up visits occurred or will occur at 2-4 weeks, 3 months, 6 months and 12 months post-procedure. Two- and three-year safety and effectiveness outcomes are also being collected for this study. Device labeling will be updated when these data become available.

The primary safety endpoint was occurrence of adverse events. The applicant evaluated safety by determining the number and percentage of subjects who experienced one or more adverse events and the number of subjects who experienced serious adverse events (SAEs) compared to the control rollerball subjects during the study.

The primary effectiveness endpoint was menstrual blood loss as assessed by the alkaline hematin (AH) method. An individual patient was considered a success if her AH value is ≤ 80 mL at twelve months post-treatment. The AH method is a validated method of measuring blood loss by assessing collected validated sanitary products (G.F. Ray, P. Burnett, D. Dadgar. Rapid quantitation of menstrual blood loss from feminine hygiene products. Fertility and Sterility, Volume 96, Issue 3, Supplement, Pages S281–S282, September 2011). Twelve month data are not complete at the time of PMA approval and will be provided post-market.

The secondary endpoints included treatment time, anesthesia type, amenorrhea rates, and patient satisfaction.

The 30-day safety outcomes from this study were used to support approval of this PMA application.

The control of hysteroscopic rollerball ablation is a legally marketed alternative with similar indications for use.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the randomized, controlled study was limited to patients who met the following inclusion criteria:

- Refractory menorrhagia with no definable organic cause
- Female subject from (and including) age 25 to 50 years

- Uterine sound measurement of no greater than 10.0cm (external os to internal fundus) and a minimum uterine cavity length of 4.0cm
- One of the following:
    - A minimum menstrual blood loss of ≥ 160 ml for two baseline cycles within three months prior to treatment as measured by alkaline hematin extraction; or
    - A minimum menstrual blood loss of ≥ 160 ml for one baseline cycle for women who either
        - had at least 3 prior months documented failed medical therapy; or
        - had a contraindication to medical therapy
- Premenopausal at enrollment as determined by FSH measurement ≤ 40 IU/L
- Not pregnant and no desire to conceive at any time
- Subject agrees to use a reliable form of contraception up to the 12-month follow-up visit. If a hormonal birth control method is used for contraception, the subject must have been on said method for ≥ 3 months prior to enrollment and agrees to remain on the same hormonal regimen through the initial 12-month follow-up
- Able to provide written informed consent using a form that has been approved by the reviewing IRB/EC
- Subject agrees to follow-up exams and data collection requirements
- Subject who demonstrates an understanding on how to collect menstrual blood loss products for the Alkaline Hematin method of analysis

Patients were <u>not</u> permitted to enroll in the randomized, controlled study if they met any of the following exclusion criteria:

- Pregnancy or subject with a desire to conceive
- Endometrial hyperplasia as confirmed by histology
- Presence of active endometritis
- Active pelvic inflammatory disease
- Active sexually transmitted disease (STD)
- Presence of bacteremia, sepsis, or other active systemic infection
- Active infection of the genitals, vagina, cervix, uterus or urinary tract at the time of the procedure
- Known/suspected abdominal pelvic or gynecological malignancy within the past 5 years
- Known clotting defects or bleeding disorders
- Untreated/unevaluated cervical dysplasia, except CIN I
- Prior uterine surgery (except low segment cesarean section) that interrupts the integrity of the uterine wall (e.g., transmural myomectomy or classical cesarean section)
- Previous endometrial ablation procedure
- Presence of an implantable contraceptive device (e.g., Essure or Adiana)

- Currently on medications that could thin the myometrial muscle, such as long-term steroid use (except inhaler or nasal therapy for asthma)
- Currently on anticoagulants
- Abnormal or obstructed cavity as confirmed by hysteroscopy, SIS or vaginal ultrasound, specifically:
    - Septate or bicornuate uterus or other congenital malformation of the uterine cavity
    - Any myoma that distorts the uterine cavity
    - Polyps larger than 2cm which are likely to be the cause of the subject's menorrhagia
- Presence of an intrauterine device (IUD) which the subject is unwilling to have removed at the time of the operative visit
- Subject currently on hormonal birth control therapy (including the Mirena™ device) for < 3 months prior to enrollment
- Subject who is unwilling to use birth control post-ablation whether non-hormonal birth control or the same hormonal birth control therapy as before the procedure
- Subject who is within 6-weeks post partum
- Any subject who is considering participation in a research study of an investigational drug or device that would begin during the course of this investigational study
- Any general health condition which, in the opinion of the Investigator, could represent an increased risk for the subject

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at 2-4 weeks, 3 months, 6 months and 12 months post-procedure. One, two- and three-year safety and effectiveness outcomes are currently being collected for this study.

   Preoperatively, each subject was required to complete AH collection for at least one menstrual cycle as part of the screening assessment. The investigator provided the subjects with instructions on the AH collection method and the catamenial products to be used during the study. The subjects also completed a Menstrual Impact Questionnaire (MIQ) at baseline.

   Postoperatively, menstrual blood loss was assessed at baseline, 6-months, and 12-months using the AH method. The subjects also completed the MIQ at each follow up visit. Adverse events and complications were recorded at all visits.

   The 30-day safety outcomes from this study were used to support approval of this PMA application. The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

   With regards to safety, the primary safety endpoint was occurrence of adverse events. The applicant evaluated safety by determining the number and percentage

of subjects who experienced one or more adverse events and the number of subjects who experienced serious adverse events (SAEs) compared to the control rollerball subjects.

With regards to effectiveness, the primary effectiveness endpoint was menstrual blood loss as assessed by the alkaline hematin (AH) method. An individual patient was considered a success if her AH value is ≤ 80 mL at twelve months post-treatment.

The secondary endpoints included treatment time, anesthesia type, amenorrhea rates, and patient satisfaction.

The 30-day safety outcomes from this study were used to support approval of this PMA application.

B. Accountability of PMA Cohort

At the time of the database lock, of the 153 subjects randomized (102 (66.7%) with the Minerva Endometrial Ablation System and 51 (33.3%) with rollerball ablation), 100% (153) were available for analysis at the one month follow-up visit. All subjects underwent treatment with either the Minerva Endometrial Ablation System or rollerball ablation.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population may not reflect the US patient population. African American women are not represented in this study, which was conducted both inside and outside of the United States. African American women have a higher prevalence of uterine fibroids compared to other groups. The Minerva Endometrial Ablation System is not indicated for treating uterine fibroids.

Table 3 includes the baseline demographic and gynecological history parameters for the randomized, controlled trial.

Table 3 Baseline demographic and gynecological history parameters

Subject Characteristic	Minerva (N = 102)	Rollerball (N = 51)	p-value
Age (Years)			
Mean ± SD (Median)	42.6 ± 4.2 (42.9)	42.5 ± 4.7 (43.1)	0.97
Range (Min - Max)	31.6 – 50.1	32.3 - 49.3	
Race			
American Indian or Alaskan Native	1 (1.0 %)	0 (0.0 %)	1.00
Black or African American	3 (2.9 %)	2 (3.9 %)	
White	98 (96.1 %)	49 (96.1 %)	
Ethnicity			
Hispanic or Latino	30 (29.4 %)	15 (29.4 %)	1.00
Not Hispanic or Latino	72 (70.6 %)	36 (70.6 %)	

Subject Characteristic	Minerva (N = 102)	Rollerball (N = 51)	p-value
Body Mass Index (BMI) (Kg/m^2)			
Mean ± SD (Median)	30.0 ± 7.1 (29.7)	28.8 ± 5.3 (28.6)	0.28
Range (Min - Max)	16.6 – 52.1	19.8 - 40.6	
Reproductive History			
Gravida			
Mean ± SD (Median)	3.1 ± 1.7 (3)	3.3 ± 1.5 (3)	0.65
Range (Min - Max)	0.0 – 10.0	0.0 - 7.0	
Para			
Mean ± SD (Median)	2.6 ± 1.3 (3)	2.5 ± 1.2 (2)	0.65
Range (Min - Max)	0.0 - 9.0	0.0 - 6.0	
Menstrual History			
Regular Cycle Pattern	97 (95.1 %)	48 (94.1 %)	1.00
Dysmenorrhea	57 (55.9 %)	32 (62.7 %)	0.49
PMS	66 (64.7 %)	35 (68.6 %)	0.72
AH Score at Baseline			
Mean ± SD (Median)	310.2 ± 169.0 (247.5)	301.8 ± 176.1 (249.0)	0.78
Range (Min - Max)	161.5 – 1120.0	160.0 – 1026.1	
Laboratory Results - FSH (IU/L)			
Mean ± SD (Median)	7.5 ± 5.5 (6.0)	8.0 ± 6.3 (6.0)	0.60
Range (Min - Max)	1.0 – 30.0	2.0 – 35.3	

D. 30-Day Safety Results

The analysis of safety was based on all 153 enrolled patients. The key safety outcomes for this study are presented below in **Table 7** and **Table 8**.

Table 7 shows the number and percent of patients in each study who reported specific endometrial ablation-related adverse events and symptoms (one or more times) during the 30-day follow-up period.

Table 7 Number and Percent of Patients with One or More Related* Adverse Events and Symptoms by Time of Occurrence

Adverse Event/Symptom	Minerva Randomized Study	
	Minerva (n=102)	Rollerball (n=51)
Intra-operative Adverse Events		
Skin Rash and/or Itching or Burning Sensation	1 (1.0%)**	0 (0.0%)
Post-operative Adverse Events (< 24 hours) * **		
Pelvic Cramping	51 (50.0%)	23 (45.1%)
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	32 (31.4%)	16 (31.4%)
Bleeding or Spotting	39 (38.2%)	15 (29.4%)
Nausea and/or Vomiting	17 (16.7%)	7 (13.7%)
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	5 (4.9%)	1 (2.0%)
Abdominal Pain and/or Bloating	0 (0.0%)	0 (0.0%)
Circulatory Symptoms	5 (4.9%)	3 (5.9%)
Headache	0 (0.0%)	2 (3.9%)
Backache	1 (1.0%)	0 (0.0%)

Fever	1 (1.0%)	0 (0.0%)
Agitation	1 (1.0%)	2 (3.9%)
Vulvar Pruritus	1 (1.0%)	0 (0.0%)
Urinary Disturbance	1 (1.0%)	1 (2.0%)
Post-operative Adverse Events (≥ 24 hours – 2 Weeks) * **		
Pelvic Cramping	0 (0.0%)	0 (0.0%)
Abdominal Pain and/or Bloating	3 (2.9%)	1 (2.0%)
Nausea and/or Vomiting	0 (0.0%)	1 (2.0%)
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	1 (1.0%)	0 (0.0%)
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	1 (1.0%)	1 (2.0%)
Circulatory Symptoms	0 (0.0%)	0 (0.0%)
Constipation	0 (0.0%)	1 (2.0%)
Pelvic Inflammatory Disease	0 (0.0%)	0 (0.0%)
Fever	0 (0.0%)	0 (0.0%)
Endometritis or Endomyometritis	1 (1.0%)	2 (3.9%)
Skin Rash and/or Itching or Burning Sensation	1 (1.0%)	1 (2.0%)
Post-operative Adverse Events (>2 Weeks – 4 Weeks)†		
Abdominal Pain and/or Bloating	0 (0.0%)	1 (2.0%)

* Possibly, probably, or highly probably related to Device or Procedure

** Percent of patients who reported related adverse events and symptoms

*** Two patients reported the same AE at the < 24 hours and the 24 hours – 2 Weeks visits

† SAE (PID) occurred in one Minerva subject at 34 days

Table 8 shows the frequency (number of occurrences) of endometrial ablation-related adverse events and symptoms reported during the 30-day follow-up period.

Table 8 Number of Occurrences of Related* Adverse Events and Symptoms

Adverse Event/Symptom	**Minerva Randomized Study**	
	Minerva (n=102)	**Rollerball (n=51)**
Intra-operative Adverse Events		
Skin Rash and/or Itching or Burning Sensation	1	0
Post-operative Adverse Events (< 24 hours)		
Pelvic Cramping	51	23
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	32	16
Bleeding or Spotting	39	16
Nausea and/or Vomiting	19	8
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	6	2
Abdominal Pain and/or Bloating	0	0
Circulatory Symptoms	5	3
Backache	2	0
Headache	0	2
Fever	1	0
Agitation	1	2

Vulvar Pruritus	1	0
Urinary Disturbance	1	1
Post-operative Adverse Events (≥ 24 hours – 2 Weeks)		
Pelvic Cramping	0	0
Abdominal Pain and/or Bloating	3	1
Nausea and/or Vomiting	0	1
Vaginal Discharge and/or Unpleasant Vaginal Smell or Burning or Other Abnormal Sensation	1	0
Weakness, Fatigue, Sleepiness, Lack of Concentration, Dizziness	1	1
Circulatory Symptoms	0	0
Constipation	0	1
Pelvic Inflammatory Disease	0	0
Fever	0	0
Endometritis or Endomyometritis	1	2
Skin Rash and/or Itching or Burning Sensation	1	1
Post-operative Adverse Events (>2 Weeks – 4 Weeks)†		
Abdominal Pain and/or Bloating	0	1

* Possibly, probably, or highly probably related to Device or Procedure

† SAE (PID) occurred in one Minerva subject at 34 days

Procedure time was determined for each subject by recording the time of device insertion and the time of device removal. The mean procedure time for the Minerva procedure (3.1 ± 0.5 minutes) was statistically significantly less than the procedure time for the rollerball ablation procedure (17.2 ± 6.7 minutes).

The anesthesia regimen was not dictated by the clinical protocol and was left to the discretion of each patient, clinical investigator and attending anesthesiologist. The type of anesthesia used in the Minerva procedure was nearly identical to the anesthesia regimen in the rollerball ablation procedure.

The mean cervical dilation used for the Minerva subjects (6.8 ± 1.1mm) was statistically significantly less than the cervical dilation used for the Rollerball Group (9.3 ± 1.5 mm).

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Obstetrics and

Gynecology Devices Panel, an FDA advisory committee, for review and recommendation, because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the single arm study, the overall success rate was 91.8% with a 95% confidence interval (CI) of (85.0%, 96.2%) at 12 months. This success rate is statistically significantly greater than the OPC of 66% (p-value <0.0001).

B. Safety Conclusions

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

The safety profile for the subject device appears favorable based on both the 12-month outcomes from the single arm study and the 30-day safety outcomes from the randomized, controlled trial. Most of the adverse events occurred within 30 days of the procedure and resolved without clinical sequelae. The most common adverse events included pelvic cramping, vaginal discharge, and anesthesia related events.

A large proportion of patients can be expected to experience a non-serious adverse event. Serious adverse events are expected to be rare (i.e., <1%). The most serious adverse events, e.g., thermal injury to bowel and sepsis, would manifest within two weeks of the procedure and would require aggressive management including possibly major surgery and/or intensive care.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The benefit of the Minerva Endometrial Ablation System is reduction in menstrual blood loss. At 12-months, 91.8% (95% CI: 85.0%, 96.2%) of treated subjects met the study definition of success and experienced a reduction in menstrual blood loss from excessive to normal or less than normal. Based on available clinical performance outcomes, the risks associated with the Minerva procedure are modest and similar to risks associated with approved global endometrial ablation systems.

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

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The FDA considered the data from a single arm study in which device effectiveness was compared to an OPC. This represented a shift from the randomized, controlled, studies provided for the five previously approved PMA's for global endometrial ablation systems. Considering that global endometrial ablation systems have become a mature technology, the FDA performed an analysis of the data from the approved PMAs to determine the OPC. The single arm study demonstrated effectiveness outcomes at 12 months that were greater than the OPC. In addition, the applicant provided data from an ongoing randomized, controlled study to provide additional safety information on the use of the device. The reported clinical outcomes from these studies are adequate for premarket approval.

The applicant has agreed to follow the single arm study subjects, as well as the subjects treated with the Minerva Endometrial Ablation Device from the randomized study, to obtain long-term safety and effectiveness data. One-, two- and three-year effectiveness outcomes will be collected post-market for these subjects. The labeling for the Minerva Endometrial Ablation System will be revised with this information when it becomes available.

XIII. CDRH DECISION

CDRH issued an approval order on July 27, 2015. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – Minerva Single-Arm Study: The Office of Device Evaluation will have the lead for this clinical study, which was initiated prior to device approval. The Minerva Single-Arm Study is a single-arm, non-randomized, multicenter study conducted outside of the United States to evaluate the safety and effectiveness of the Minerva Endometrial Ablation System. The study includes up to 110 pre-menopausal women with menorrhagia (excessive uterine bleeding) due to benign causes for whom childbearing is complete or who no longer wish to retain fertility. The 1-year outcome data from this study were provided premarket. The 2- and 3-year outcomes from this study will be provided postmarket and will consist of the following:

    - Any treatments or hysterectomy for dysfunctional uterine bleeding
    - Compliance with contraception
    - Any pregnancies
    - Menstrual status (questions assess bleeding, i.e., amenorrhea, spotting, hypomenorrhea, eumenorrhea or menorrhagia)
    - Any gynecological adverse events
    - Completion of Quality of Life Questionnaire

The post approval study protocol for the Minerva Single-Arm Study was provided in Amendment 4 of P140013 dated December 30, 2014 and was amended in an e-mail dated March 10, 2015. Progress reports for this post approval study should be provided on an annual basis.

2. ODE Lead PMA Post-Approval Study – Minerva Pivotal Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The Minerva Pivotal Study is a randomized (2:1), controlled, multicenter study to evaluate the safety and effectiveness of the Minerva Endometrial Ablation System. The control group for this study consists of patients who undergo rollerball ablation. The study includes up to 162 pre-menopausal women with menorrhagia (excessive uterine bleeding) due to benign causes for whom childbearing is complete or no longer wish to retain fertility. The 30-day safety outcomes for this study were provided pre-marketed. The 1-, 2-, and 3-year outcomes will be provided postmarket and will consist of the following:

    - Any treatments or hysterectomy for dysfunctional uterine bleeding
    - Compliance with contraception
    - Any pregnancies
    - Menstrual status (questions assess bleeding, i.e., amenorrhea, spotting, hypomenorrhea, eumenorrhea or menorrhagia)
    - Any gynecological adverse events
    - Completion of Quality of Life Questionnaire

    The post approval study protocol for the Minerva Pivotal Study was provided in Amendment 4 of P140013 dated December 30, 2014 and was amended in an e-mail dated March 10, 2015. Progress reports for this post approval study should be provided on an annual basis.

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

XIV. APPROVAL SPECIFICATIONS

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

None