SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Absorbable Adhesion Barrier

Device Trade Name: Womed Leaf® Resorbable Adhesion Barrier

Device Procode: MCN

Applicant's Name and Address: WOMED SAS
1919 Route de Mende
Bâtiment Balard – CIT
Montpellier, France 34090

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240015

Date of FDA Notice of Approval: September 09, 2025

II. INDICATIONS FOR USE

The Womed Leaf® Resorbable Adhesion Barrier is intended to reduce the reoccurrence and severity of post-surgical adhesion formation inside the uterus. It is indicated for adult women undergoing hysteroscopic surgery for symptomatic moderate to severe intrauterine adhesions.

III. CONTRAINDICATIONS

The Womed Leaf® Resorbable Adhesion Barrier is contraindicated for use in:

- Patients with known hypersensitivity to Womed Leaf® Resorbable Adhesion Barrier or any of its components
- Patients with infection or contamination of the procedure site

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Womed Leaf® Resorbable Adhesion Barrier labeling.

V. DEVICE DESCRIPTION

The Womed Leaf® Resorbable Adhesion Barrier is a sterile, single use, resorbable polymeric film composed of poly(D,L-lactide) (PLA) and poly(ethylene oxide) (PEO) obtained by polymerization of PEO and D,L-lactide. Womed Leaf® Resorbable Adhesion Barrier is composed of one inserter in which the folded polymeric film (uterine film) is loaded. The uterine film is introduced transcervically through the vaginal orifice using the inserter. The uterine film is delivered from its inserter into the uterus where the film self-deploys by unfolding and swelling when contacted by body fluids. Once deployed, it forms a mechanical barrier between the anterior and posterior endometrial walls keeping wound tissues separated during healing. The uterine film is then fragmented by hydrolytic degradation and self-discharged after through the cervix and the vagina by 8 weeks.

1-Uterine film, 2-Uterine length scale, 3-Uterine length ring, 4-Outer handle, 5-Plunger mark, 6-Proximal grip, 7-Inner tube, 8-Outer sheath

Figure 1. Womed Leaf® Resorbable Adhesion Barrier Inserter Components

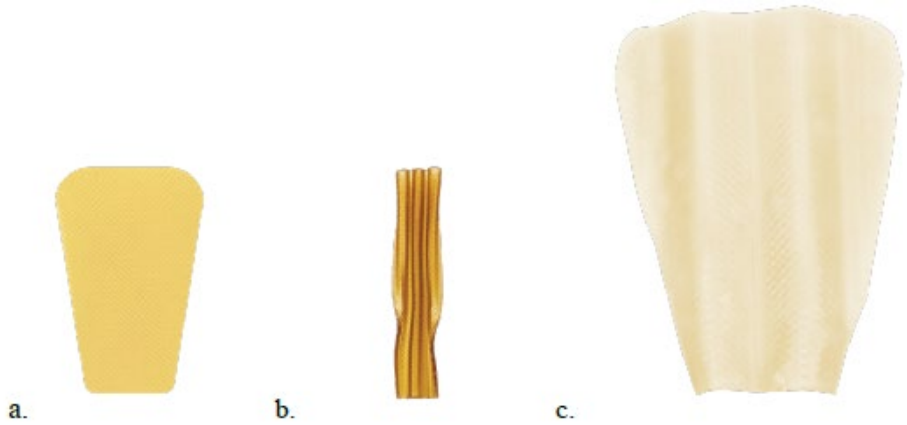

Figure 2. Womed Leaf® Resorbable Adhesion Barrier Uterine Film

a. Trapezoidal shape of uterine film b. Folded uterine film (inside the inserter) c. Unfolded and swollen uterine film (after soaking fluids)

Womed Leaf® Resorbable Adhesion Barrier is available in three models. The models are designed to be adapted to the size of different uterine cavities.

Table 1. Sizes of Womed Leaf® Uterine Film

Model	Size	Uterine Length
LEAF-S	Small	<5 cm
LEAF-M	Medium	5-7 cm
LEAF-L	Large	7-10 cm

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the prevention of intrauterine adhesions (IUAs); however, none of the interventions are approved drug or device treatments, and there are limited data regarding subsequent fertility outcomes when these interventions are used. The practice guidelines on Intrauterine Adhesions from the American Association of Gynecologic Laparoscopists (AAGL), developed in collaboration with the European Society of Gynaecological Endoscopy (ESGE), for primary prevention of intrauterine adhesions describe the short-term benefit in reduction of the development of IUAs by use of an adhesion barrier following surgery that may lead to endometrial damage. For secondary prevention of intrauterine adhesions, the AAGL Practice Guidelines describe the use of an intrauterine device (IUD), stent, catheter, or semi-solid barriers to reduce the rate of postoperative adhesion reformation. In addition, following hysteroscopic-directed adhesiolysis, AAGL considers that postoperative hormone treatment using estrogen, with or without progestin, may also reduce recurrence of IUAs[1].

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Womed Leaf® Resorbable Adhesion Barrier was issued a CE Mark under Directive 93/42/EEC in April 2020 and under Regulation (EU) 2017/745 in November 2023, as a class IIa device by Medical Device Certification Notified Body (MDC, Germany). In the European Union (EU), it is intended for the prevention or reduction of new or recurrent intrauterine adhesions formation by creating a temporary mechanical barrier.

Womed Leaf® Resorbable Adhesion Barrier has also been approved for the same indication in Brazil by ANVISA (80102519156) since July 2022.

Womed Leaf® Resorbable Adhesion Barrier has not been withdrawn or recalled from the market for any reason related to the safety or effectiveness of the device.

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 device.

- Allergic reaction (including pruritus, vulvovaginal pruritus),
- Infection (rash, fever),
- Persistent pelvic pain,
- Bleeding,
- Urethral pain.

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Biocompatibility testing was performed in accordance with the 2023 FDA guidance document, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"*.

The following biocompatibility endpoints were assessed:

- The Womed Leaf® Resorbable Adhesion Barrier Uterine Film is classified as a surface device contacting breached/compromised surfaces for a long-term duration (>30 days)
    - Cytotoxicity (ISO 10993-5:2009)
    - Sensitization (ISO 10993-10:2021)
    - Irritation (ISO 10993-23:2021)
    - Material-mediated pyrogenicity (ISO 10993-11:2017 and USP <161>)
    - Implantation (ISO 10993-6:2016)
    - Subacute/subchronic systemic toxicity (ISO 10993-11:2017)
    - Chemical characterization followed by toxicological risk assessment of compounds extracted from the device to evaluate acute systemic toxicity, subacute/subchronic toxicity, chronic toxicity, genotoxicity, carcinogenicity, and reproductive/developmental toxicity endpoints of the Womed Leaf® Film (ISO 10993-17:2023 and ISO 10993-18:2020)

- The Womed Leaf® Resorbable Adhesion Barrier Inserter is classified as a surface device in contact with a breached/compromised surface for a limited duration (<24 hours)
    - Cytotoxicity (ISO 10993-5:2009)
    - Sensitization (ISO 10993-10:2010)
    - Irritation (ISO 10993-10:2010)
    - Material-mediated pyrogenicity (ISO 10993-11:2017 and USP <161>)
    - Acute systemic toxicity (ISO 10993-11:2017)

The results of the biocompatibility studies demonstrated that both the uterine film and inserter are biocompatible.

2. Pharmacokinetics Studies

A comprehensive literature search was conducted to characterize the absorption, distribution, metabolism, and excretion (ADME) of the Womed Leaf® Resorbable Adhesion Barrier materials. The information was provided for raw materials/ingredients used in the manufacture of the Womed Leaf® Resorbable Adhesion Barrier uterine film and the predicted degradants. This information in

conjunction with the in vitro degradation studies and the in vivo animal studies were used to determine residency time of the Womed Leaf® Resorbable Adhesion Barrier uterine film in the body of 8 weeks.

3. Sterilization Validation

The Womed Leaf® Resorbable Adhesion Barrier is a single-use device that is sterilized using electron beam irradiation. Sterilization validation was performed per ISO 11137-1:2016, ISO 11137-2:2015, and ISO 11137-3:2017 using the VD_{max}^{25} approach and results support that the device has a sterility assurance level (SAL) of 10^{-6}.

Package integrity was validated per ISO 11607-1:2019 and 11607-2:2019 to ensure sterile barrier was maintained following shipping (ASTM D4169-22) and environmental conditioning (ASTM D4332-22). Packages were inspected for visual inspection (ASTM F1886/F1886M-16), seal strength (ASTM F88/F88M-21), and leakage testing by dye penetration (ASTM F3039-15).

4. Shelf-Life Testing

Shelf-life studies were conducted to verify that the device meets its specifications through 24 months.

Table 2. Shelf-Life Packaging Tests

Test	Acceptance Criteria	Results
Electron beam irradiation sterilization (VDmax 25 approach)	Achieve SAL of 10^{-6}	Pass
Bacterial endotoxin testing (ANSI/AAMI ST72)	≤ 20 EU/product	Pass
Packaging integrity testing – assessment of physical damage	No defect	Pass
Packaging integrity testing – legibility of labeling	Label remains legible	Pass
Packaging integrity testing – integrity of seals	No penetration of liquid through the seal	Pass
Packaging integrity testing – strength of seals	≥ 1.2 N for 15 mm of width	Pass
Packaging integrity testing – peelability	No default of sealing – no cleavage > 10 mm from the edges of the line of the heat sealing – width of sealing ≥ 6 mm	Pass

Table 3. Functional Shelf-Life Tests

Test	Acceptance Criteria	Results
Flexibility test	Flexibility of the inserter shall be comparable to the flexibility of the Bayer Mirena	Pass
Inserter and uterine film inspection	The uterine film is properly held inside the outer tube. All specifications about the inserter are met (Table 4).	Pass
Visual inspection of labels	Label is readable; label does not peel away.	Pass

Table 4. Inserter and Uterine Film Inspection Tests

Step description	Acceptance criteria
Inserter Inspection	
Visual inspection outer	Surface should be smooth
Visually inspect the outer tube distal end	Distal tip should be round and opened; no sharp edge
Measure outer length	Total length including outer handle = 210 ± 1 mm
Wipe the pad printed scale on the outer once with a finger and ensure scale number from 4 to 9 clearly visible	Every number can be read
Ruler inspection	Ruler should be pad printed on one side of the tube
	Numbers from 4 to 9 should be readable
	Distance between distal tip and 4 cm mark is 40 mm ± 1 mm
Outer handle inspection	Outer handle is visually compliant with drawing
	Outer handle is positioned at the outer tube proximal end
	Outer handle is aligned with printed ruler
Plunger inspection	Clear cut at the distal end
	Proximal grip visually compliant to drawing
	Proximal grip positioned at the proximal end
	Inner tube spacer protruding at 33 mm ± 1 mm from the handle
Use a calibrated ruler to measure plunger length excluding the proximal grip	212.5 ± 1 mm
Insert plunger into outer	Plunger fits into outer
Inspect component colors	Outer tube: translucid white
	Proximal grip: light blue
	Hysterometry ring: light blue
	Outer handle: milky color

Step description	Acceptance criteria
Measure Outer ID	4.5 mm ± 0.1
Uterine film inspection inside inserter	
Visual inspection	Distance between the inserter distal end and the uterine film distal end is 2 mm ± 1 mm
Visual inspection	The uterine film does not protrude at all from the inserter outer tube
Visual inspection	The orientation of the uterine film with the plane perpendicular to the top of the inserter forms an angle is no more than 35°
Measure outer tube OD	OD ≤ 5.1 mm
Pull the outer to release the uterine film	The force required to release the Womed Leaf® uterine film from the Womed Leaf® inserter shall not exceed 30N
Shake inserter	Uterine film does not move inside the tube
Visual inspection	Uterine film has no hole and no cracks

5. Bench Testing

In addition to the shelf-life tests discussed above, the Womed Leaf® Resorbable Adhesion Barrier underwent the following bench tests to ensure the design met the requirements for its intended use.

- *In vitro* Degradation Testing: This test was conducted to characterize the chemical and physical changes of the Womed Leaf® Resorbable Adhesion Barrier uterine film during degradation and to establish the time needed for complete in vitro degradation of the uterine film by its complete solubilization. ISO 13781:2017 describes methods for the determination of chemical and mechanical changes in poly(lactide)-based homopolymers, copolymers and/or blends induced under in vitro degradation testing conditions and was followed to establish the *in vitro* degradation study protocol. The sterile, finished device was tested in *in vitro* uterine cavity models with test conditions designed to model the clinical conditions of use.

  The degradation tests were carried out using the temperature of the uterus in a solution simulating the uterine fluids, distension solutions used during hysteroscopy procedures, and human blood to evaluate the degradation of the uterine film when residual blood is present in the uterus. The Womed Leaf® Resorbable Adhesion Barrier uterine film was placed under these conditions using the minimal volume of fluid present in the uterus after a hysteroscopy procedure and collected at different time intervals to characterize the chemical and mechanical changes, until the film was fully solubilized. The chemical and physical changes of Womed Leaf® Resorbable Adhesion Barrier uterine film were characterized by assessing

the visual appearance of uterine films, the average percentage mass loss, and the measure of molar masses and polydispersity index by Size Exclusion Chromatography (SEC). The uterine film was completely solubilized on day 73 under *in vitro* degradation conditions.

- Pressure testing: The pressure exerted by the three models of Womed Leaf® Resorbable Adhesion Barrier uterine film while it expands was characterized in *in vitro* models. The impact of the uterine film was evaluated in in vitro models whose length corresponded to the minimum uterine length for which the uterine films are indicated in clinical use. The folded uterine film was placed into a container, containing saline solution, and the film was placed between two walls in contact with the film, one of which moves when the film exerts pressure. The force and pressure applied by the film on the wall were calculated by measuring the displacement of the movable wall. Based on this evaluation and compared to the intrauterine pressure during a woman's menstrual phase or during a diagnostic procedure, the maximum pressure applied by the uterine film does not exceed pressures observed during diagnostic procedures.

- Flexibility testing: The Womed Leaf® Resorbable Adhesion Barrier inserter was tested to verify that the inserter is flexible to navigate through the cervix angle and remain fairly straight without kinking to reach the uterine fundus. The purpose of this test was to characterize the flexural properties of the inserter with a three-point bending flexural test. A continually increasing load was applied in the center of the tested sample until there was a break or permanent bend in the material. The Womed Leaf® Resorbable Adhesion Barrier inserter required more force than the Mirena inserter, indicating that the inserter is more rigid than the Mirena inserter. However, the clinical studies demonstrated effectiveness with no adverse events related to the inserter; therefore, the increased rigidity of the Womed Leaf® Resorbable Adhesion Barrier inserter compared to the Mirena inserter is acceptable.

6. Human Factors

A human factors study was performed in accordance with the 2016 FDA guidance document, *Applying Human Factors and Usability Engineering to Medical Devices*. This study was used to demonstrate usability and ease of deployment the Womed Leaf® Resorbable Adhesion Barrier across different users. Evaluated tasks included positioning of the uterine depth ring, inserter introduction, uterine film release in the cavity, and Instructions for Use and label content verification. All participants were able to correctly use the device per the Instructions for Use.

B. Animal Studies

1. *In vivo* Infectivity Study

A 6-day implantation study was conducted in an infectious rat peritoneal model to assess the impact of Womed Leaf® Resorbable Adhesion Barrier uterine film when implanted in an infected site. The study was composed of 6 groups of 5 rats each. Animals were challenged with three different mixtures of vaginal microorganisms. Two groups were inoculated with a mixture of *Escherichia Coli* with *Bacteroides Fragilis* (mixture A), two groups with a mixture of *Enterococcus Faecalis* and *Bacteroides Fragilis* (mixture B), and two groups with *Staphylococcus Aureus* and *Gardnerella Vaginalis* (mixture C). For each mixture, one group received the Womed Leaf® Resorbable Adhesion Barrier uterine film (treatment group) into the peritoneal cavity and one group received a Vicryl suture (control group). Vicryl suture is a sterile, synthetic, absorbable, surgical suture composed of a copolymer made from 90% glycolide and 10% L-Lactide. This suture is widely used as a surgical suture and not known to exacerbate infection. At 6 days, the mortality rate was recorded, the peritoneal fluid was collected in each animal for bacterial counting, and a macroscopic examination of the peritoneal cavity was performed to establish the abscess rate in each group. No abscesses were observed in any of the groups, and no deaths occurred during the study. The bacterial level in the peritoneal cavity was equivalent between the Womed Leaf® Resorbable Adhesion Barrier group and the control group.

2. Intrauterine Implantation Studies

Intrauterine implantation of the Womed Leaf® Resorbable Adhesion Barrier uterine film was evaluated in two animal studies to assess *in vivo* proof-of-concept and safety.

- 7-Day Proof-of-Concept Study

  A 7-day study was conducted in an intrauterine adhesion model in female rats to assess proof-of-concept of the Womed Leaf® Resorbable Adhesion Barrier uterine film. The study compared the incidence of de novo intrauterine adhesion formation across three groups: animals treated with Womed Leaf® Resorbable Adhesion Barrier uterine film, animals treated with Hyalobarrier GEL ENDO (anti-adhesive gel, CE marked, not FDA-approved), and sham-operated animals. All animals were euthanized on day 7 and the uteri were collected for histological analysis to evaluate the incidence of intrauterine adhesions. All animals in the sham-operated group (100%) demonstrated at least one portion of the uterine length that was completely closed by adhesions. In comparison, 26.7% of animals treated with Womed Leaf® Resorbable Adhesion Barrier uterine film and 80% of animals treated with Hyalobarrier GEL ENDO demonstrated at least one complete intrauterine adhesion. Based on this short-duration study, the

Womed Leaf® Resorbable Adhesion Barrier uterine film demonstrated a reduction in the incidence of de novo intrauterine adhesion formation compared to control groups in this rat model.

- 13-Week Safety Study
  A 13-week study was conducted in an intrauterine adhesion model in female rats to evaluate safety of the Womed Leaf® Resorbable Adhesion Barrier uterine film. Female rats treated with Womed Leaf® and sham-operated female rats were euthanized at 15 days, 6 weeks, and 13 weeks after surgery. No animals in any study group developed partial or complete intrauterine adhesions, which limited the ability to demonstrate efficacy of the device in this study model. Basic safety endpoints including monitoring body weight, morbidity, and mortality indicated that Womed Leaf® Resorbable Adhesion Barrier uterine film was well-tolerated in this rat model. Histological analysis of uterine horns demonstrated that the Womed Leaf® Resorbable Adhesion Barrier uterine film does not delay or prevent healing in an intrauterine adhesion model in female rats.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

WOMED SAS performed two (2) clinical studies as follows:

- PREvention of intrauterine adhesion after hysteroscopic surgery with novel deGradable film (PREG1)
- PREvention of intrauterine adhesion after adhesiolysis with novel tri-block deGradable film (PREG2)

1. PREG1

The pilot study population is different from the approved study population. Pilot study information is provided to communicate safety and effectiveness outcomes that may be relevant to the approved patient population for the Womed Leaf. The safety and effectiveness of Womed Leaf® has not been established in the pilot study population.

A. Study Design

The applicant conducted a prospective multicenter, single arm clinical study between December 2019 and March 2021 at six European investigational sites to evaluate the safety of Womed Leaf® Resorbable Adhesion Barrier after hysteroscopic myomectomy and evaluate its potential efficacy in preventing IUA at second look hysteroscopy (SLH). Women ≥ 40 years with no childbearing wish, or history of permanent sterilization and one or more myoma(s), including one myoma ≥ 10mm, who qualified for hysteroscopic myomectomy were the

target study population. Twenty-three subjects were enrolled, received an investigational device and completed the study follow-up visits.

B. Study Endpoints

The primary safety endpoint was the number of device-related adverse events (AEs) at 30 days and polymer film tolerance defined as fever, pain or bleeding between 48 hours post procedure and 30 days. The primary efficacy endpoint was freedom from intrauterine adhesions (IUAs) at SLH between 4 and 8 weeks and evaluation of severity according to American Fertility Society (AFS) and ESGE classification system of adhesions.

Secondary safety and effectiveness endpoints were also evaluated and included the performance of the inserter defined as the insertion into the uterus with the loaded uterine film and the release of the uterine film in the uterus defined as empty inserter after withdrawal, the device manipulation duration, the menstrual periods following index procedure and before SLH according to Higham score, the subject estimation of film discharge timing and duration, as well as the discomfort assessment and qualitative impression were recorded at SLH, and the presence of uterine film remnants in the uterus at SLH.

C. Safety Results

There were no device or procedure related events.

D. Efficacy Results

Twenty (20) of 23 (87%) patients were free from IUAs at SLH. Intrauterine adhesions were diagnosed in the remaining 3 patients (13%), with two classified as mild and one as moderate according to the American Fertility Society, and one classified as mild and two classified as moderate according to the European Society of Gynecological Endoscopy scoring systems.

2. PREG2

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Womed Leaf® Resorbable Adhesion Barrier for preventing the reoccurrence of intrauterine adhesions following hysteroscopic adhesiolysis in the European Union (EU) and China. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between November 29, 2021 and November 21, 2023. The database for this PMA reflected data collected through November 21, 2023 and included 163 patients. There were 16 investigational sites in 7 countries.

The study was a prospective, multi-center, international, double-blind, randomized, controlled, two-arm, superiority clinical study. The objective of the study was to evaluate the safety and effectiveness of the Womed Leaf® Resorbable Adhesion Barrier in preventing intrauterine adhesions recurrence after hysteroscopic adhesiolysis when compared to adhesiolysis without an intrauterine adjuvant (control). The primary effectiveness endpoint was the change in IUA severity, according to the American Fertility Society (AFS) score, between pre-adhesiolysis and SLH as measured by the surgeon and blinded SLH evaluator, respectively compared to the control.

To reach 90% power in the primary endpoint analysis, 138 patients needed to be randomized and followed up to 6 weeks. This was based on a 1:1 randomization ratio, an expected mean difference of AFS score in subjects randomized to adhesiolysis alone of 5 points (control group), an expected mean difference of AFS score in subjects randomized to adhesiolysis plus Womed Leaf® of 6 points (test group), an expected standard deviation of 1.8, a two-sided test, and a probability of Type 1 error (α) of 0.05. Considering potential loss to follow-up of 10%, a total of 154 patients were needed in the study.

In the study group, Womed Leaf® was inserted immediately after completion of the hysteroscopic adhesiolysis whereas, in the control group, no additional step or placebo was used after hysteroscopic adhesiolysis. Hormonal treatment could be provided if it was the site's standard of care. The randomization was stratified by the baseline IUA severity (moderate/severe).

The safety population was defined by all randomized patients. The effectiveness analysis was based on a modified intention to treat (mITT) population. The mITT included all randomized patients (ITT population), apart from three patients who were incorrectly randomized prior to their baseline hysteroscopy and were excluded after the adhesiolysis for not fulfilling the preset operative criteria without contributing any effectiveness data to the study. No replacement of missing data was performed for the analysis of the primary effectiveness endpoint. A sensitivity analysis of the primary effectiveness endpoint was performed on all randomized subjects (ITT population) with replacement of missing AFS score. Standard descriptive statistics were used to summarize data per randomization group. Continuous variables were described by the number of data, number of missing data, mean ± standard deviation, median, and interquartile ranges. Categorical variables were described as frequencies of missing data, frequencies, and percentages. All statistical tests were two-sided at the 0.05 statistically significant threshold.

A Data Safety Monitoring Board (DSMB) was involved in the PREG2 clinical study in an advisory capacity to monitor the safety of the subjects and effectiveness and evaluate the conduct of the PREG2 study throughout subject enrollment on an on-going basis.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the PREG2 study was limited to patients who met the following inclusion criteria:

1. Women with symptomatic moderate or severe intrauterine adhesions according to the AFS classification, i.e., AFS score ≥ 5, confirmed by hysteroscopy during the adhesiolysis
2. Scheduled for hysteroscopic adhesiolysis
3. Age ≥ 18 years
4. Subjects who were willing to provide written informed consent
5. Subjects who could comply with the study follow-up (and benefit from SLH) and other study requirements
6. Subjects who agreed to refrain from intercourse or use a reliable form of barrier contraception to prevent unintended pregnancy until the follow-up hysteroscopy
7. Subjects who agreed to avoid all intrauterine devices (IUDs) until the follow-up hysteroscopy

Patients were not permitted to enroll in the PREG2 study if they met any of the following exclusion criteria:

Pre-operative criteria

1. Post menopausal
2. Pregnant (confirmed by a positive pregnancy test) or lactating
3. Abnormal uterine cavity according to ESHRE classification I to V such as unicornis, bicornis, septate, duplex
4. Known or suspected endometrial hyperplasia
5. History of cervical or endometrial ablation
6. Active pelvic infection or history of pelvic peritonitis
7. History of endometrial ablation
8. Known contraindication or hypersensitivity to Womed Leaf® component
9. Current participation in another clinical investigation that has not yet received the primary endpoint
10. Any other condition that makes participation in the study contrary to the patient's best interests

Intra-operative criteria, determined during or at the end of the adhesiolysis:

11. Perforation during adhesiolysis
12. Uterine length <5 cm or >10 cm

2. Follow-up Schedule

Starting in protocol version 3.2, patients received a telephone call at 2 weeks ± 1 week to assess for procedure and device related adverse events. All patients were scheduled to return for follow-up examinations at 6 weeks ± 2 weeks where a SLH was carried out to assess the severity of intrauterine adhesions, if any, and occurrence of adverse events, if any. The SLH evaluator also collected patient

reported outcomes related to post operative pain, description of vaginal discharge, and level of associated discomfort at the 6-week visit. Long-term follow-up is planned through 3 years to assess menstrual pattern and pregnancy status.

Patient reported outcomes related to postoperative pain, description of vaginal discharge, and level of associated discomfort were also collected by the investigator at the 6-week visit; however, assessment of these outcomes reported by patients did not follow the same pathway for evaluation as adverse events. These events were not evaluated or adjudicated by the investigator.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint corresponds to the percentage of patients presenting one or more adverse events reported from the point of enrollment in the study, at randomization, until the SLH at 6 weeks.

With regards to effectiveness, the primary effectiveness endpoint was the change of IUA severity (according to the AFS score) between pre-adhesiolysis and SLH at 6 weeks.
The following key secondary effectiveness endpoints were evaluated:

- High responder rate, i.e., percentage of patients whose adhesion severity category has improved between baseline and SLH either (i) from severe to mild adhesions or (ii) from severe to no adhesions or (iii) from moderate to no adhesion
- Change of "extent of cavity involved" component (according to the 10-zone diagram) between pre-adhesiolysis and SLH
- Chage of "extent of cavity involved" component (AFS extent component) between post-adhesiolysis and SLH
- AFS score at SLH
- "Extent of IUA" score component at SLH
- Type of IUA at SLH (AFS type component)
- Menstrual pattern at SLH (AFS menstrual component)
- Percentage of patients who have Mild adhesions or no adhesion at SLH

The following exploratory endpoints were also evaluated:

- Freedom from IUA
- ESGE stage at SLH
- Change of menstrual pattern
- IUA severity according to Chinese score system at SLH
- Responder rate

With regards to success/failure criteria, individual patient success was defined as a high-responder rate corresponding to an improvement from severe to mild adhesions, or from severe to no adhesion or from moderate to no adhesion.

B. Accountability of PMA Cohort

At the time of database lock, of 163 patients enrolled in the PMA study, 94% (153) patients are available for analysis at the 6-week post-operative visit for analysis of the primary endpoints.

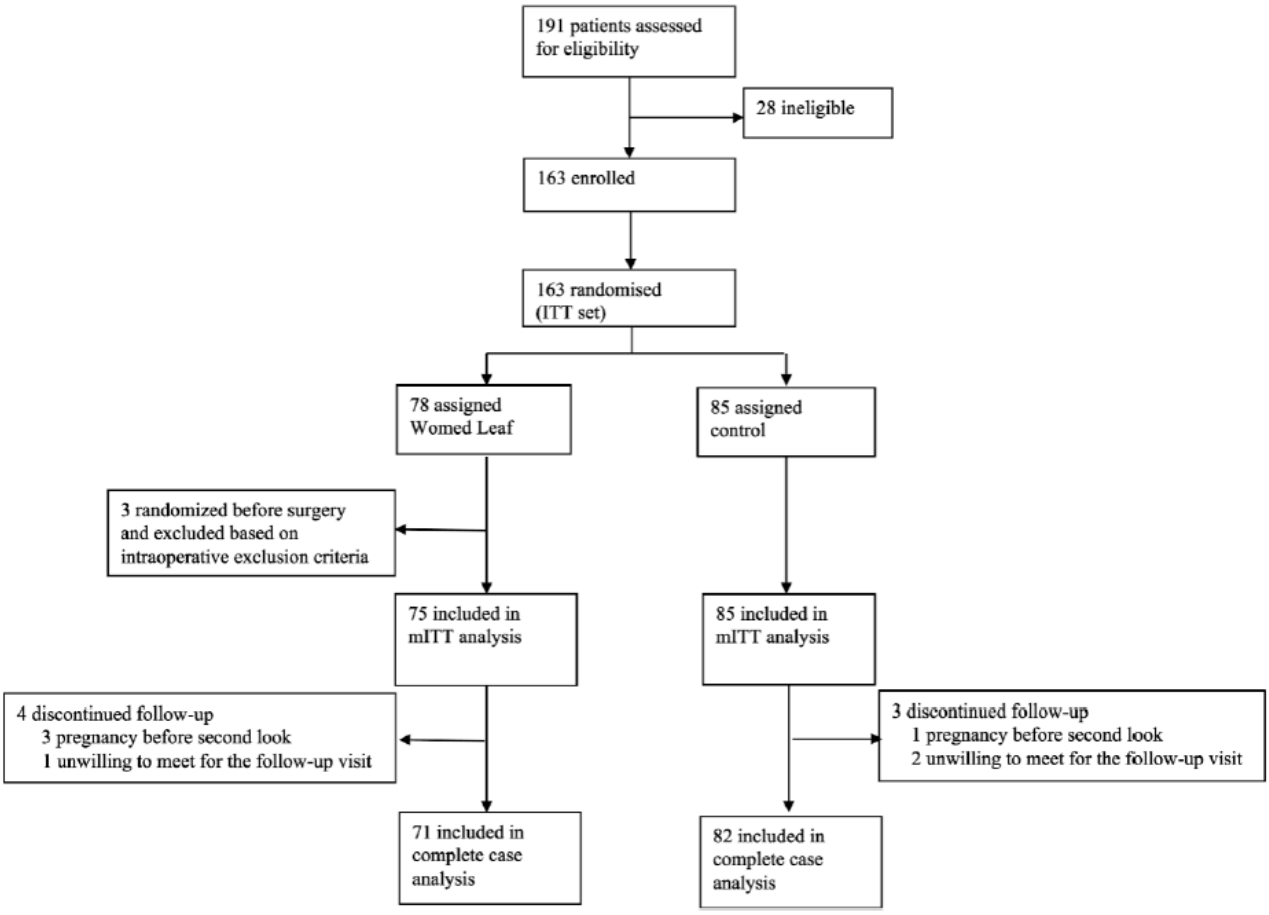

Figure 3. Subject Accountability Tree

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an intrauterine adhesion study performed in the US, as outlined in Tables 5 and 6 below.

Table 5. Study Demographics

Study demographics	Control Group (n=85)	Womed Leaf® Group (n=75)
Age, mean ± SD, year	35.9 ± 5.1	35 ± 5.2
BMI, mean ± SD, (kg/m^2)	23.8 ± 4.8	24.1 ± 4.3
BMI in classes*		
• Underweight	7 (8.2%)	3 (4.0%)
• Normal	52 (61.2%)	49 (65.3%)
• Overweight	15 (17.6%)	15 (20.0%)
• Obese	11 (12.9%)	8 (10.7%)
Ethnicity		
• Hispanic or Latino**	5 (5.9%)	4 (5.3%)
• Not Hispanic or Latino	80 (94.1%)	71 (94.7%)
Race		
• Asian	15 (17.6%)	13 (17.3%)
• Black or African	18 (21.2%)	15 (20.0%)
• White (from Europe, the Middle East, or North Africa)	52 (61.2%)	47 (62.7%)
Clinical manifestations		
• Dysmenorrhea	23 (27.1%)	18 (24.0%)
• Noncyclic pelvic pain	8 (9.4%)	1 (1.3%)
• Infertility	57 (67.1%)	49 (65.3%)
• Abnormal placentation	5 (5.9%)	2 (2.7%)
• Recurrent pregnancy loss	10 (11.8%)	9 (12.0%)
• Amenorrhea/hypomenorrhea/oligomenorrhea	11 (12.9%)	13 (17.3%)
• Other	5 (5.9%)	2 (2.7%)
Menstrual Pattern		
• Absent (amenorrhea)	31 (36.5%)	24 (32.0%)
• Light (hypomenorrhea)	35 (41.2%)	30 (40.0%)
• Normal	19 (22.4%)	21 (28.0%)

mITT set
*World Health Organization Classification
**Hispanic or Latino from Cuba, Mexico, Puerto Rico, South or Central America or other Spanish culture or origin, regardless of race

Table 6. Baseline Characteristics of Participants

Baseline Parameters	Control (n=85)	Womed Leaf® (n=75)
IUA related clinical history		
• Dysmenorrhea	23 (27.1%)	18 (24.0%)
• Noncyclic pelvic pain	8 (9.4%)	1 (1.3%)
• Infertility	57 (67.1%)	49 (65.3%)
• Abnormal placentation	5 (5.9%)	2 (2.7%)
• Recurrent pregnancy loss	10 (11.8%)	9 (12.0%)
• Amenorrhea/hypomenorrhea / oligomenorrhea	11 (12.9%)	13 (17.3%)
• Other	5 (5.9%)	2 (2.7%)
Menstrual pattern		
• Absent (amenorrhea)	31 (36.5%)	24 (32.0%)
• Light (hypomenorrhea)	35 (41.2%)	30 (40.0%)
• Normal	19 (22.4%)	21 (28.0%)
Number of previous adhesiolysis		
• None	44 (51.8%)	40 (53.3%)
• 1	18 (21.2%)	15 (20.0%)
• 2	11 (12.9%)	9 (12.0%)
• 3	6 (7.1%)	7 (9.3%)
• >3	6 (7.1%)	4 (5.3%)
Number of previous operative hysteroscopies		
None	32 (37.6%)	33 (44.0%)
• 1	26 (30.6%)	17 (22.7%)
• 2	9 (10.6%)	12 (16.0%)
• 3	8 (9.4%)	7 (9.3%)
• >3	10 (11.8%)	6 (8.0%)
History of uterine artery embolization	6 (7.1%)	11 (14.7%)
Suspected cause of IUA*		
• Dilatation and curettage for miscarriage or termination of pregnancy	48 (56.5%)	39 (52.0%)
• Postpartum dilatation and curettage (retained product of conception)	18 (21.2%)	13 (17.3%)
• Uterine embolization	5 (5.9%)	10 (13.3%)
• Hysteroscopic myomectomy	8 (9.4%)	3 (4.0%)
• Hysteroscopic polypectomy	2 (2.4%)	2 (2.7%)
• Hysteroscopic uterine septum (resection/metroplasty)	1 (1.2%)	0(0.0%)
• Laparoscopic myomectomy	3 (3.5%)	1 (1.3%)
• Abdominal myomectomy	5 (5.9%)	6 (8.0%)
• Cesarean section	9 (10.6%)	13 (17.3%)
• Other	11 (12.9%)	10 (13.3%)

Baseline Parameters	Control (n=85)	Womed Leaf® (n=75)
Parity		
• None	25 (30.6%)	32 (42.7%)
• 1	36 (42.4%)	33 (44.0%)
• 2	15 (17.6%)	6 (8.0%)
• 3	6 (7.1%)	3 (4.0%)
• >3	2 (2.4%)	1 (1.3%)
Gravidity		
• None	9 (10.6%)	8 (10.7%)
• 1	26 (30.6%)	31 (41.3%)
• 2	18 (21.2%)	17 (22.7%)
• 3	15 (17.6%)	8 (10.7%)
• 4	9 (10.6%)	5 (6.7%)
• >4	8 (9.4%)	6 (8.0%)
Number of previous dilation and curettage procedures		
• None	28 (32.9%)	27 (36.0%)
• 1	36 (42.4%)	24 (32.0%)
• 2	16 (18.8%)	15 (20.0%)
• 3	3 (3.5%)	4 (5.3%)
• >3	2 (2.4%)	5 (6.7%)
Number of previous spontaneous miscarriage		
• None	42 (49.4%)	46 (61.3%)
• 1	22 (25.9%)	14 (18.7%)
• 2	12 (14.1%)	8 (10.7%)
• 3	8 (9.4%)	0 (0.0%)
• 4	0 (0.0%)	3 (4.0%)
• >4	1 (1.2%)	4 (5.3%)
Number of previous pregnancy termination		
• None	56 (65.9%)	52 (69.3%)
• 1	22 (25.9%)	14 (18.7%)
• 2	3 (3.5%)	6 (8.0%)
• 3	3 (3.5%)	2 (2.7%)
• 4	1 (1.2%)	1 (1.3%)
Baseline AFS score Mean ± Standard Deviation	8.2 ± 2.0	8.2 ± 2.2
IUA AFS stage before adhesiolysis		
• Stage II (moderate, i.e. 5 ≤ AFS score ≤ 8)	59 (69.4%)	51 (68.0%)
• Stage III (severe, i.e. 9 ≤ AFS score ≤ 12)	26 (30.6%)	24 (32.0%)
mITT set *several possible answers		

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety cohort of 163 patients/procedures, available for the 6-week evaluation. The key safety outcomes for this study are presented below in Table 7. Adverse effects are reported in Tables 8 and 9.

Table 7. Summary of Primary Safety Endpoint

	Control (n=86)	Womed Leaf® (n=77)
Subjects having at least one AE (serious or non-serious)	3 (3.5%)	6 (7.8%)
Subjects having at least one AE or adverse patient-reported outcome (postoperative pain, vaginal discharge, discomfort)	31 (36.0%)	20 (26.0%)
Subjects having at least one SAE	0 (0.0%)	0 (0.0%)

Adverse effects that occurred in the PMA clinical study:

Table 8. List of Adverse Events Reported Within the 6-Week Window

	Percentage of control patient with events	Percentage of Womed Leaf® patients with event
Number of Adhesiolysis patients	86	77
Neuralgia	1 (1.2%)	
Pyrexia (Fever)	1 (1.2%)	
Abdominal pain	1 (1.2%)	
Uterine perforation at SLH		1 (1.3%)
Liver function test abnormal		1 (1.3%)
Urethral pain		1 (1.3%)
Vulvovaginal pruritus		1 (1.3%)
Cervix disorder		1 (1.3%)
Pruritus		1 (1.3%)

Table 9. List of Patient Outcomes Collected by Questionnaire

	Percentage of control patient with events	Percentage of Womed Leaf® patients with event
Number patients that reported the outcome	82	71
Presence of post-operative pain	22 (26.8%)	12 (16.9%)
Presence of discomfort related to vaginal discharge	8 (9.8%)	7 (9.9%)
Presence of something in vaginal discharge	19 (23%)	25 (35%)

2. Effectiveness Results

The analysis of effectiveness was based on the 153 evaluable patients at the 6-week time point. Key effectiveness outcomes are presented in Table 10.

Table 10. Primary and Secondary Outcomes Collected

	Control group (n=85)	Womed Leaf® group (n=75)	P value	Odds ratio
Missing data	3	4	-	-
Primary endpoint				
Change in AFS score Mean ± standard deviation	4.2 ± 3.2	5.2 ± 2.8	0.0153	NA
Secondary Endpoints				
High-responder rate	29.3%	50.7%	0.0052	2.72 [1.35; 5.45]
Change of "extent of cavity involved" between pre-adhesiolysis and SLH	2.9 ± 2.4	3.6 ± 2.0	0.0209	2.72 [1.119; 3.863]
Change of "extent of cavity involved" between post-adhesiolysis and SLH	-1.9 ± 2.4	-1.2 ± 2.1	0.0167	2.15 [1.15; 4.02]
AFS score at SLH	4.0 ± 3.3	3.0 ± 3.2	0.0052	0.40 [0.211; 0.757]
"Extent of IUA" score component at SLH: • **0** • **< 1/3** • **1/3 – 2/3** • **> 2/3**	20 (24.4%) 22 (26.8%) 11 (13.4%) 29 (35.4%)	29 (40.8%) 33 (46.5%) 8 (11.3%) 1 (1.4%)	0.0162	2.22 [1.16; 4.24]
"Type of IUA" score component at SLH: • **No IUA** • **Filmy** • **Filmy and Dense** • **Dense**	20 (24.4%) 22 (26.8%) 11 (13.4%) 29 (35.4%)	29 (40.8%) 16 (22.5%) 7 (9.9%) 19 (26.8%)	0.0747	1.82 [0.94; 3.52]
"Menstrual pattern" score component at SLH: • **Normal** • **Hypomenorrhea** • **Amenorrhea**	n=83 52 (62.7%) 17 (20.5%) 14 (16.9%)	n=71 49 (69.0%) 14 (19.7%) 8 (11.3%)	-	-
Patients with mild adhesions or no IUA at SLH	46 (56.1%)	46 (64.8%)	-	-

	Control group (n=85)	Womed Leaf® group (n=75)	P value	Odds ratio
Exploratory Endpoint				
Freedom from IUA	n=82 20 (24.4%)	n=71 29 (40.8%)	-	-
ESGE stage at SLH • **Grade I** • **Grade II** • **Grade IIa** • **Grade III** • **Grade IV** • **Grade Va** • **Grade Vb**	n=62 19 (30.6%) 18 (29.0%) 1 (1.6%) 11 (17.7%) 7 (11.3%) 2 (3.2%) 4 (6.5%)	n=42 14 (33.3%) 7 (16.7%) 0 (0.0%) 13 (31.0%) 5 (11.9%) 1 (2.4%) 2 (4.8%)	-	-
Change of menstrual pattern • **Worsening** • **No change** • **Improvement**	n=83 4 (4.8%) 34 (41.0%) 45 (54.2%)	n=71 5 (7.0%) 28 (39.4%) 38 (53.5%)	-	-
IUA severity according to Chinese score system at SLH **Mean ± Standard Deviation**	n=7 7.6 ± 2.4	n=4 5.5 ± 3.4	-	-
Responder Rate	57 (69.5%)	55 (77.5%)	-	-

The trial met its primary endpoint and demonstrated that the device significantly reduced the severity of intrauterine adhesions after hysteroscopic adhesiolysis compared to the control group. In addition, the high-responder rate, positioned as the first key hierarchical secondary endpoint, extent of cavity involved between pre-adhesiolysis and SLH, extent of cavity involved between post-adhesiolysis and SLH, AFS score at SLH and Extent of IUA were also significantly higher in the Womed Leaf® Resorbable Adhesion Barrier group compared to the control group. The type of IUA score component at SLH, menstrual pattern score component at SLH, and patients with mild adhesions or no IUA at SLH endpoints did not demonstrate a statistically significant difference between the treatment arm and control arm.

A sensitivity analysis of the primary effectiveness endpoint was performed on all randomized subjects (ITT population) with replacement of missing AFS score. Twenty (20) imputation sets were used, and the p-value of the primary endpoint was <0.05. Therefore, the results of the ITT analysis are consistent with the mITT analysis.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: hormonal treatment and race. The effect of these characteristics on the primary endpoint and secondary endpoints was not significant, as noted in Table 11 and 12 below.

The study was not specifically powered for hormonal treatment and race subgroups.

Table 11. Summary of Change of AFS Score per Race

	Control group			Womed Leaf® group		
	Asian	**Black or African**	**White**	**Asian**	**Black or African**	**White**
Primary outcome: Change of AFS score between pre-adhesiolysis and SLH per race						
n	14	17	51	12	14	45
n missing	1	1	1	1	1	2
Mean ± standard deviation	5.1 ± 3.3	4.4 ± 4.0	3.9 ± 2.8	6.2 ± 2.3	4.7 ± 2.5	5.1 ± 3.0
Median; min; max	6 (-2; 12)	5 (-3; 12)	4 (-4; 10)	6 (3; 10)	6 (-2; 8)	6 (-2; 10)
Secondary outcomes						
High-responder Rate	5 (35.7%)	6 (35.3%)	13 (25.5%)	5 (41.7%)	7 (50.0%)	24 (53.5%)
Change of "extent of cavity involved" component between pre-adhesiolysis and SLH (mean ± standard deviation)	3.3 ± 3.4	3.7 ± 3.2	2.5 ± 1.7	3.5 ± 2.2	4.0 ± 2.1	3.5 ± 1.9
Change of "extent of cavity involved" component between post-adhesiolysis and SLH (mean ± standard deviation)	-2.0 ± 2.6	-1.4 ± 2.3	-2.1 ± 2.3	-1.0 ± 1.0	-1.2 ± 2.2	-1.3 ± 2.3
AFS score at SLH (mean ± standard deviation)	3.0 ± 2.9	3.6 ± 3.5	4.4 ± 3.4	1.8 ± 1.8	3.5 ± 3.9	3.2 ± 3.2
"Extent of IUA" score component at SLH • 0 • <1/3 • 1/3 – 2/3 • >2/3	 0 (35.7%) 7 (50.0%) 1 (7.1%) 1 (7.1%)	 5 (29.4%) 10 (58.8%) 1 (5.9%) 1 (5.9%)	 10 (19.6%) 31 (60.8%) 6 (11.8%) 4 (7.8%)	 5 (41.7%) 7 (58.3%) - -	 7 (50.0%) 4 (28.6%) 3 (21.4%) -	 17 (37.8%) 22 (48.9%) 5 (11.1%) 1 (2.2%)
"Type of IUA" score component at SLH • No IUA • Filmy • Filmy and Dense • Dense	 5 (35.7%) 5 (35.7%) 1 (7.1%) 3 (21.4%)	 5 (29.4%) 2 (11.8%) 4 (23.5%) 6 (35.3%)	 10 (19.6%) 15 (29.4%) 6 (11.8%) 20 (39.2%)	 5 (41.7%) 3 (25.0%) 4 (33.3%) -	 7 (50.0%) 1 (7.1%) 1 (7.1%) 5 (35.7%)	 17 (37.8%) 12 (26.7%) 2 (4.4%) 14 (31.1%)
"Menstrual pattern" score component at SLH • Normal • Hypomenorrhea • Amenorrhea	 10 (71.4%) 3 (21.4%) 1 (7.1%)	 12 (66.7%) 2 (11.1%) 4 (22.2%)	 30 (58.8%) 12 (23.5%) 9 (17.6%)	 9 (75.0%) 3 (25.0%) -	 9 (64.3%) 1 (7.1%) 4 (28.6%)	 31 (68.9%) 10 (22.2%) 4 (8.9%)
Patients with mild adhesions or no IUA at SLH	9 (64.3%)	11 (64.7%)	26 (51.0%)	11 (91.7%)	7 (50.0%)	28 (62.2%)

Table 12. Summary of Change of AFS Score per Hormonal Treatment

	Control group		Womed Leaf® group	
	No hormonal treatment	**Hormonal treatment**	**No hormonal treatment**	**Hormonal treatment**
Primary outcome: Change of AFS score between pre-adhesiolysis and SLH per hormonal treatment				
n	56	26	50	21
n missing	3	0	4	0
Mean ± standard deviation	4.2 ± 3.3	4.2 ± 3.0	5.3 ± 2.7	5.1 ± 3.1
Median; min; max	4 (-4; 12)	4 (0; 12)	6 (-2; 10)	5 (-2; 10)
Secondary Outcomes				
High-responder Rate	18 (32.1%)	6 (23.1%)	29 (58.0%)	7 (33.3%)
Change of "extent of cavity involved" component between pre-adhesiolysis and SLH (mean ± standard deviation)	2.8 ± 2.5	3.0 ± 2.2	3.7 ± 1.8	3.3 ± 2.3
Change of "extent of cavity involved" component between post-adhesiolysis and SLH (mean ± standard deviation)	-2.0 ± 2.7	-1.8 ± 1.4	-1.2 ± 2.4	-1.2 ± 1.2
AFS score at SLH (mean ± standard deviation)	3.9 ± 3.5	4.1 ± 3.1	3.1 ± 3.4	2.9 ± 2.7
"Extent of IUA" score component at SLH • 0 • <1/3 • 1/3 – 2/3 • >2/3	 14 (25.5%) 32 (57.1%) 4 (7.1%) 6 (10.7%)	 6 (23.1%) 16 (61.5%) 4 (15.4%) 0 (0.0%)	 22 (44.0%) 20 (40.0%) 7 (14.0%) 1 (2.0%)	 7 (33.3%) 13 (61.9%) 1 (4.8%) 0 (0.0%)
"Type of IUA" score component at SLH • No IUA • Filmy • Filmy and Dense • Dense	 14 (25.0%) 17 (30.4%) 7 (12.5%) 18 (32.3%)	 6 (23.1%) 5 (19.2%) 4 (15.4%) 11 (42.3%)	 22 (44.0%) 11 (22.0%) 3 (6.0%) 14 (28.0%)	 7 (33.3%) 5 (23.8%) 4 (19.0%) 5 (23.8%)
"Menstrual pattern" score component at SLH • Normal • Hypomenorrhea • Amenorrhea	 37 (64.9%) 9 (15.8%) 11 (19.3%)	 15 (57.7%) 8 (30.8%) 3 (11.5%)	 34 (68.0%) 9 (18.0%) 7 (14.0%)	 15 (71.4%) 5 (23.8%) 1 (4.8%)
Patients with mild adhesions or no IUA at SLH	33 (58.9%)	13 (50.0%)	31 (62.0%)	15 (71.4%)

4. Pediatric Extrapolation

   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. 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 76 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.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Obstetrics and Gynecology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was met with a reduction of AFS score between baseline and SLH being significantly higher in the Womed Leaf® Resorbable Adhesion Barrier group as compared to the control group. The first five key hierarchical secondary endpoints, high-responder rate, extent of cavity involved between pre-adhesiolysis and SLH, extent of cavity involved between post-adhesiolysis and SLH, AFS score at SLH, and extent of IUA were also significantly higher in the Womed Leaf® Resorbable Adhesion Barrier group compared to the control group.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. Safety results of the clinical study demonstrated reasonable assurance of safety for the device when used in the indicated patient population in accordance with the instructions for use. No subjects experienced a serious device-related adverse event. Of the reported adverse events, three were listed as possibly related to the device by the investigator: urethral pain, vulvovaginal pruritus, and pruritus.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. A statistically significant reduction in the AFS adhesion classification severity score between baseline and the SLH was reported in the Womed Leaf® Resorbable Adhesion Barrier group

compared to that of the control group who received no intrauterine adhesion barrier. The primary effectiveness endpoint was also met. Additionally, the clinically meaningful high-responder rate, defined as at least two-category improvement in AFS category, was greater in the Womed Leaf® Resorbable Adhesion Barrier group compared to that in the control group (50.7% versus 29.3%). Other key secondary endpoints achieved statistical significance when comparing the treatment group to the control.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. There is potential for risks similar to those marketed for pelvic use (e.g., infection, foreign body reaction, prevention of healing, reproductive toxicity, persistence of material at delivery site).

Additional factors to be considered in determining probable risks and benefits for the Womed Leaf® Resorbable Adhesion Barrier device included:

- The 6-week timepoint for analysis of the surrogate effectiveness endpoint, in place of the longer term clinically relevant fertility endpoint, pregnancy, leads to some uncertainty regarding the long-term effectiveness and clinical benefit.
- There is potential for risks similar to adhesion barriers marketed for pelvic use (e.g., infection, foreign body reaction, prevention of healing, reproductive toxicity and persistence of material at delivery site).

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for reduction of the reoccurrence and severity of post-surgical adhesion formation inside the uterus 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 PREG2 study data demonstrate a benefit of reducing the reoccurrence and severity of intrauterine adhesions following hysteroscopic adhesiolysis with an acceptable safety profile. The overall uncertainty of both the benefits and risks are low.

XIV. CDRH DECISION

CDRH issued an approval order on September 09, 2025. The final clinical conditions of approval cited in the approval order are described below.

1. The Womed Leaf® Resorbable Adhesion Barrier Post Approval Study is a long-term follow-up of the PREG2 randomized controlled trial.

   The PREG2 trial was an international, double blind, randomized controlled trial conducted at 16 sites in Europe and China. There were 160 participants randomized to the intervention (n=75) and control (n=85) arms who contributed to the modified intention-to-treat (mITT) analysis and will be followed-up in the PAS study. Continued follow-up from this study through three (3) years will be used to evaluate the long-term safety of the Womed Leaf® device.

   At least 85% of the patient cohort in each arm must be followed out to three years post procedure. Follow-up must be conducted once a year for the PAS study (i.e., one, two, and three years).

   The applicant must collect and report the following:

   Primary endpoint: The primary endpoint is the live birth rate. Live birth rate must be reported at one, two, and three years follow-up. Live birth is defined as the delivery of a live born infant who breathes or shows any other evidence of life, such as heartbeat or movement, and refers to an individual newborn.

   Secondary endpoints:

   1. Clinical pregnancy rates, whether spontaneous or assisted (ovulation induction, intrauterine insemination; in vitro fertilization (IVF) and embryo transfer (ET)), at one, two, and three years, where clinical pregnancy is defined as the presence of fetal sac or heartbeat confirmed by ultrasound.
   2. Average time to first pregnancy (i.e., time between the second look hysteroscopy and estimated date of conception) at one, two, and three years.
   3. Pregnancy rate leading to a live birth at one, two, and three years, where pregnancy rate is defined as the presence of fetal sac or heartbeat by ultrasound or a positive urinary test or blood test leading to a live birth.
   4. Pregnancy related events at one, two, and three years:
      a. Miscarriage (intrauterine pregnancy loss before 20 weeks gestation)
      b. Ectopic pregnancy (defined as pregnancy outside of the endometrial cavity, diagnosed by ultrasound, surgical visualization, or histopathology)
      c. Retained products of conception
      d. Termination of pregnancy
      e. Intrauterine growth restriction
      f. Premature rupture of the membranes
      g. Placenta previa

h. Premature delivery (defined as a delivery before the 37th week of pregnancy)
i. Uterine rupture
j. Postpartum hemorrhage
k. Placenta accreta spectrum (accreta, increta, percreta)
l. Intrauterine fetal demise defined as the death of a fetus of at least 20 weeks gestational age
m. Other

5. Reintervention rate (repeat adhesiolysis) after SLH up to one year following the index procedure.
6. Average number of adhesiolysis procedures per patient after SLH up to one year following the index procedure.
7. Improvement in menstrual pattern at one, two, and three years compared to baseline. Menstrual pattern is considered improved if menses is resumed for amenorrheic patients or if hypomenorrhea (scant spotting or light period) patients experience an increased duration or increased volume of periods compared to that previously reported.

Data must be summarized descriptively, without statistical testing.

Version 4 of the Womed Leaf® Post Approval Study protocol, received via email on September 4, 2025 must be followed.

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

XV. 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.

XVI. REFERENCES

1. AAGL Practice Report: Practice Guidelines on Intrauterine Adhesions Developed in Collaboration With the European Society of Gynaecological Endoscopy (ESGE), Journal of Minimally Invasive Gynecology, Volume 24, Issue 5, 2017, Pages 695-705, ISSN 1553-4650, https://doi.org/10.1016/j.jmig.2016.11.008. (https://www.sciencedirect.com/science/article/pii/S1553465016311700)