Protocol synopsis

Name	PREG1
Title	**PRE**vention of intrauterine adhesion after hysteroscopic surgery with novel tri-block de**G**radable polymer film
Protocol version number	06 (April 27th 2020)
Study rationale	Intrauterine adhesions (IUA) are defined as "fibrous strings at opposing walls of the uterus and/or cervix leading to partial or complete obliteration of the cavity"[1]. IUAs are the major long-term complication of operative hysteroscopy. Their prevalence following myomectomy is high and varies significantly across the literature (7.5%-45.5%)[2,3,4]. hey are frequently associated with pelvic pain. The prevention tools available today do not sufficiently meet the specifications required for the prevention of IUAs which are: 1) ergonomic device, specifically designed for intrauterine use and adapted to the cervical passage and 2) anti-adhesion barrier that keep the wound tissue apart during the repair phase for optimal efficiency.
Study device	Name: Womed Leaf Device group: Anti-adhesion barrier Device status: CE marked Classification (according to MDD 93/42/EEC as amended per 2007/47/EC): IIa according to rule 5 Intended purpose: Womed Leaf™ is a sterile, degradable film of poly(D,L-lactide) (PLA) and poly(ethylene oxide) (PEO). PEO is a biocompatible polymer with anti-adhesion and swelling properties. Polymerized with hydrophobic PLA, it forms a degradable film that swells and expands in contact with water to form a degradable mechanical barrier. Womed Leaf™ is inserted in the uterine cavity by a gynecologist surgeon as a film folded into a 5 mm diameter

[1] Hooker et al. Prevalence of intrauterine adhesions after the application of hyaluronic acid gel after dilatation and curettage in women with at least one previous curettage: short-term outcomes of a multicenter, prospective randomized controlled trial, Fertility and Sterility, 2017;107:1223-31

[2] Taskin et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. The Journal of the American Association of Gynecologic Laparoscopists 2000;7(3):351–4

[3] Guida et al. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. Human Reproduction 2004;19(6):1461-64

[4] Touboul et al. Uterine synechiae after bipolar hysteroscopic resection of submucosal myomas in patients with infertility. Fertility and Sterility 2009;92(5):1690-93

	flexible inserter. Once released, the film will unfold and swell into the uterine cavity to keep uterus walls separated during approximately 5 days. It is degraded and discharged naturally through the cervix and vagina in less than 30 days.
Intended use	Womed Leaf™ is intended to be used for the prevention or reduction of new or recurrent intrauterine adhesion formation subsequent to a transcervical procedure by creating a mechanical barrier.
Design	Prospective, multi-center, single arm clinical study. Subjects will be followed up for 4 to 8 weeks.
Objective	Evaluate the safety of Womed Leaf after hysteroscopic myomectomy and its potential efficacy in preventing IUA at second look hysteroscopy.
Number of subjects	20 subjects
Sites	● Kremlin Bicêtre (APHP), Paris, France, ● CHU Nîmes, France, ● AMC, Amsterdam, The Netherlands ● Zaans, The Netherlands ● Isala, Zwolle, The Netherlands ● Gent, Belgium ● CHR La Citadelle, Liège, Belgium
Population	Women with one or more myoma(s), one myoma being larger than 10mm, who qualify for hysteroscopic myomectomy
Co-primary endpoints	● Safety endpoint: number and type of device-related adverse events (AE) up to 30 days: ○ Per-operative AEs during device use (cervical trauma, uterine perforation…) ○ Polymer film tolerance defined as fever, pain or bleeding between 48 hours post procedure and 30 days An Interim Analysis of the safety endpoint will be conducted on the first 10 subjects at 30 day follow-up. ● Efficacy endpoint: freedom from intrauterine adhesion at second look hysteroscopy between 4 and 8 weeks, and evaluation of severity according to American Fertility Society (AFS) and European Society of Gynecological Endoscopy classifications systems of adhesions.
Secondary endpoints	1. Number, type and severity of adverse events (AE) at 30 days 2. Performance: device technical success, defined as success of the following 2 steps :

	a. Insertion of the inserter into the cervix with loaded film b. Release of the film in the uterus defined as empty inserter after withdrawal 3. Menstrual bleeding according to Higham score 4. Presence of Womed Leaf residuals in the uterus at hysteroscopic control 5. Uterine film discharge experience as recalled by subject at second look hysteroscopy visit : a. Subject estimation of film discharge timing and duration. b. Vulvar pruritus or other discomfort c. Qualitative impression 6. Device manipulation duration, from insertion to withdrawal
Inclusion criteria	1. Women ≥ 40 years AND no childbearing wish, OR history of permanent sterilization 2. Subject scheduled for myomectomy for one or more myoma(s) where one myoma is at least 10mm in size (≥10mm) as estimated by pre-operative ultrasound measurement of the largest diameter 3. Hysterometry ≥6 cm and ≤9 cm as measured prior to device insertion 4. Subjects who are willing to provide a written informed consent as approved by the applicable Ethics Committee prior to participating in this clinical investigation. 5. Subjects who can comply with the study follow-up or other study requirements
Exclusion criteria	1. Current pregnancy 2. Abnormal uterine cavity according to ESHRE classification I to VI, such as unicornis, bicornis, septate, duplex 3. Known or suspected endometrial hyperplasia 4. Medical history of cervical or endometrial cancer 5. Active pelvic infection or medical history of pelvic peritonitis 6. Intrauterine device in situ 7. Known contraindication or hypersensitivity to Womed Leaf components and to medications such as aspirin; 8. Concurrent medical condition with a life expectancy of less than 12 months; 9. Full endometrial ablation

	Per-operative exclusion criteria: 10. Adenomyosis 11. Inflammation (endometritis) 12. Abnormal uterine cavity, including IUA 13. Hysterometry < 6cm or >9cm 14. Any complication during the intervention that is deemed to potentially interfere with the objective of the study by the investigator
Intervention technique	● No monopolar energy ● Resection is limited to myoma and excludes full endometrial ablation
Drug regimen	According to local practice of the participating site
Assessment / Data and image collection / Follow up schedule	● Intervention: recording of hysteroscopy procedures and 2D or 3D US imaging ● 2 hours after the procedure (i.e.before discharge): 2D or 3D ultrasound in order to visualize the polymer position and swelling in the uterine cavity. ● All subjects will be contacted at 30 days post procedure to assess their clinical status and adverse events. ● All subjects will undergo “second look” hysteroscopic procedure between 4 to 8 weeks. Recording of hysteroscopy images.
Timelines	First subject will be included in S2 2019. Enrollment of the 20 subjects will last 12 months. Study is expected to be closed by Q4 2020.
Statistical Analysis Plan	Descriptive statistics will be provided for all variables considered in the analysis. For categorical variables, the data will be presented as counts and incidence rates. For continuous variables, the data will be presented as mean, standard deviation, median, minimum, maximum and number of observations.
Applicable Norms	ISO 14155