PREG2 protocol synopsis

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| **Name** | PREG2 |
| **Title** | **PRE**vention of intrauterine adhesion after adhesiolysis with novel tri-block de**G**radable polymer film.<br>NCT04963179. |
| **Protocol version date** | December 16th 2022 |
| **Rationale for study** | 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]. IUA can lead to recurrent pregnancy loss, infertility, abnormal placentation, menstrual abnormalities, and pain.[1,2] Treatment by hysteroscopic lysis is recommended if the patient has clinical symptoms. However, one of the greatest challenge is the recurrence of adhesive disease[1,3]: the recurrence rate after intrauterine synechiae lysis is 20% to 32% and 42% to 60% in the case of severe synechiae[4,5,6,7]. The high rate of recurrences makes reproductive outcomes unsatisfactory, even after hysteroscopic treatment[8]. It is acknowledged that the use of an intrauterine barrier potentially reduces postoperative adhesion reformation. However, existing barriers have suboptimal efficacy due to their limited residence time in the uterus (HA gel) or need of manual removal (IUD, balloon, amnion graft). As a result, a golden standard to prevent adhesive disease does not exist.<br><br>Therefore, there is an unmet medical need for an evidence based effective secondary prevention method. Hence the evaluation of the efficacy of the anti adhesion effects of Womed Leaf after adhesiolysis. |
| **Study device** | Name: Womed Leaf<br>Device group: Anti-adhesion barrier<br>Device status: CE marked |

[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(5):0015-0282.
[2] Tuuli MG et al. Uterine synechiae and pregnancy complications. Obstet Gynecol 2012 ; 119 :810-4
[3] Warembourg S et al. Prevention and treatment of intrauterine synechiae : Review of literature. J Gynecol Obstet Biol Reprod. 2015 Apr ; 44 :366-79.
[4] Pabuccu 1999
[5] Valle 1988 Valle and Sciarra Intrauterine ·adhesions: Hysteroscopic diagnosis, classification, treatment, and reproductive outcome Am J Obstet Gynecol 1988;158(6):1459-70
[6] Accunzo et al., Effectiveness of auto-cross linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. Human Reproduction 2003;18(9):1918–21
[7] Yu et al., Factors affecting reproductive outcome of hysteroscopic adhesiolysis for Asherman's syndrome. Fertility and Sterility 2008;89(3):715-722.
[8] March CM. Intrauterine adhesions. Obstet Gynecol Clin North Am 1995;22:491–505.

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| | <u>Description:</u><br>Womed Leaf™ device is composed of a uterine anti-adhesion film pre-loaded inside a flexible inserter.<br><br>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 fluid to form a degradable mechanical barrier.<br><br>Womed Leaf™ is inserted in the uterine cavity by a gynecologist surgeon as a film folded into a 5 mm diameter 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. |
| **Objective** | Evaluate the effectiveness of Womed Leaf in preventing intrauterine adhesions recurrence after hysteroscopic adhesiolysis (secondary prevention) by comparing it to adhesiolysis without IUA prevention. |
| **Design** | Prospective, multi-center, stratified, randomized, controlled, two-arm superiority clinical trial<br>Subjects will be followed up for 6 weeks as per AAGL/ESGE guidelines[9] for the primary endpoint and up to 2 years for the secondary fertility endpoints. |
| **Study group** | IUA prevention: Womed Leaf is inserted immediately after completion of the hysteroscopic adhesiolysis |
| **Control group** | No IUA prevention - no placebo after adhesiolysis |
| **Estimated number of subjects** | 154 subjects |
| **Sites** | At least 7 specialized centers |
| **Population** | Women with moderate or severe intrauterine adhesions (AFS score >=5) confirmed by hysteroscopy, scheduled for hysteroscopic adhesiolysis |
| **Randomization** | Computer generated randomization in 1:1 ratio<br>Randomization will be stratified by IUA severity (moderate/severe) determined at the beginning of adhesiolysis. |
| **Primary effectiveness endpoint**<br><br>**Primary safety endpoint** | The primary effectiveness endpoint is: Change of AFS score between pre-adhesiolysis and second-look hysteroscopy (AFS) score.<br><br>The primary safety endpoint is: Adverse events up to second look hysteroscopy (6 weeks +/- 2 weeks). |

[9] AAGL practice report: practice guidelines on intrauterine adhesions developed in collaboration with the European Society of Gynecological Endoscopy (ESGE), 2017

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| **Key Secondary Effectiveness Endpoints**<br><br>**Other secondary endpoints** | 1. High-responder rate i.e: percentage of patients who have improved from severe to mild adhesions or from severe to no adhesions or from moderate to no adhesions at second look<br>2. Change of "extent of cavity involved", according to the 10-zone uterine diagram, between pre-adhesiolysis and second-look hysteroscopy<br>3. Change in "extent of cavity involved" component between post-adhesiolysis and second look hysteroscopy<br>4. AFS scores at second look hysteroscopy<br>5. Extent of IUA AFS score component<br>6. Type of IUA AFS score component<br>7. Menstrual pattern AFS score component<br>8. Percentage of patients who have Mild adhesions or no adhesion at second look<br><br>1. Freedom from IUA (rate) at second look hysteroscopy (6 weeks +/- 2 weeks)<br>2. ESGE stage at second look hysteroscopy<br>3. Level of post-operative pain on a numeric rating scale, with 0 = no pain and 10 = the worst pain.<br>4. Level of discomfort related to vaginal discharge on a numeric rating scale, with 0 = no discomfort and 10 = extremely disturbing.<br>5. Timing of vaginal discharge as recalled by the patient<br>6. Duration of the vaginal discharge<br>7. Qualitative description of the vaginal discharge<br>8. Change of menstrual pattern at second look hysteroscopy, 1 year and 2 years<br>9. Reintervention rate, during second look hysteroscopy or scheduled later up to one year<br>10. Number of adhesiolysis procedures after second look up to one year<br>11. Pregnancy rate defined as presence of foetal sac or heartbeat by ultrasound at 1 year and 2 years, whether spontaneous or IVF<br>12. Live birth rate at 1 year and 2 years<br>13. Pregnancy complication rate<br>14. Time to pregnancy (i.e. time between the second look hysteroscopy and pregnancy start)<br>15. IUA severity according to Chinese scoring system (for patients enrolled in China only)<br>16. Responder rate: Percentage of patients with an improvement of one clinical category i.e from Severe to Moderate or from Moderate to Mild |
| **Inclusion criteria** | 1. Women with moderate or severe intrauterine adhesions according to the AFS classification, i.e AFS score >=5, confirmed by hysteroscopy right before adhesiolysis<br>2. Scheduled for hysteroscopic adhesiolysis<br>3. Age above or equal to 18<br>4. Subjects who are willing to provide a written informed consent. |

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| | 5. Subjects who can comply with the study follow-up (second look hysteroscopy) and other study requirements.<br>6. Subjects who agree to refrain from intercourse or use a reliable form of barrier contraception to prevent unintended pregnancy until the follow-up hysteroscopy.<br>7. Subjects who agree to avoid all intrauterine devices (IUDs) until the follow-up hysteroscopy. |
| **Exclusion criteria** | Pre-operative criteria<br>1. Post menopause<br>2. Pregnant (confirmed by a positive pregnancy test) or lactating<br>3. Abnormal uterine cavity according to ESHRE classification I to V such as unicornis, bicornis, septate, duplex<br>4. Known or suspected endometrial hyperplasia<br>5. History of cervical or endometrial cancer<br>6. Active pelvic infection or history of pelvic peritonitis<br>7. History of endometrial ablation<br>8. Known contraindication or hypersensitivity to Womed Leaf component<br>9. Current participation in another clinical investigation that has not yet received the primary endpoint.<br>10. Any other condition that makes participation in the study contrary to the patient's best interests.<br><br>Intra-operative criteria, post adhesiolysis:<br>11. Perforation during adhesiolysis<br>12. Uterine depth < 5cm or > 10cm |
| **Intervention technique** | Hysteroscopic adhesiolysis using tools according to local practice of the participating center. |
| **Procedure and drug regimen** | According to local practice of the participating site |
| **Data collection and Follow up schedule** | ● Assessment of IUA severity at the beginning and at the end of operative hysteroscopy<br>● Assessment of procedure or device related adverse event at 2 weeks and 6 weeks<br>● Second-look hysteroscopy at 6 weeks (+/-2 weeks) to assess recurring IUA.<br>● All patients will be contacted at 1 year and 2 years (+/- 1 month) by email and/or phone call to assess their pregnancy status.<br>See table below. |
| **Timelines** | The first patient will be included in Q4 2021.<br>Patient inclusion will last 24 months.<br>Evaluation of the primary outcome will be done by Q1 2024.<br>Total study duration (including long term follow-up): 4 years<br>Data gathering and analysis before manuscript submission: 3 months. |

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| **Blinding** | Open label to the surgeon<br>Blinded to the study subjects and the hysteroscopy evaluator. |
| **Sample Size Calculation** | ● Two sided test<br>● Confidence interval: 95% (5% alpha/type I error)<br>● Power: 90% (10% beta/type II error)<br>● Hypothesis*:<br>○ Control group: mean difference of AFS score = 5<br>○ Study group: mean difference of AFS score = 6<br>○ Standard deviation: 1,8<br>⇒ Sample size: 138<br>● Loss to follow up: 10%<br>⇒ Total population: 154 subjects with a 1:1 randomization |
| **Statistical Analysis Plan** | The Intention To Treat (ITT) population is defined by all randomized patients.<br>The safety population is defined by all randomized patients.<br><br>Standard descriptive statistics will be used.<br>Randomization being stratified on IUA severity, statistical analysis will be adjusted on IUA severity.<br><br>For the primary effectiveness endpoint (classification of adhesions): A covariance analysis (ANCOVA) with the mean change of AFS score between pre-adhesiolysis and SLH as dependent parameter, with IUA severity stratum as covariate will be conducted to compare the 2 groups. The two-sided 95% CI of the mean change of AFS score between pre-adhesiolysis and SLH will be estimated independently in each randomization group using standard error (SE). If H0 is rejected and $\Delta_{WOMED} > \Delta_C$ then, superiority of Womed Leaf over no IUA prevention method will be concluded.<br>If the normality of the change of AFS score cannot be assumed, the tertiles of the parameter will be used as a dependent parameter and an ordinal logistic regression model will be used.<br><br>For the primary safety endpoint, all AE will be presented.<br><br>For key secondary efficacy endpoints: The list of key secondary endpoints has been hierarchically ordered. For each endpoint, the hypotheses will be tested using a fixed-sequence method following the order defined, using 2-sided statistical tests, all at the same significance level alpha ($\alpha = 0.05$), moving to a second endpoint only after a success on the previous endpoint. |
| **Applicable Norms** | ISO 14155:2020, Good Clinical Practice, 21 CFR Parts 11, 50, 54, 56, and 812, Medical Device Regulation (EU) 2017/745 (MDR) and MDCG 2020-10/1 guidance, Good Clinical Practice for Medical Devices Clinical trials (Decree No. 28, 2022) promulgated by NMPA in 2022. |

| | | D-7 days (±7days) | D0 | | 2 weeks (+/-1 week) | 6 weeks (+/-2 weeks) | 1 year (+/-1 month) | 2 years (+/-1 month) |
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| **Data / imaging collection** | **Enrollment** | **Pre-operative visit** | **Before adhesiolysis** | **After adhesiolysis** | **Phone call** | **Second look HSC** | **Phone call and/or email** | **Phone call and/or email** |
| Patient information | X | | | | | | | |
| Inclusion criteria validation | X | | X | X | | | | |
| Informed consent* | X | | | | | | | |
| Pregnancy test | X | | | | | | | |
| Medical History | | X | | | | | | |
| Baseline characteristics | | X | | | | | | |
| Uterine depth | | | | X | | | | |
| AFS score | | | X | X | | X | | |
| Presence and location of IUA (diagram) | | | | X | | X | | |
| Hysteroscopy recordings (not mandatory) | | | X | X | | X | | |
| Intervention report | | | | X | | X | | |
| Device performance related event | | | | X | | | | |
| Adverse events (AE) | | | | X | X | X | | |
| Medication | | X | | X | X | X | X | X |
| Menstrual pattern | | X | | | | X | X | X |
| Patient reported outcomes | | | | | | X | X | X |
| Pregnancy status (and date) | | | | | | X | X | X |
| Live birth | | | | | | | X | X |
| Pregnancy complications | | | | | | | X | X |

Data collection and follow-up table