PILOT STUDY OF SAFETY AND EFFICACY OF 2.5% ADHESIABLOC® GEL TO REDUCE ADHESIONS FOLLOWING PERITONEAL CAVITY SURGERY

Device Clinical Study Protocol No. P-D015 Ver. 1.4

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1 Background

An adhesion is defined as abnormal binding of adjacent fibrous tissue surfaces. Adhesions formed at sites which had no pre-existing adhesions are called "*de novo* adhesion". These include adhesions formed at sites traumatized after surgical procedures (surgical site *de nova* adhesions) and at sites which had no surgical intervention (non-surgical *de novo* adhesion). Adhesions reformed at sites which had pre-existing adhesion but are lysed are called "reformed adhesions". De nova adhesion and reformed adhesions can be further classified depending on the extent and severity of the adhesion at particular sites. Peritoneal adhesions, a frequent complication which are formed or reformed following abdominal surgery, can cause clinical symptoms including, but not limited to, abdominal discomfort, chronic pelvic pain, bowel obstruction and infertility in women.

Corrective surgeries are often needed to resolve adhesion-related complications. Preventive measures are therefore of considerable clinical importance. Increased awareness of peritoneal adhesions has encouraged the use of surgical techniques such as laparoscopy, designed to minimize peritoneal trauma. Also, numerous potential adjutants are intended to separate peritoneal surface during post-surgical healing in order to prevent or reduce adhesion formation. Saline peritoneal lavage, antibiotic therapy and HYSKON® are the most common examples, but clinical experience with these treatments has been equivocal. FDA-approved INTERCEED® (TC7) Absorbable Adhesion Barrier (Gynecare, Somerville, NJ), Preclude® (Gore-Tex, Flagstaff, AZ) and Seprafilm® Bioabsorbable membrane (Genzyme, Cambridge, MA) has been proven efficacious, but as is inherent with barrier fabric or film products, the effect is localized and therefore site specific, requiring the surgeon to predict where adhesion would most likely form. Interest therefore continues in the development of an intraperitoneal device which functions more broadly as a post-surgical adhesion prophylactic.

Propylene Glycol, known also by the systematic name propane-1, 2-diol, is an organic compound (a diol alcohol), containing two hydroxyl groups (-OH groups) attached to adjacent by vicinal diols. It is produced by hydration of optically pure propylene oxide and fully miscible with water. Propylene Glycol has been shown to significantly reduce adhesion formation in animal models by means of hydro floatation and is believed to function through a physical effect by providing a viscous, lubricious coating on the peritoneal surfaces. In clinical evaluations conducted by Device Med-Systems, Propylene Glycol is found to be safe and marginally effective, with the greatest effect coming from a reduction in *de novo* adhesions. However, these solutions are rapidly absorbed from peritoneal cavity, allowing for an extended period of time for adhesion formation.

2.5 % ADHESIABLOC® Gel, Propylene Glycol and Isoleucine crosslinked by the addition of a sodium chloride, is a colorless, viscous aqueous solution formulated to a specific viscosity range. Crosslinking among the hydroxyl groups on the Propylene Glycol, the divalent sodium (Na^{+2}) and hydrocarbon groups on the Isoleucine is ionic in nature, resulting in a significant increase in solution viscosity compared to the starting

Propylene Glycol solution. The ionically crosslinked 2.5% ADHESIABLOC® Gel has shown to prevent or reduce adhesion formation by hydro floatation is as effective as the starting solution in preclinical animal models. Moreover, 2.5% ADHESIABLOC® Gel showed prolonged intraperitoneal residence time of at least 15 days, which is enough time for peritoneal healing. It is packaged in 250 mL Type I borosilicate transparent vials with 25 mm flip tear-off seals, and is a sterile, non-pyrogenic gel of a highly purified light molecular weight amino-diol alcohol adjusted to isotonicity with sodium chloride.

2 Objective

The objective of this single center pilot study is to demonstrate whether the investigative study device, 2.5% ADHESIABLOC® Gel is as safe and efficacious as, or superior to the routine Ringer's Lactated Saline control in preventing or reducing adhesions in patients undergoing peritoneal cavity surgery.

3 Study Enrollment

3.1 Inclusion Criteria

1. female patients aged over 18
2. patients undergoing peritoneal cavity surgery via laparotomy due to infertility, pain, and/or irregular vaginal bleeding with preservation of fertility
3. patients who are able to participate in the Week 1 - 4 post-surgical laboratory determinations
4. patients who will be required to schedule for a second-look laparoscopy as part of their treatment
5. patients agreeing on written, witnessed informed consent to participate in the study prior to any study-mandated determinations or procedures to be performed with the exception of the physical examinations as discussed on page 6

3.2 Exclusion Criteria (Pre-operative or Intra-operative)

1. patients in pregnancy (including etopic pregnancy) or lactation period
2. patients undergoing tubal sterilization, reversal of sterilization, or tubal implantation during the surgical procedure
3. patients receiving cancer therapy including drugs and radiation within the last 3 weeks from the surgery
4. patients with lymphatic (WBC ≥ 12 K/mm^3), hematologic or coagulation disorders (HGB ≤ 8.5 g/dL), or taking anticoagulants
5. patients who have a history of hemochromatosis
6. patients who have hepatic (AST ≥ 50 U/L or ALT ≥ 50 U/L) or renal (BUN ≥ 25 mg/dL or Creatinine ≥ 1.5 mg/dL) disorders

7. patients taking oral or parenteral hypoglycemic agents for diabetes
8. patients whose pre-operative laboratory values are outside 20% of the normal range and considered clinically significant
9. patients who are immunocomprised or have autoimmune disorders
10. patients who are unsuitable for processing large fluid loads, such as patients with congestive heart failure
11. patients receiving any other peritoneal instillate containing corticosteroids, NSAID's, or HYSKON® (Dextran) (During the procedure, irrigants which may or may not contain heparin and/or antibiotics may be used if completely aspirated.)
12. patients in whom any other absorbable hemostat is left in the abdominal cavity (Surgicel® Avitene®, Gelfoam®, etc.)
13. patients receiving any other adhesion prevention adjuvant (INTERCEED® (TC7) Absorbable Adhesion Barrier, GoreTex®, Seprafilm® Bioabsorbable Membrane)
14. patients who will require post-surgical hydrotubation
15. patients with active pelvic or abdominal infection
16. patients who will undergo peritoneal grafting as part of their operative procedure
17. any surgical procedure at the time of the initial laparotomy that involves opening of the gastrointestinal or urinary tract
18. patients with 12 or more of the 24 anatomical sites contained adhesions as noted during the initial operative procedure (refer to Appendix I for list of the 24 anatomical sites)
19. patients who will have one or more of their anatomical sites removed during the initial operative procedure (refer to Appendix I for list of the 24 anatomical sites)

3.3 Duration of Study

The study duration is scheduled up to 20 weeks, from the first surgical procedure to the second-look laparoscopy (maximum not to exceed 24 weeks). Total enrollment is projected to take eight months.

4 Study Design

4.1 Design Consideration

A single (1) center will participate in this third-party blinded, parallel group, randomized and controlled study. A maximum of seventy (70) patients will be asked to participate,

but no more than fifty (50) patients, including those who are not evaluable, will be entered into the study. An evaluable subject, defined as one who has completed her scheduled second-look laparoscopy targeted for six (6) to twenty (20) weeks from the initial surgical procedure (minimum of six (6) weeks, maximum not to exceed twenty-four (24) weeks), are targeted total of forty (40), or 20 per group. These evaluable subjects will undergo peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy.

At the initial laparotomy, adhesiolysis, myomectomy, ovarian cystectomy, Fallopian tube repair, surgical treatment of endometriosis, ovulation enhancing surgical procedures, or other pelvic reconstructive surgical procedures will be performed. Subjects will be administered 1000 mL of 2.5% ADHESIABLOC® Gel or Ringer's Lactated Saline as an intraperitoneal instillate by a surgical assistant (third party) after the surgeon has completed the primary laparoscopy procedure, achieved complete hemostasis, aspirated all irrigants, removed all packs and sponges, and has left the operating area. Second-look laparoscopy will be carried out at the appropriate time interval. Instillation of solution by surgical assistant or third party is to maintain the blind study.

Safety assessment will be based on the preparative and post-surgical laboratory test values, concomitant medications and conditions, frequency and severity of adverse events, and overall evaluation at second-look laparoscopy.

The primary efficacy variable will be a total adhesion score using the modified American Fertility Society (mAFS) Scoring System applied to 24 anatomical sites. Scores from all potential adhesion sites will be averaged (divided into 24) to yield a total adhesion score, ranging from 0 to 16. Adhesions will be characterized as either *de novo* or *reformed* depending on their characteristics and classifications. Sites with *de novo* adhesions will also be further classified as surgical versus non-surgical.

The secondary efficacy variable will be proportion of sites with adhesions, a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. As above, adhesions will be characterized as *de novo* versus reformed and surgical versus non-surgical. Additional secondary variables will include the extent and severity of all categories of adhesions.

In addition, adhesion sites will be organized by the presence or absence of endometriosis, use of sutures, and the method of adhesiolysis (sharp dissection; laser).

4.2 Study Procedure

Each patient asked to participate in the study will be assigned sequentially, by means of a random number scheme, to one (1) of two (2) following groups:

1. A study device group: 2.5% ADHESIABLOC® Gel, or
2. A control solution group: Ringer's Lactated Saline (RLS)

Case Report Forms (CRF) for the evaluations presented in Appendix II will be provided in individual binders, one set per patient, for recording purposes with exceptions of Concomitant Medication and Adverse Events. These exceptions will be further discussed in 4.2.7.

Patients participating in the study will undergo the following evaluations and procedures:

4.2.1 Preparative Procedures (VISIT 1)

Within the three (3) weeks prior to the initial surgical procedure, patient's general background information such as past surgical history, current medications (prescription, non-prescription, and iron supplements) and checklists for inclusion/exclusion including informed consent will be obtained and recorded on the CRF.

Each patient will undergo physical examination including vital sign (temperature, weight and height, respiration rate, blood pressure and pulse) measurement. Since these physical examinations are a standard pre-operative practice, they may be performed prior to the patient's signing of the consent form as long as the examinations are performed within the three (3) weeks prior to the initial surgical procedure. The results will be recorded on the CRF.

Also, each patient will perform the below-listed laboratory tests within the three (3) weeks before the initial surgical procedure. These test results will be used as a baseline for evaluating the safety of intraperitoneal instillation of the study solution:

1. Hematology (CBC)
2. Serum electrolytes (sodium, potassium, calcium, chloride)
3. Blood Chemistries: BUN, creatinine. albumin, total protein, total bilirubin, phosphorus, SGPT, SGOT, alkaline phosphatase, and uric acid.
4. Urinalysis, including a human chorionic gonadotropin (hCG) urine pregnancy test

The investigator will review the laboratory data and record the information on the CRF. All values should be within 20% of the normal range. If any values are outside of 20% of the normal range, the investigator will consider whether the value is clinically significant and provide comments on the CRF regarding their decision to include or exclude the patient. The principal investigator will review and sign on the CRF after carefully examining and verifying all of the entries in this section.

4.2.2 Initial-Operative Procedures (VISIT 2.1)

The patient will be assigned the next available study number four (4) hours prior to the scheduled surgery. The investigator will assess the existence of any adhesion at each of the 24 anatomical sites listed in Appendix I prior to any adhesiolysis.

If an adhesion is present, this information will be recorded on the CRF. If an adhesion is fully lysed, this information will also be recorded on the CRF by answering YES to the lysing question for each anatomical sites, along with the method of adhesiolysis (sharp

dissection, cautery, laser). The severity and extent of the adhesion(s) will characterized as shown in Appendix I.

The presence of endometriosis and whether the tissue was excised or fulgurated will be assessed at each of the 24 anatomical sites. The investigator will also note suture use and any other surgical intervention for each of the 24 anatomical sites on the CRF. The type(s) of sutures used will be noted along with a synopsis of the procedure(s) on the CRF.

The investigator will also provide data regarding the following:

- an account of the actual surgical procedures (*e.g.*, cystectomy, myomectomy, *etc.*) rendered
- estimate of total operative time of these procedures
- estimate of blood loss (in mL/cc) due to these procedures
- all concomitant medications used
- the stage of endometriosis (if present) utilizing the MAFS scoring system

All pre-existing adhesions will be drawn at the time of the surgical procedure, or shortly thereafter within 36 hours. Careful attention needs to be paid clearly identifying the anatomical site, extent, and severity of each adhesion. Any adhesions not lysed will be recorded on the CRF. All incision lines will also be recorded on the appropriate diagrams. An optional worksheet will be provided as an aide for recording this adhesion assessment.

The study device or control solution, as determined by the blinded randomization schedule, will be administered into the peritoneal cavity by the surgical assistant after the surgeon has completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs and sponges, providing the intraoperative exclusions criteria do not apply. The Principal Investigator will identify the surgical assistant on the CRF.

4.2.3 Initial Post-Surgical Procedures (VISIT 2.2)

The patient will be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. The result will be recorded on the CRF. Any adverse experiences noted by the patient and/or observed by the staff, i.e., post-surgical pain, nausea, infection, and etc, also will be recorded on the CRF. Serum electrolytes, hematology (CBC with differential) and blood chemistries will again be conducted prior to the patient's discharge from the hospital or within 4 days of the initial surgery, whichever comes first. The date of discharge will also be noted.

Additional comments may be made on the CRF. The principal investigator will review and sign the CRF after carefully examining and verifying all of the entries in this section.

The patient will also be provided with a Patient Log (P/L) to record medications taken following discharge and to comment on their general status. This log will be collected on VISIT 3.

4.2.4 Materials and Methods

Supplies

The study device and control solution will be provided by DEVICE MED-SYSTEMS without any charge. The study device and control solution will be packaged in sealed boxes so that there is one (1) carton for each patient appropriately labeled with the protocol number and patient number from the randomization schedule. Each box will contain one (1) of the following:

1. 2.5% ADHESIABLOC® Gel, four (4) separate vials each containing 250 mL, or
2. RLS, one package containing at least 1000 mL.

Two (2) part labels, consisting of the affixed part and the tear-off part will be provided with the study device per each bottle. An affixed part will be permanently attached to the study device. Also, a tear-off part, which contains the concealed identity and lot number and which can be revealed by rubbing off the silver paint in case of an emergency, will be attached to the Label Check Form (LCF). Both parts of the label will have enough spaces for entering the patients' initials. The Manufacturer's label, which is to be attached to the control solution, will be provided along with the study label. Three (3) additional tear-off labels will also be provided, such that four (4) labels including one (1) study label and three (3) tear-off labels can be attached to the LCF for either treatment or control.

Storage

All the boxes containing the study device and the control solution will be stored in a refrigerator kept at 37.4 - 44.6°F.

Dispensing of Solution

Approximately four (4) hours prior to the scheduled surgery, the appropriate box will be removed from the refrigerator and warmed to room temperature. The box may be placed in a 104°F warming oven to facilitate the warming process.

When the patient is confirmed as a suitable study subject, the pre-warmed study device or control solution will be distributed by surgical assistant after the surgeon has completed the primary surgical procedure as discussed below. All 1000 mL of the study device or 1000 mL of control solution are to be delivered into the abdominal cavity. The amount of material to be administered (1000 mL) is based on the normal instillation volume of RLS in practice and is believed to be sufficient enough to allow for the floatation of the adnexal structures. A slight excess (3 to 8 mL), the amount that has been added to each

study device vial, will remain in each of the study device vials. Excess control solution (250 mL) will also remain.

The patient's initials will be recorded on both parts of the label, i.e. the tear-off parts and attached parts. All four (4) tear-off labels are to be attached to the LCF. If the patient is determined not to be eligible for the study at the time of surgery, the sealed box will be returned to storage and quarantined from the remaining study clinical supplies. At that time, a reason for the patient's disqualification will also be recorded in the CRF.

Application of Solution

The study device or control solution will only be administered into the peritoneal cavity by surgical assistant after the surgeon has completed the initial surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs, sponges, and materials.

Since the outer portion of each study device and control solution container is not sterile, its contents will be transferred to the sterile field by using conventional aseptic operating room techniques. Instillation will be achieved using large syringes (60 mL catheter tip) fitted with 5 mm diameter urological catheter irrigation canulas.

Administering the study will involve conducting the following procedures:

1. Approximately 500 mL of solution will be administered either directly into the pelvis or through an irrigation canula while the small bowel is still out of the operative field. Distribution throughout the peritoneal cavity can be facilitated by the surgical assistant's hand or probe.

2. The remaining material, approximately 500 mL will be administered after the small bowel has been returned to its normal position. Distribution of the solution over the serosal surfaces can be facilitated by the surgical assistant's hand or probe.

Additional comments may be made on the CRF. The principal investigator will review and sign on the CRF after examining and verifying all of the entries in this section.

4.2.5 Post-Surgical Week 1 - 4 Evaluations (VISIT 3)

Serum electrolytes, hematology (CBC with differential) and blood chemistries will again be conducted at the VISIT 3.

The investigator will also record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-surgical pain, nausea, infection, and etc, between the patient's discharge and VISIT 3. The patient will again be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. These results will be recorded on the CRF.

New P/L will be provided after collecting the first P/L. Prior to completing this visit, the patient will be interviewed to assess any ongoing or new adverse experience(s).

Additional comments may be made on the CRF. The principal investigator will review and sign on the CRF after carefully examining and verifying all of the entries in this section.

4.2.6 Second-Look Laparoscopy (VISIT 4)

The patients will undergo a second-look laparoscopy six (6) weeks to twenty (20) weeks after the initial surgery (minimum of six (6) weeks, maximum not to exceed twenty-four (24) weeks).

Serum electrolytes, hematology (CBC with differential), blood chemistries, and urinalysis (including a urine pregnancy test) will again be conducted prior to the second-look laparoscopy. These data will be recorded on the CRF

The second P/L will be collected, and the patient will again be interviewed regarding any ongoing or new adverse experience(s). These data will be recorded on the CRF.

The VISIT 4 surgical procedure will be videotaped. The investigator will perform an examination of the peritoneal cavity, unusual lesions or the presence of ascites, and assessment of the presence, severity and extent of adhesions at the same 24 anatomical sites during the surgical procedure. Specific adhesion sites will again be sketched and recorded on the CRF. The presence of endometrial tissue at this VISIT 4 procedure will also be noted for the same 24 anatomical sites and recorded on the CRF. The stage of endometriosis utilizing the mAFS scoring system is also to be noted on the CRF. Also, an optional worksheet will be provided as an aide for recording the adhesion assessment in the operating room.

The patient status will be examined upon study completion or discontinuation and recorded on the CRF. If the potential evaluable patient fails to complete the entire study, ex., intraoperative exclusion criteria applies during initial surgical procedure or does not return for the VISIT 4 procedure, she is considered a screen failure or an early termination respectively, and the reason for the discontinuation will be indicated.

Additional comments may be made on the CRF if needed. The principal investigator will review and sign the CRF after carefully examining and verifying alt of the entries in this section.

4.2.7 Concomitant Medications and Adverse Events

The concomitant medications and adverse events will be grouped together in the separate section of the binder since this information is to be gathered throughout all phases of the study.

All baseline and concomitant medications (with the exception of IV hydrating solutions, anesthetics, and muscle relaxants administered during the surgical procedure) will be recorded on CRF, along with a copy of the anesthesiologists report.

The concomitant and baseline medications, including prescription and non-prescription medications will be derived from interviewing the patient or from the following source documents:

1. Patient history (office chart)
2. Patient medication records
3. Pre-operative anesthesia notes and anesthesia records
4. Post-anesthesia care records

All of the above source documents will be made available at the time of monitoring but will not be removed from the study site.

Other medications will also be reviewed by the investigator to determine whether it is considered necessary for the patient's welfare and whether it will not either directly or indirectly modify the actions and assessment of the study solution.

The patient will also be provided with a P/L to record medications taken following the surgery. The patient will be instructed in the use of the P/L and the need to bring the P/L to VISIT 3 and 4. At these visits, the investigators will review the P/L for completeness and accuracy. If the patient fails to return the P/L, this fact will be noted in the comments section on the CRF.

Any adverse events and/or intercurrent illnesses occurring during the study (including the nature, severity and the relation of the incident to the study) solution will also be recorded on the CRF.

5 Statistical Considerations

5.1 Study Populations

The safety populations will consist of all patients who receive 2.5% ADHESIABLOC® Gel or RLS during initial surgical procedure. A subset of the efficacy population will exclude patients who fail to conduct the VISIT 4 procedure. Thus, the evaluable efficacy population will consist of all patients who receive 2.5% ADHESIABLOC® Gel or RLS during initial surgical procedure and who participate in VISIT 4 procedure.

Patients who are randomized but do not receive treatment, i.e. intraoperative exclusion criteria applies during the initial surgical procedure will be described but will not be otherwise analyzed.

5.2 Sample Size

As this is a pilot study, no formal sample size calculation is undertaken. Based on a pilot study evaluating the safety and efficacy of anti-adhesion device in other indication (Baxter Healthcare Corporation, 2000), 46 patients (23 per treatment group) were selected as an achievable number to complete the study. The 40 evaluable patients (20 per group, approximately 50 total enrollments) appear to provide sufficient sample size to reject the null hypothesis if the observed trends are maintained.

The study enrollment number is based on a worse case 30% screen failure rate and 20% loss to follow-up rate. 70 patients will be requested for participation in the study, with 50 expected to receive treatment, and 40 to participate in VISIT 4 procedure. All patients assigned study numbers and receiving treatment will be carefully followed and all screen failure and loss to follow-up patients documented. All efforts will be made to keep these to a minimum.

Any patient who fails to return for the VISIT 3 and/or the VISIT 4 will be contacted and interviewed if possible as to her reason for not returning and her medical status ascertained relative to the effects of the study device. All attempts to contact the patient will be documented on the CRF.

A patient may be discontinued from the study at any time in the event of a serious or intolerable adverse event, the need for an excluded medication, an intercurrent illness, a protocol violation or at the patient's request.

5.3 Safety Considerations

Safety considerations will include patient self-reporting of adverse events categorized using standard COSTART terms. Laboratory values will be recorded as a mean deviation from the baseline and as transition tables showing the proportions of patients above, below and within the normal range (20%) both before and after treatment.

5.4 Efficacy Variables

The primary efficacy variable will be a total adhesion score using the modified American Fertility Society (mAFS) scoring system applied to 24 anatomical sites. Grading the extent of adhesions and the adhesion score derived from severity and extent will be discussed in Appendix III.

Scores from all potential adhesion sites will be averaged (divided into 24) to yield a total adhesion score which will range from 0 to 16. Adhesions will be categorized as either *de novo* or *reformed* depending on their characteristics. Sites with *de novo* adhesions will also be characterized as surgical versus non-surgical.

A secondary efficacy variable, i.e. the proportion of sites with adhesions will also be analyzed. This will be a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. Adhesions will be characterized as *de novo* versus reformed, surgical versus non-surgical as above.

In addition, adhesion sites will be categorized by the presence or absence of endometriosis, use of sutures and the method of adhesiolysis (sharp dissection, cautery, and laser).

Each anatomical site will also be analyzed regarding the severity and extent of all categories of adhesions. Appendix III discusses on Severity and Extent scores.

5.5 Statistical Analysis

Adhesion scores from the records of VISIT 4 procedures will be analyzed using treatment groups (2.5% ADHESIABLOC® Gel versus RLS) as a factor and adhesion scores as a variance. Interactions between baseline adhesion scores and treatment groups will also be examined to test Homogeneity.

Age, race, height, weight, blood pressure, previous and concomitant medications categorized by AHFS codes, presence of endometriosis, surgical-procedures categorized by CPT codes, estimated blood loss, operative time and baseline adhesion scores will be analyzed.

If the two groups differ on any important demographic or surgical variables mentioned above or if these variables appear to strongly predict VISIT 4 adhesion scores by using multiple linear regression with treatment group forced into the model as a dummy variable, these variables may be added to the model as covariates. Interactions between covariates and treatment group will be examined to test the Homogeneity of slopes. Covariates may be transformed in order to yield homogeneous slopes.

The mean proportion of sites with adhesions observed at VISIT 4 will be analyzed in the same fashion as the mean VISIT 4 adhesion scores. Other continuous variables will be analyzed using factorial variance analysis.

Categorical variables will be analyzed by using the Cochran-Mantel-Haenszel test with individual sites as strata. Proportions with small expected event rates such as adverse events will be analyzed using Fisher's exact test. Laboratory value transition tables will be compared by using 2×9 Fisher's exact test. Two-sided p- values will be recorded and p-values less than 0.05 will be considered indicating statistical significance.

6 Other Considerations

6.1 Reporting and Recording of Data

All information required by the protocol will be provided or an explanation given for omissions. All CRFs will be made available as soon as they are completed in order that the monitor may verify the validity and completeness of the forms.

All data and information on these CRFs will be neatly recorded in type or legibly printed in black ink for ease of duplication, interpretation and analysis. If a correction is needed on CRF, the correction will be crossed out neatly with a single line and the new entry initialed and dated by the staff making the correction.

6.2 Records Retention

Federal law requires that a copy of all records (e.g., informed consent documents, laboratory data slips, source documents, safety reports, study device dispensing record, etc.) which support the CRF for this study, be retained in the files of the responsible investigator for a minimum of two years following notification by Device Med-Systems that all studies (not merely the investigator's portion) are discontinued or that the Premarket Approval application is approved by Food and Drug Administration.

If the principal investigator retires, are relocated, or for other reasons withdraws from the responsibility of keeping the study records, custody will be transferred to a person who will succeed the position.

6.3 Adverse Events

All adverse events during the study including the nature, severity and the relation of the incident to the study solution will be recorded on the relevant section on the CRF. A serious adverse event includes one that is life-threatening, results in death, results in or prolongs hospitalization, results in severe or permanent disability, or involves cancer, a congenital anomaly, or an overdose. Device Med-Systems designated contact is:

Jonathan Q. Kruger, MD
Phone: 410-916-3795

There are no anticipated adverse events. The theoretical risks that associated with the use of the study solution are ascites, allergic reactions, sepsis, and wound dehiscence, although these were not observed in preclinical animal testing.

6.4 On-site Audits

The United States Food and Drug Administration may request on-site, including access to all study records, including source documents, for inspection and copying.

6.5 Patient Confidentiality

The investigators may keep key patient information on the CRF, which will be used for the purpose of long-term follow-up, if needed. This form will be treated confidential and will be filed with restricted access. Otherwise, all reports and communications relating to the study will identify patients by assigned patient numbers only.

6.6 Modification of Protocol

This protocol shall not be modified without confirmation of Device Med-Systems. If it is to be modified, the party requesting the modification shall submit written request to Device Med-Systems. Device Med-Systems will then notify Food and Drug Administration of the modification.

6.7 Discontinuation of the Study

This study will be terminated in case of certain administrative condition including, but not limited to, a decision to discontinue further clinical investigation with the device, improper conduct of the study by the investigator(s) or an inability to obtain the number of patients required by the protocol.

APPENDIX I

- Anatomical Sites Evaluated -

Anterior peritoneum	caudal, right cephalad, left cephalad, incision
Uterus	anterior, posterior
Omentum	
Bowel	small, large right, large left, rectosigmoid large
Cul-de-sac	
Pelvic sidewall	Right, left
Right ovary	lateral, medial, fossa
Left ovary	lateral, medial, fossa
Fallopian tube	right, left
Ampulla	right, left

- Classifications regarding severity and extent of the adhesion(s)[2] -

Severity	**Description**
Mild	filmy, avascular adhesion
Severe	dense, organized, cohesive, vascular adhesion
Extent	**Description**
Localized	less than 1/3 of the site covered
Moderate	1/3 to 2/3 of the site covered
Extensive	more than 2/3 of the site covered

[2] The extent of adhesions will not be determined for the small bowel, omentum, and large bowel right and left, since their size precludes adequate visualization or evaluation.

APPENDIX II

- Case Report Forms recorded for the evaluations -

Evaluations/Procedures	Schedule of Evaluations				
	VISIT 1	VISIT 2.1	VISIT 2.2	VISIT 3	VISIT 4[3]
Informed Consent	X				
Inclusion/Exclusion	X	X			
Background Information (Demog., Med. & Surg. History)	X				
Physical Exam (& Vital Signs)	X		X[4]	X[4]	
Concomitant Medications	X	X	X[5]	X[56]	X[6]
Blood Chemistries	X		X	X	X
Hematology	X		X	X	X
Pregnancy Test / Urinalysis	X				X
Confidential Patient Follow-Up	X				
Device Label Check		X			
Adhesion Assessment		X			X
Suture Use, Surg. Intervention		X			
Endometriosis Evaluation		X			X
Abdominal Drawings		X			X
Adverse Events		X	X	X	X
Patient Status				X	X
Principal Investigator Signature & Comment	X	X	X	X	X

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3 Concomitant Medications, Blood Chemistries, Hematology, and Pregnancy Test / Urinalysis are to be completed prior to VISIT 4.

4 A limited physical examination prior to discharge and at VISIT 3 is for the purpose of performing an abdominal auscultation and percussion for assessment of the presence of ascites

5 Dispense P/L.

6 Collect P/L.

APPENDIX III

- Extent of adhesion[7] -

Localized	Moderate	Extensive
<1/3 of site covered	1/3-2/3 of site covered	>2/3 of site covered

- Severity Score -

None	0
Mild	1
Severe	4

- Extent Score -

None	0
Localized	1
Moderate	2
Extensive	4

- Adhesion scores using AFS scoring system -

Severity and Extent of adhesion	Score
No Adhesion	0
Severity: Mild Extent: Localized	1

[7] The extent of adhesions will not be scored for the small bowel, omentum and left and right large bowel since their size precludes adequate visualization. These sites will be assigned a classification of Moderate in order to determine the total adhesion score.

Severity: Mild Extent: Moderate	2
Severity: Mild Extent: Extensive	4
Severity: Severe Extent: Localized	4
Severity: Severe Extent: Moderate	8
Severity: Severe Extent: Extensive	16