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**IV. D. 4. PRE-HYSTERECTOMY STUDIES  
(HYSTERECTOMY 6-12 WEEKS AFTER  
IMPLANT)**

## **2.6 Pre-Hysterectomy Studies- Pilot Studies**

### **2.6.1 Overview**

After successful completion of animal fertility studies and human Peri Hysterectomy studies, Adiana undertook a series of *in-vivo* clinical studies to determine the ability of the Adiana System to occlude fallopian tubes.

Pre-Hysterectomy protocol [REDACTED] was designed to evaluate the Adiana System with regard to safety and efficacy in the human anatomy. The Pre-Hysterectomy studies are organized into a series of “Pilot-Pre” studies and a single “Pivotal-Pre” study. The Pilot-Pre studies were a series of implant studies designed to gain information relating to lesion parameters, matrix configurations and/or device designs to optimize the treatment. Once confidence was obtained that the treatment had been optimized and the ingrowth period defined, the Pivotal-Pre study was conducted to confirm the results with a larger number of subjects.

In addition, following submission of the Pre-Hysterectomy data for the first five studies, and pursuant to FDA’s guidance in the IDE approval letter, additional Pre-Hysterectomy data was collected after the EASE trial was begun. These additional studies, Pivotal-Pre 6, 7 and 8 include additional confirmatory data. Data from these additional studies are included in Section 2.7, “Pre-Hysterectomy Studies- Pivotal Study”. (Report [REDACTED] can be found in Appendix 3)

The Pilot-Pre series examined [REDACTED]

[REDACTED] The subsequent Pivotal-Pre Hysterectomy Study utilized one matrix design, one ingrowth period and one basic catheter configuration.

The key differences of the five Pilot-Pre studies had are shown below:

**Table 2.7:** Pilot Study Parameters

Study	Sterilization	Lesion Parameters	Matrix Used	Ingrowth Duration
Pilot-Pre 1	[REDACTED]	[REDACTED]	Standard Matrix	6 weeks
Pilot-Pre 2	Steam	64°C/60 seconds	Standard Matrix	6 weeks
Pilot-Pre 3	Steam	64°C/60 seconds	Standard Matrix	12 weeks
Pilot-Pre 4	Steam	64°C/60 seconds	[REDACTED]	6 weeks
Pilot-Pre 5	Steam	64°C/60 seconds	[REDACTED]	12 weeks

\* Note: The standard matrix refers to Adiana Matrix part [REDACTED] which remains the final matrix configuration. The [REDACTED]  
 [REDACTED]

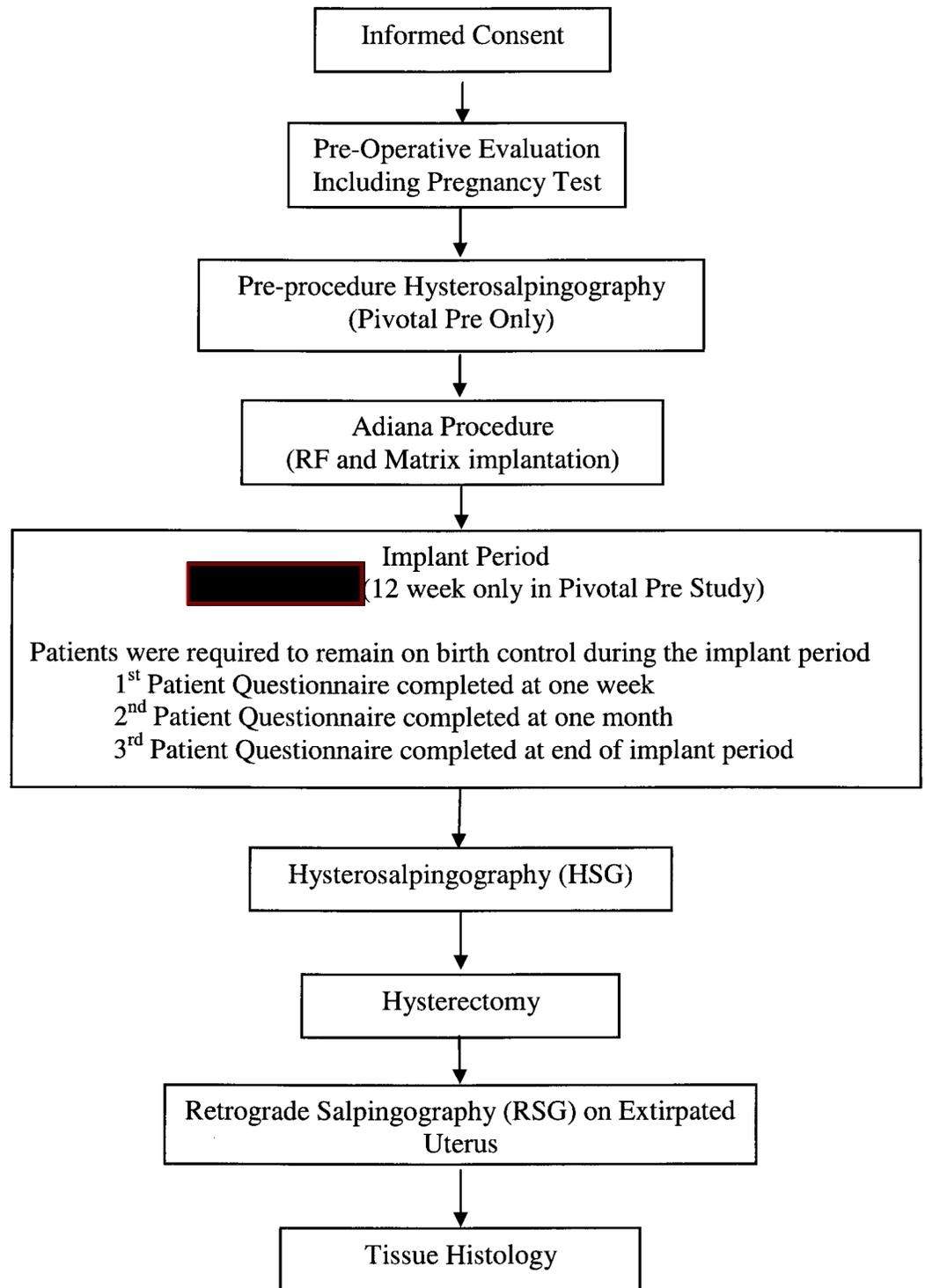
All Pilot Pre-Hysterectomy Studies were performed in [REDACTED] under protocol approved by the local Ethics Committee [REDACTED]  
 [REDACTED]  
 Informed consent was obtained from all patients. [REDACTED]  
 [REDACTED] were investigators for these studies.

**2.6.2 Patient Population- Pilot Pre-Hysterectomy Study**

Patients enrolled in this study were seeking a hysterectomy for clinical indications. All patients were pre-menopausal. There were a total of 23 patients in the Pilot Pre-Hysterectomy studies. Patients ranged in age from 35 to 51 years, with an average age of 43.0 years. All except one patient had at least one pregnancy and birth. The average gravidity was 4.4 and average parity was 3.6.

### 2.6.3 Study Design

The design of the Pre-Hysterectomy studies, followed the same format with these elements:



## 2.6.4 End Points of Aiana Pre-Hysterectomy Studies

### **Access Rate**

Ability of the investigator to place the Delivery Catheter within the fallopian tube (access rate). Access rate is defined as the number of successful placements into the fallopian tube divided by the number of tubes in which access was attempted. Attempted access was defined as placing the catheter into the hysteroscope with the intent to treat.

### **Patient Tolerance of Procedure & Characterization of Post Operative Period**

Patients were asked via questionnaires to self assess pain at different stages of the procedure.

### **Matrix Retention**

Ability of the matrix to remain in position within the fallopian tube for extended periods (several weeks). This is assessed by histological analysis of the tubal specimen. Histological analysis is used to verify matrix retention and identify its location.

### **Fallopian Tube Occlusion:**

Ability of the Aiana treatment to occlude the fallopian tube. 



### **Tissue Response to RF treatment and Ingrowth:**

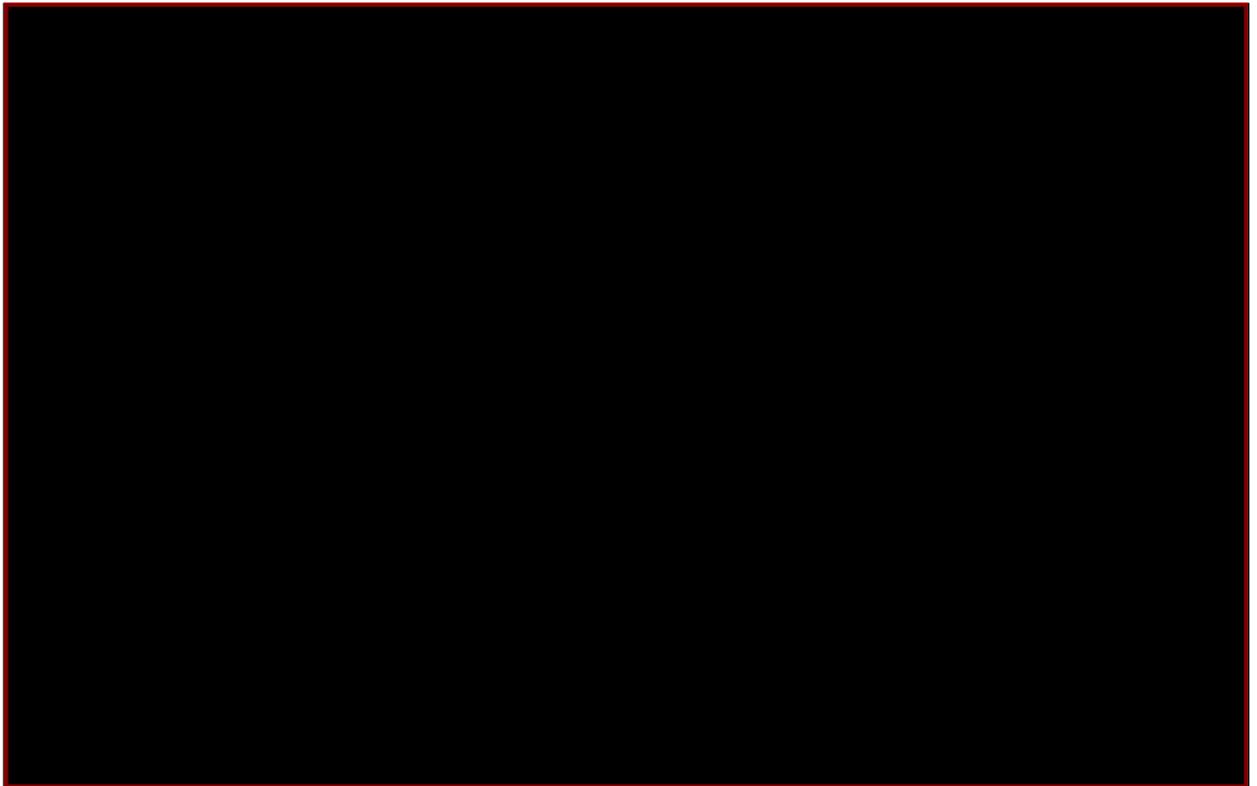
The ability of the combination of RF treatment and matrix implantation to achieve the desired wound-healing response was evaluated by histological analysis. This is assessed by an in-house derived scoring system, as previously described. The scoring system is explained in more detail in Appendix 8. In addition, determination of the occlusive ingrowth was evaluated by the presence of space filling ingrowth into the matrix.

It is important to note that in the Pre-Hysterectomy studies it is not possible to assess acute lesion creation, since tissue is obtained at 6 and 12 weeks after treatment. Therefore, measurements such as lesion length and lesion depth are not obtained. Percent epithelial ablation is not obtained, but rather percent residual epithelium is reported as simply the amount of epithelium at explant.

### **2.6.5 Adverse Events**

Absence of adverse events which affect the safety of the patient. Adverse events could include but are not limited to: adverse reaction to anesthesia, uterine or tubal perforation, uterine tubal rupture or hemorrhage, infection, fluid overload, bleeding or pregnancy.

### **2.6.6 Results: Pilot Pre Studies**



### **2.6.7 Overall Results: Access, Occlusion and Tissue Ingrowth**

Study results for each of the Pilot Pre Studies are included in Table 2.9 below. Access rates, tubal occlusion (by HSG and RSG) and tissue ingrowth scores are summarized.

**Table 2.9: Pilot Pre Results**

<b>Study</b>	<b>Patients</b>	<b>Access Rate</b>	<b>HSG Occlusion Rate</b>	<b>RSG Occlusion Rate</b>	<b>Tissue Ingrowth Score</b>
<b>Pilot-Pre 1</b>	6	83% (10/12)	30% (3/10)	30% (3/10)	1.08
<b>Pilot-Pre 2</b>	6	83% (10/12)	78 (7/9)	50% (5/10)	1.38
<b>Pilot-Pre 3</b>	4	87.5% (7/8)	100% (7/7)	85.7% (6/7)	1.62
<b>Pilot-Pre 4</b>	3	83% (5/6)	100% (5/5)	60% (3/5)	1.12
<b>Pilot-Pre 5</b>	4	100% (8/8)	100% (8/8)	100% (8/8)	1.51

**Pilot Pre 1**

Pilot pre 1 study did not employ the same temperature time parameters as currently utilized. In addition, the Delivery Catheter and matrix used in these studies was sterilized using [REDACTED]. The implant period was [REDACTED].

**Pilot Pre 2**

Results with the Pilot Pre 2 study at 6 weeks showed much less inflammation, and ingrowth was improved. Ingrowth was not completely occlusive, and dye leakage was seen.

**Pilot Pre 3**

Results in the Pilot Pre 3 at 12 weeks showed only slight inflammation, consistent with normal tubal histology. The ingrowth scores were improved. 100% occlusion on HSG, and the single leak on RSG assay at 100mmHg was in patient with a large, rapidly growing myoma close to that tube.

**Pilot Pre 4 & 5**

**Adverse Events**

There were no adverse events reported for any of the patients in any of the Pilot Pre-Hysterectomy Studies.

### **Patient Tolerance**

Acute pain during the procedure and in the hours after the procedure was assessed using a Visual Analog Scale (VAS) which yields numeric values between 0 and 100. Patients were asked by clinical staff to rate their pain on an analogue scale (either an unmarked ruler or a simple line on paper) between “No Pain”(a value of 0) and “Worst Pain Imaginable” (a value of 100).

Patients reported little pain with the placement procedure (mean scores less than 5/100). However, it should be noted that all patients had received IV sedation in addition to paracervical block.

Pain and discomfort were also assessed over the course of the device wearing. This assessment was based on patient questionnaire during follow-up. Patients were questioned at baseline (prior to implant), at one week after the procedure, at one month after the procedure, and immediately prior to explant or hysterectomy. Patients were asked to rate their pain at these specific time points, by selecting one of the following responses: None, Mild, Moderate, Severe. (For numeric analysis, these were converted to values of 0,1,2,3, respectively.)

Three types of pain were assessed: pelvic pain, abdominal cramping and back pain.

Mean pain scores were between “none” and “mild” for cramping, pelvic pain and back pain at baseline, and also when assessed during follow up: post procedure (with 48 hours), up to one week, and one month, and again at return hysterectomy.

### **Histological Analysis**

Overall, histological results from these five studies were mixed. As discussed above, results from the first study showed poor ingrowth due to [REDACTED]. The best tissue response was seen with the Pilot Pre 3 study, which demonstrated good ingrowth: vascularized tissue was seen filling the pores of the matrix, with low levels of undesirable tissue responses. (A detailed discussion of the results using this product configuration are included in the Pivotal Pre-Hysterectomy discussion in Section 2.7.8.)

Matrix retention was excellent when the matrix was properly placed. Early implants during the Pilot Pre 1 study included two instances in which the matrix was not properly placed and likely fell out after delivery. (Videotape review of the placement procedure confirmed misplacement.) These two matrices were not located at histological evaluation following hysterectomy. All other matrices were retained and were found at histological evaluation.

### 2.6.8 Discussion

The five studies performed in the Pilot Pre-Hysterectomy study provided important information which was used to define the subsequent Pivotal Pre-Hysterectomy study:

- The clinical procedure for Delivery Catheter placement and handling evolved during the pilot study. Proper identification of the tubal ostium and accurate catheter placement were refined in the early Pilot Studies.
- The configuration of the Delivery Catheter evolved during the study. Although all delivery catheters used during these studies employed identical electrode configurations and matrix release mechanisms, there were small differences in the distal tip of the catheter, and in the shaft design to improve catheter handling and trackability.
- Two different Matrix configurations were evaluated. The “disk wall” matrix, which is identical to the current, “standard” matrix except that it contained a single solid disk within the internal architecture was investigated. It was found to offer no benefit and was not pursued.
- Assay development improved during these studies. It was found that excessive pressures could damage the tube, so pressure was more carefully controlled on the retrograde assay for future studies. Tissue processing procedures were optimized to eliminate tissue damage and ensure appropriate samples were obtained.

### 2.6.9 Overall Conclusion- Pilot Pre-Hysterectomy Studies

There were several major conclusions in the Pilot Pre-Hysterectomy Studies:

- The access rate in this population was high, with 84.1% of attempted tubes successfully accessed.
- Patients were comfortable with the Adiana Matrix during the period following implantation.
- When properly placed, the matrix was retained during the period following implantation.
- Tubal occlusion was demonstrated by utilizing:
  - Treatment parameters of 64°C/60 seconds

- Standard matrix [REDACTED] (This same matrix has been used for all future studies, including the EASE Pivotal Trial.)
- 12 week ingrowth period
- Steam Sterilization
- Tissue ingrowth (at the temperature-time parameters and device configuration described above) was found to be space filling and to consist of cell types which would lead to stable, long term occlusive ingrowth.

On the basis of the Pilot Pre-Hysterectomy Studies, Adiana undertook the Pivotal Pre hysterectomy Study utilizing the same parameters as the Pilot Pre 3 study.

## **2.7 Pre-Hysterectomy Studies- Pivotal Study**

The Pre-Hysterectomy studies (Adiana Protocol [REDACTED]) are organized into a series of Pilot Pre-Hysterectomy (Pilot Pre) studies previously discussed in Section 2.6, which were then followed by the larger single Pivotal Pre-Hysterectomy study (Pivotal Pre).

There were two Phases to the Pivotal Pre-Hysterectomy study: Phase I included all data from 18 patients previously submitted to FDA in [REDACTED]. Phase II includes additional data from 24 patients treated following the IDE approval.

### **2.7.1 Pivotal-Pre Study Design**

The study design used in the Pivotal Pre-Hysterectomy study is shown in section 2.6.3.

### **2.7.2 End Points of Pivotal Pre Studies**

The endpoints evaluated in the Pivotal Pre Hysterectomy study are the same as in the pilot study and were discussed in section 2.6.4. Briefly, these are:

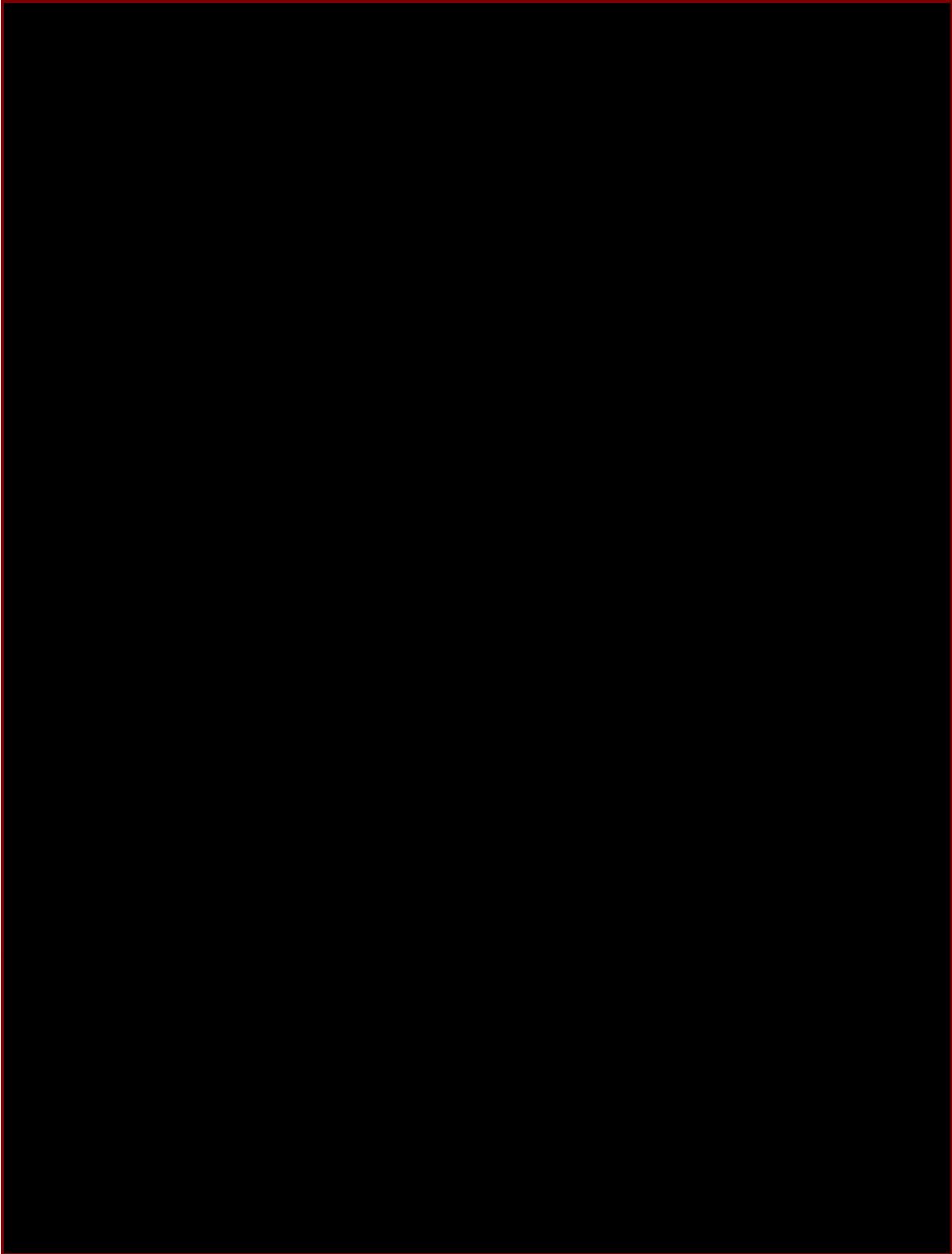
- Access Rate
- Patient Tolerance of Procedure & Characterization of Post Operative Period
- Matrix Retention
- Fallopian Tube Occlusion
- Tissue Response to RF treatment and Ingrowth:
- Adverse Events

### 2.7.3 Study Sites and Subjects

Two study sites were used for the Pivotal-Pre study. One was the Hospital [REDACTED] as the study site Principal Investigator. The second was the [REDACTED] as the study site Principal Investigator. The study was conducted in accordance with the Food and Drug Administration's guideline, "Good Clinical Practice: Consolidated Guideline", effective May 9, 1997.

All protocols were approved by the local institutional Human Subjects Review Boards (Ethics Committee) and patients signed Informed Consent forms to participate in these studies. Subjects were recruited from patients seeking an elective hysterectomy. Eligibility and exclusion criteria were detailed in the [REDACTED] Investigational Protocol.

A total of 42 patients were enrolled in the Pivotal Pre hysterectomy study. The patient demographics are included in [REDACTED]



Note: Patient study population. O.C. indicates oral contraceptives and T.L. indicates tubal ligation. AUB refers to abnormal uterine bleeding. PMS refers to Premenstrual syndrome. CIN refers to cervical intraepithelial neoplasia (dysplasia)

#### 2.7.4 Product/Device Information

The Adiana RF Generator (RFG) was used for all treatments in this study. An Adiana Delivery Catheter was used to create the lesion and deposit the matrix in all treatments in this study. Delivery Catheters used for this study were [REDACTED] and [REDACTED]. These catheters were identical except for a more rounded tip and a slightly increased stiffness in the proximal electrode section on [REDACTED] which was introduced subsequent to this study to improve trackability. (This increased proximal sheath stiffness was accomplished by the addition of a nitinol core wire.) (Catheter [REDACTED] was selected based on results of the Access Studies.) The standard Adiana Matrix (Subassembly part number [REDACTED] composed of porous silicone, was used for all implants.

#### 2.7.5. Procedure

All treatments in the Pivotal Pre study used the same lesion parameters, matrices and ingrowth period which had been optimized in the Pilot Pre studies. The lesion was created at 64°C for 60 seconds. The Adiana standard Matrix [REDACTED] was implanted for 12 weeks. The same clinical protocol was used for all delivery attempts. Briefly, the acute treatment protocol was as follows:

- The patient was given antibiotics prior to the procedure.
- The patient was prepped and draped per local procedures.
- The Adiana RF Generator, Catheter Cable and Delivery Catheter were connected and positioned for convenient operation .
- The patient was anesthetized during the procedure. In [REDACTED] [REDACTED] all patients received I.V. sedation and a paracervical block. [REDACTED] all patients received paracervical block, and only received IV Sedation as required.
- The vagina and vulva were cleaned with an antiseptic solution.
- A speculum was inserted into the vagina and the cervix is exposed.
- The sheathed hysteroscope with fiber optic light source was inserted transcervically into the uterine cavity.
- A nonconductive distention medium (Glycine) was applied via the hysteroscope. Applied pressure was limited to approximately 150mmHg.
- The uterine cavity and tubal ostia were examined. If excluding factors were identified, e.g. presence of fibroids preventing access

to the intramural portion of the fallopian tube, the Adiana System application was not performed on that tube.

- The Adiana Delivery Catheter was introduced into the hysteroscope, tubal access was attempted, and, if successful, RF energy was delivered followed by placement of the matrix. This was repeated for the other tube.
- Once treatment was complete, the sheathed hysteroscope was removed.
- Patients underwent normal post-procedure monitoring which varied based on the institution and the medications received during the procedure. Patients were asked questions related to post operative discomfort, and were then released per standard hospital procedures.

### **2.7.6 Patient Follow Up**

Patients were followed via return office visits at one week, one month, and 12 weeks post implant (i.e. immediately prior to the scheduled hysterectomy), and provided information relating to pain as well as other symptoms. Patients were asked to rate pain and other complaints as described below from the following choices: None, Mild, Moderate, Severe. (For numeric analysis, these were converted to values of 0,1,2,3, respectively.)

Specific events which were assessed using this scale included:

- Pain
- Abnormal Bleeding
- Nausea
- Fever
- Dyspareunia
- Dysuria

At the one week follow up patients were asked to rate their pain and nausea during the 48 hours following the implant (“<48hr”), and also for their pain and nausea from 48 hours up to the one week follow up (“>48hr”).

### 2.7.7 Explant Protocols- Endpoint Assays

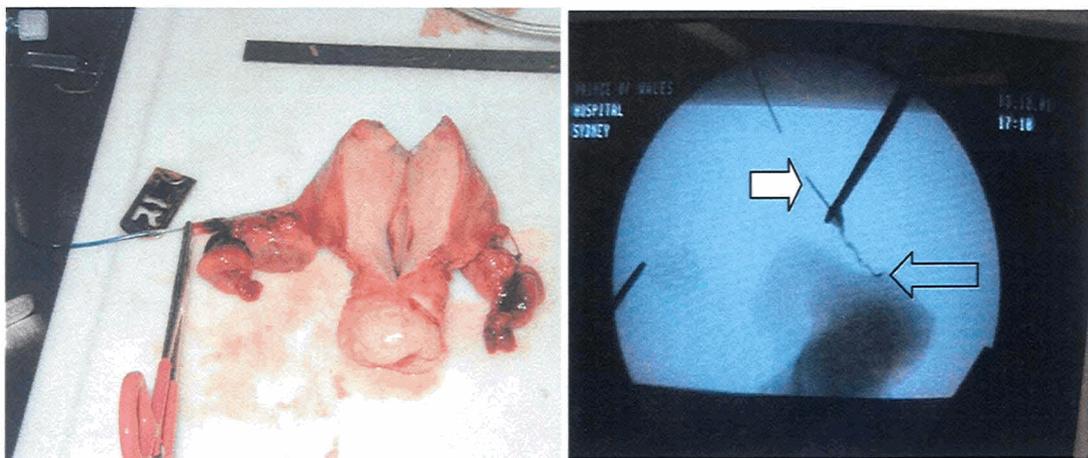
#### Hysterosalpingography (HSG)

Hysterosalpingograms (HSG) were performed just prior to the hysterectomy to assess treatment efficacy. The HSG used standard contrast media, flat plate or spot film fluoroscopy, and a standardized pressure (200 mm Hg).

#### Retrograde Salpingiogram (RSG)

Adiana developed an assay for tubal patency that is uniquely suited for the Adiana Procedure<sup>5,6</sup>. This assay is designed to test a single tube, and does not rely on x-ray detection, but rather uses visual dye detection which may be more sensitive. In addition, since the Adiana Matrix is implanted within the interstitial portion of the fallopian tube, this assay does not require cannulation from the uterine side of the tube. Based on prior work in animal studies, this assay is a rigorous test of tubal patency. In practice, tubal distension is noted as the pressurized fluid fills the fallopian tube.

The treated tubes were cannulated from the fimbriated end and then connected to an automated pressure device, delivering dye (radio-opaque water soluble with 1% methylene blue) at controlled pressures for a duration of one minute at each pressure. Pressure was maintained at 50 mmHg for 1 minute and then at 100 mmHg for one minute. The uterus was transected, and the uterine cavity was observed visually for leakage of dye. Once the endpoint was reached (either a leak or the maximum pressure for one minute) a radiograph was taken to ensure that the tube was properly cannulated and that the dye had indeed reached the blockage. (see figures 4 and 5).



**Figures 2.1 (left)** - Tube cannulated during RSG with uterus opened to observe for dye passage. **Figure 2.2 (right)**: Radiograph of RSG. Radio-opaque dye can be seen in the cannula (white arrow) entering the fallopian tube at the forceps, and traveling down the fallopian tube up to the matrix (at the open arrow).

## Histology

After hysterectomy, and subsequent retrograde pressure assay, the intramural portion of the fallopian tube with some of the proximal tube attached was removed, fixed in 10% formalin and shipped to Adiana for further processing.

Specimens were sent to a commercial histology laboratory for step sectioning and staining. Standard processing consisted of [REDACTED] sections with hemotoxyline and eosin (H&E) staining at each step. [REDACTED] additional sections were taken for immunostains which were used for confirmation of counts obtained from H&E sections. Immunostains included anti-factor viii (endothelial cell marker) to assist in verifying blood vessels (CVS).

All specimens were scored in-house and then sent to outside consultants. [REDACTED] San Diego, CA, a recognized expert in biomaterials who scored the specimens using the Adiana Scoring System. The specimens were also evaluated by [REDACTED] an authority on the human fallopian tube, for evaluation of tubal anatomy and disease. Overall assessment was also performed by [REDACTED]

## Matrix Retention and Placement

Histology was used to assess the presence and location of the Matrix within the fallopian tube.

Lesion Depth was not possible to evaluate, since all effects of the RF treatment (except lack of epithelium) had healed at the 12 week explant.

## Ingrowth Scoring

Scoring was done according to the Adiana Ingrowth Scoring System (Appendix 8). Briefly, each section containing a slice of matrix was evaluated for residual epithelium, blood vessels, inflammatory cells, giant cells, fibrotic capsule formation, and necrosis. These six components were then used to obtain a single ingrowth score for each tube. Additionally, the specimen was evaluated for tubal diseases and anatomical conditions of the fallopian tube.

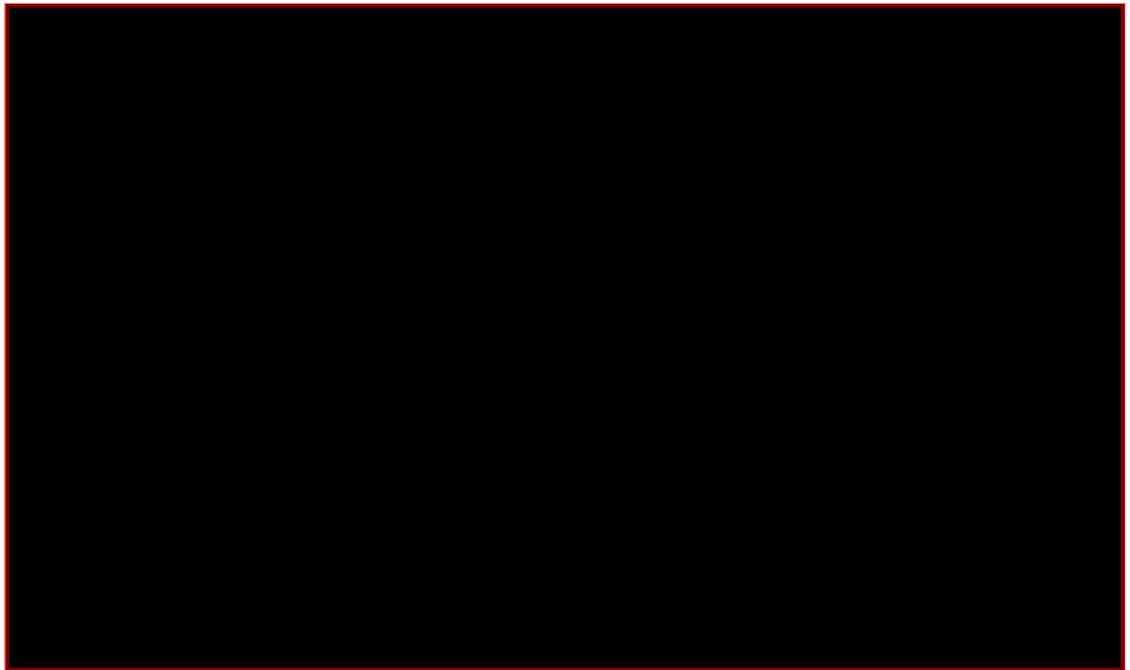
## 2.7.8 Results

### 2.7.8.1 Study Locations and Dates

The Pivotal Pre study was conducted as a series of eight different sub-studies conducted in either [REDACTED]. All implants at [REDACTED] were conducted by [REDACTED] while those in [REDACTED] [REDACTED] were performed by [REDACTED]. Patients were treated between [REDACTED].

### 2.7.8.2 Acute Success and Tubal Access

Forty-two (42) patients were enrolled in this study. Of the 72 tubes attempted, 65 were successful for an access rate of 90%. Per protocol, tubes that were blocked on screening HSG were not attempted.



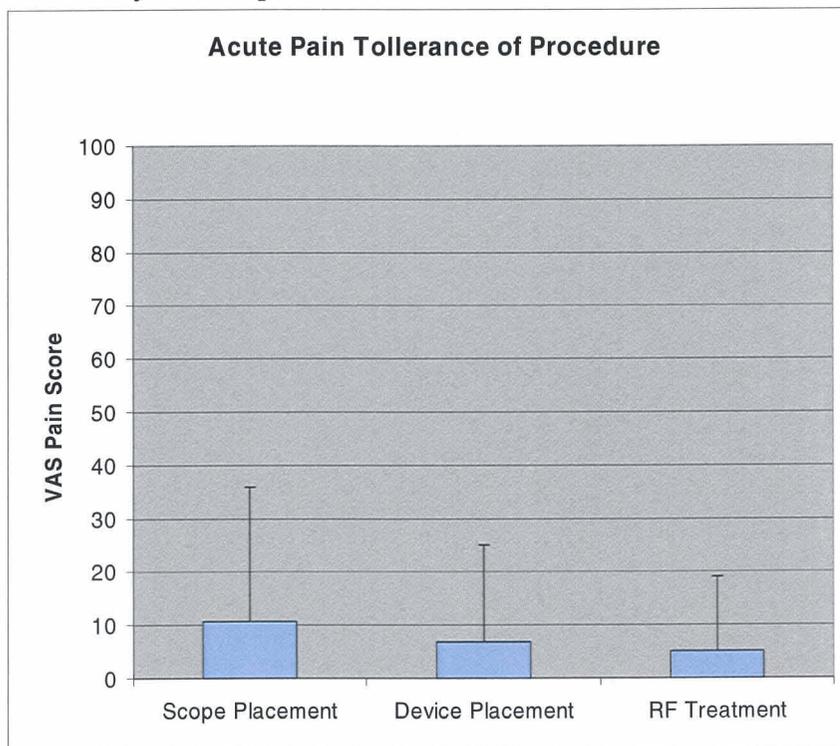
### 2.7.8.3 Patient Tolerance of Procedure

#### Acute Procedural Tolerance

Pain was assessed by the patient during the procedure and at selected times post-procedure. A visual analog scale (VAS) which provides numeric values from 0 (“no pain”) to 100 (“worst pain imaginable”) was used during the procedure at the following time points:

- During placement of the hysteroscope
- During placement of the Adiana catheter into the tubal ostium
- During creation of the lesion (RF Treatment)
- Immediately post procedure and prior to discharge

In the immediate post treatment period, uterine pain, back and shoulder pain and pelvic pain were assessed using the VAS. In all cases, VAS scores were assessed by clinical personnel.

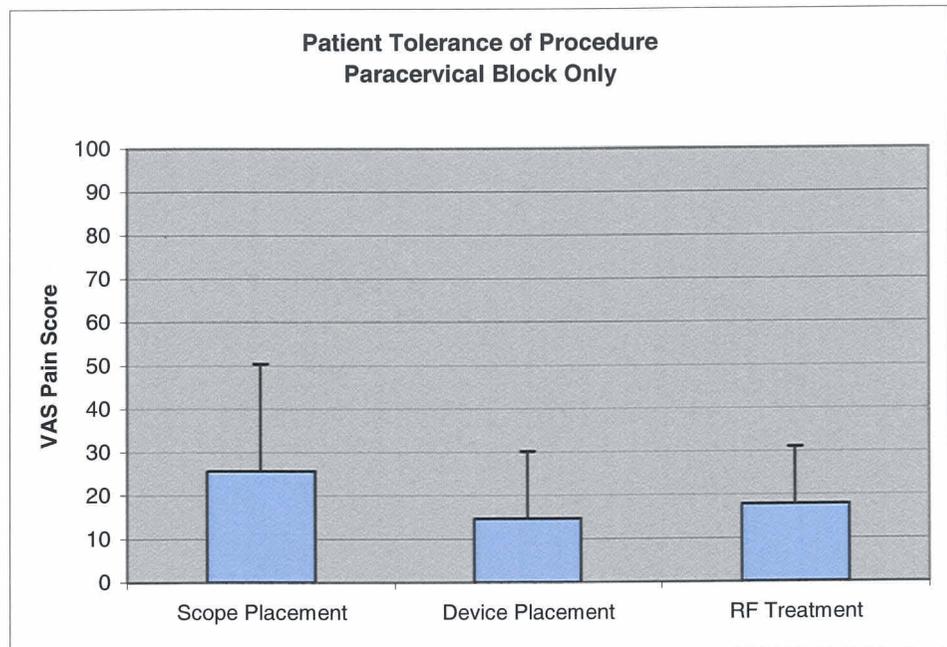


**Figure 2.3:** Intra-procedural pain scores. Mean pain scores (+/- S.D.) from 42 subjects during the Adiana Procedure. All scores assessed by clinical personnel using a Visual Analog Scale.

The highest perceived pain occurred during placement of the hysteroscope (Figure 6). The perceived pain decreased during placement of the Adiana delivery catheter and was further reduced during RF treatment.

In the Pivotal Pre Study, analgesia included either local anesthetic (paracervical block) or IV sedation along with local anesthetic. The 32 patients treated in [REDACTED] all received IV sedation with paracervical block. In the 10 patients treated in [REDACTED] all received paracervical block. For these 10 patients IV Sedation was provided as needed, based on patient comfort. IV Sedation was required for 4 patients, however the other 6 required only the paracervical block.

Figure 7 below shows the reported pain during the procedure for these 6 patients.



**Figure 2.4:** Patient Tolerance to the procedure for patients receiving only local anesthetic (paracervical block). A total of 6 patients were treated with only local anesthetic. (Mean VAS Score  $\pm$  SD)

Again, the highest perceived pain during the Adiana Procedure occurred during placement of the hysteroscope (Figure 2.8) in patients receiving only paracervical block. The perceived pain during placement of the Adiana Delivery catheter and during the RF treatment was reduced when compared to the hysteroscope placement.

### Tolerance During Wearing

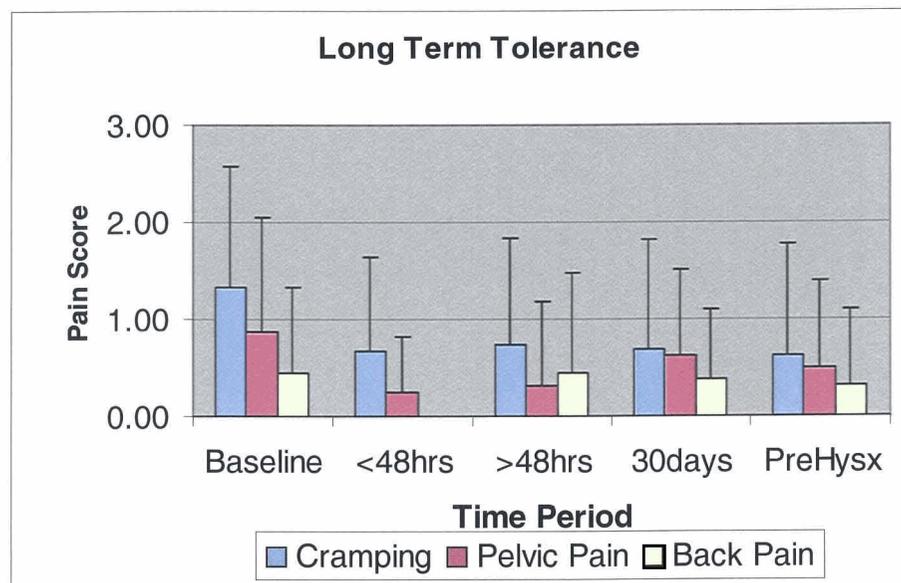
Women had follow-up visits at 1 week, 1 month and at the time of hysterectomy and provided information relating to pain as well as other symptoms. Patients were asked to rate pain and other complaints as described below from the following choices: None, Mild, Moderate, Severe. (For numeric analysis, these were converted to values of 0,1,2,3, respectively.)

Specific events which were assessed during Wearing using this scale included:

- Pain
- Abnormal Bleeding
- Nausea
- Fever
- Dysparuenia
- Dysuria

At the one week follow up patients were asked to rate their pain during the 48 hours following the implant (“<48hrs”), and also for their pain from 48 hours up to the one week follow up (“>48hrs”). For this reason, pain tolerance analysis included a time point (specifically the 48 hour time point) that was not captured for the other events.

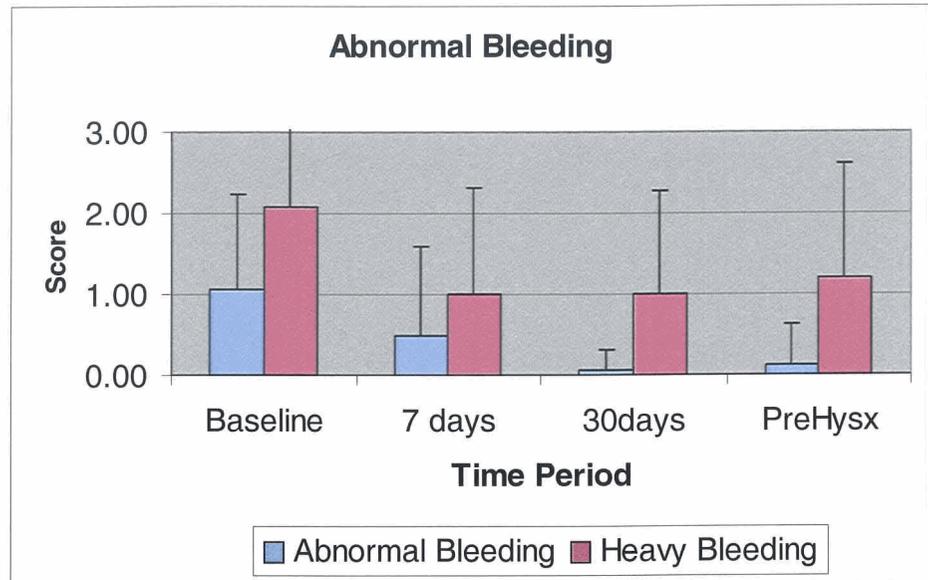
Patients were not uncomfortable during the wearing phase when compared to baseline comfort. Tolerance of the procedure during the 12 week wearing phase showed that uterine cramping, back and shoulder pain, and pelvic pain were not elevated compared to pretreatment levels (Figure 8).



**Figure 2.5:** Patient reports of pain (Cramping, pelvic pain and back pain) during the 12 week wearing period. (Mean Score  $\pm$  SD)

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There was no increase in severity of bleeding or abnormal bleeding patterns in response to the treatment (Figure 9). This population (patients requiring a hysterectomy) had a high prevalence of pretreatment abnormal bleeding. When compared to baseline complaints, follow up at one week, one month and 12 weeks showed no increase.



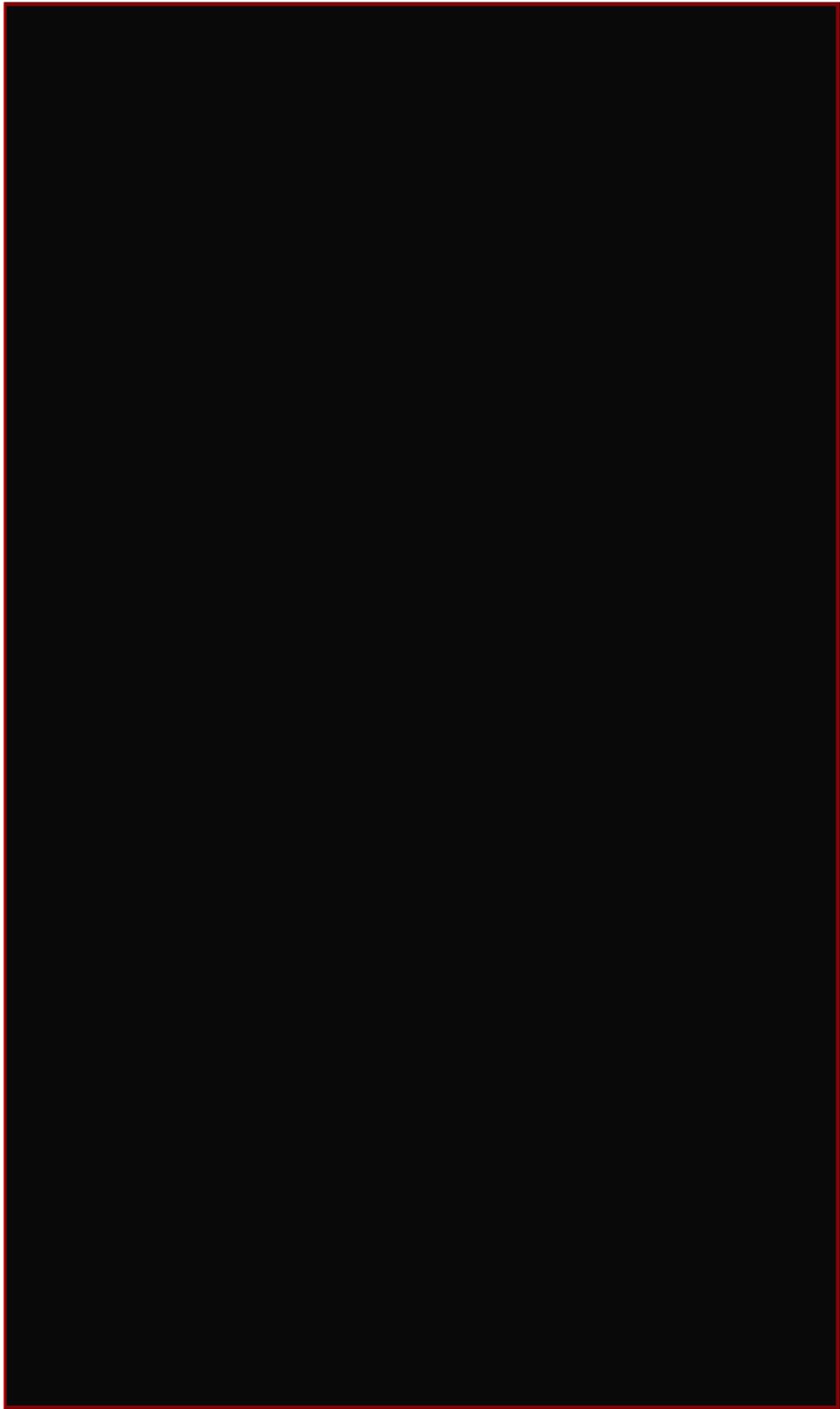
**Figure 2.6:** Patient reports of Abnormal Bleeding and Heavy Bleeding. Scale of 0 to 3 represents “None-Mild-Moderate-Severe” from patient’s self reporting. (Mean Score  $\pm$  SD)

#### 2.7.8.4 Tubal Occlusion

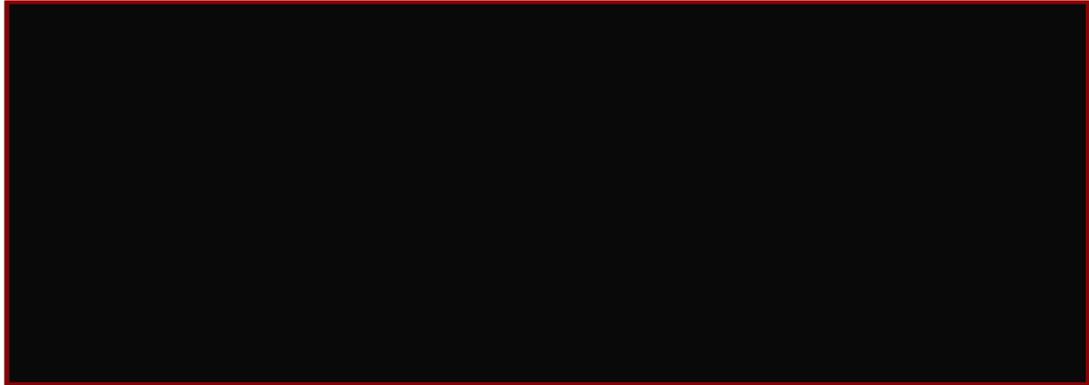
Sixty-three (63) out of the 65 tubes previously diagnosed patent by the pre-procedural screening HSG were assessed non-patent at 12 weeks as assessed by HSG. (Two were patent by both HSG and retrograde dye test.). Of the 63 tubes blocked on HSG 60 tubes were assessed by retrograde dye test. (Three tubes were not tested using the RSG due to technical limitations: Following surgical hysterectomy there was too little distal fallopian tube on the specimen to cannulate the ostial end of the tube.) Of the 60 tubes which were blocked by HSG and assessed by RSG, all were found to be non-patent at 50 mmHg of pressure (60/60, 100%), and 59 tubes non-patent at 100 mmHg of pressure (59/60, 99.3%).

Results are included in Table 2.12 below.





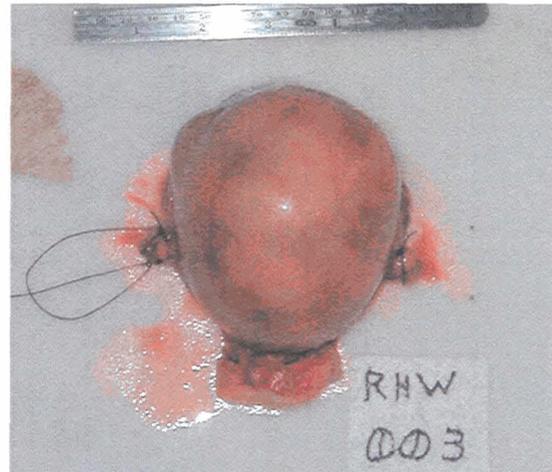
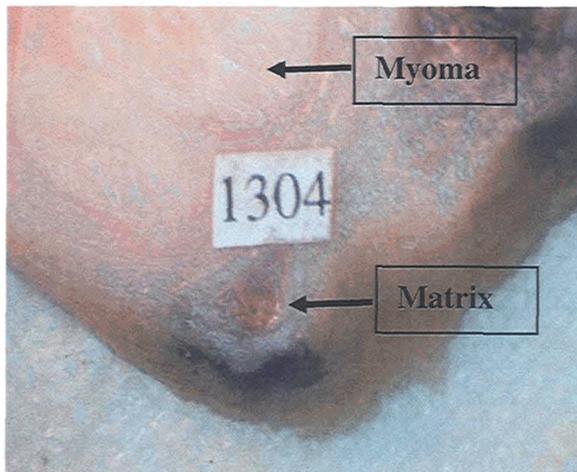
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### 2.7.8.5 Tubal Disease

The patients in the study population were scheduled for hysterectomies which ensures higher disease prevalence than would be seen in a population seeking only a tubal ligation. Two prevalent diseases encountered were adenomyosis and uterine myomas.

Adenomyosis is the growth of uterine glands and stroma into the uterine myometrial layer and can have a wide range of severity. In its more severe forms, the intramural portion of the fallopian tube is honeycombed with fistulas from the adenomyosis. This can cause channels to form around the tube and confound the HSG and dye pressure tests. Adenomyosis was observed in a minority of tubes but the severity was not sufficient to cause false HSG or RSG results.



**Figures 2.7 (left) and 2.8 (right):** Figure 2.7 – (Left) - small internal myoma in sample AR1304. Access and treatment was unaffected by this myoma. Figure 2.8 – (Right) large myoma observed externally on uterus from patient [REDACTED]. The uterus is virtually obscured by the growth. This is the tube in which the retrograde dye assay showed a patency after 30 seconds at 100mmHg dye pressure.

Myomas are benign tumors of muscle cell origin and are also called fibroids or fibromyomas. Myomas are generally slow growing and of no consequence to the studies. However, in the case of [REDACTED] (Figure 11 Right) the myoma was a very rapidly growing one. It tripled in diameter (based on serial TVUS) during the 12 week ingrowth period which represents almost a 9 fold increase in volume. This tube (AR1264) had the lowest ingrowth score and also was the tube that leaked at 100 mmHg in the retrograde HSG (Table 2.12). The other tube was not treated due to an inability to access. It is possible that the rapid growth of the myoma drained resources from the treatment area, affecting wound healing so that ingrowth was slowed and did not show the characteristic ingrowth observed in the other tubes. This may be similar to the impaired wound healing in patients with cachexia-associated infection, inflammation, and cancer<sup>49</sup>. However, ingrowth was sufficient to occlude in the HSG test and in the RSG at 50 mmHg.

#### **2.7.8.6 Matrix Retention and Placement**

##### **Matrix Retention**

Matrices were recovered from all 65 implanted tubes for a 100% retention rate.

##### **Matrix Location**

During histological examination, it appeared that on two occasions that the Matrix was located within the tubal wall of the fallopian tube (AR1414 and AR1257). The latter tube was assessed patent by the HSG and RSG assays and the former tube was assessed occluded by HSG and RSG assays. It is unclear why AR1257 was occluded in these assays, but there are several possible explanations. One explanation is that step sectioning for histology may not have capture the section containing the tubal blockage. Another explanation is that histological processing can create artifacts that appear to show the Matrix within the wall of the tube, but in actual fact is due to the plane of histological sectioning. Although the exact cause was not identified, the underlying disease state cannot be ruled out as a contributing factor.

In no case was any portion of the Matrix placed beyond the serosa and there were no lost matrices, nor tubal perforations.

#### **2.7.8.7 Ingrowth and tissue response- Histological Analysis**

##### **Histological Observations:**

The mean ingrowth score for the Pivotal Pre study was 2.31 with a range of 1.0 to 3.88. The mean of 2.31 compares favorably with Pilot Pre 3 which was

a study with the same lesion, type of matrix and ingrowth period. In Pilot Pre 3, the mean ingrowth score was 1.7, but an older version of immunostaining for factor viii (anti-factor 8 for blood vessels) was used which may have underrepresented blood vessels compared with the current method.

The blood vessel counts averaged in the range from three to four for most tubes which was considered extremely high. The blood vessels were found throughout the ingrowth and penetrated to the deeper pore layers, indicating a good perfusion of the entire ingrowth.

The residual epithelium was virtually nonexistent. The absence of epithelium is an indicator of an effective lesion and indicates that an appropriate lesion time and temperature are being consistently achieved.

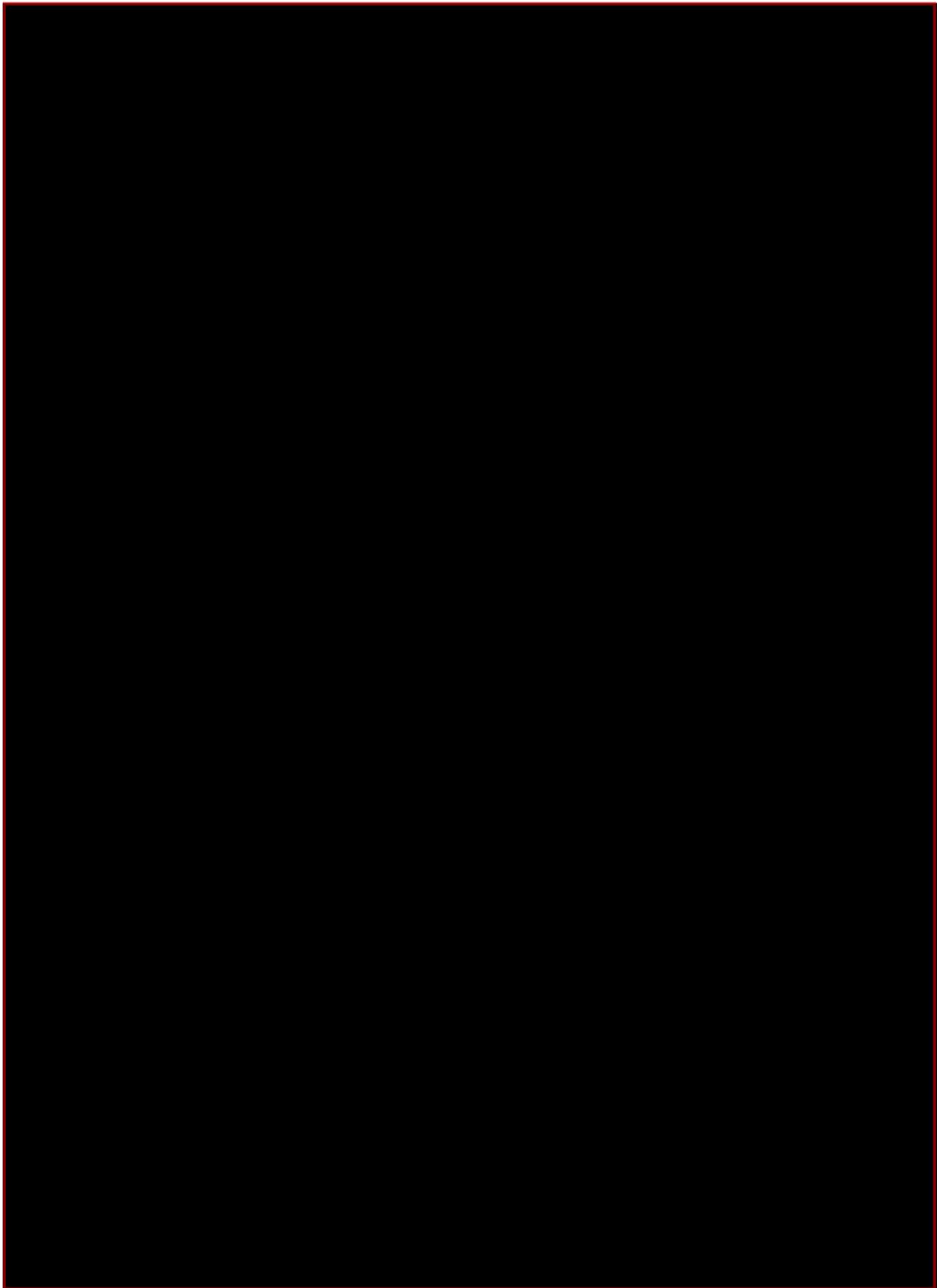
The predominant cell type in the inflammatory cell counts was the lymphocyte. Inflammatory cell counts were typical for results seen in other Adiana studies. They were not considered excessive but consistent with that found in the normal fallopian tube (Dr. Dorothy Patton, personal communication). Giant cell scores ranged from 1.0 to 3.0 and were not generally considered to be significant.

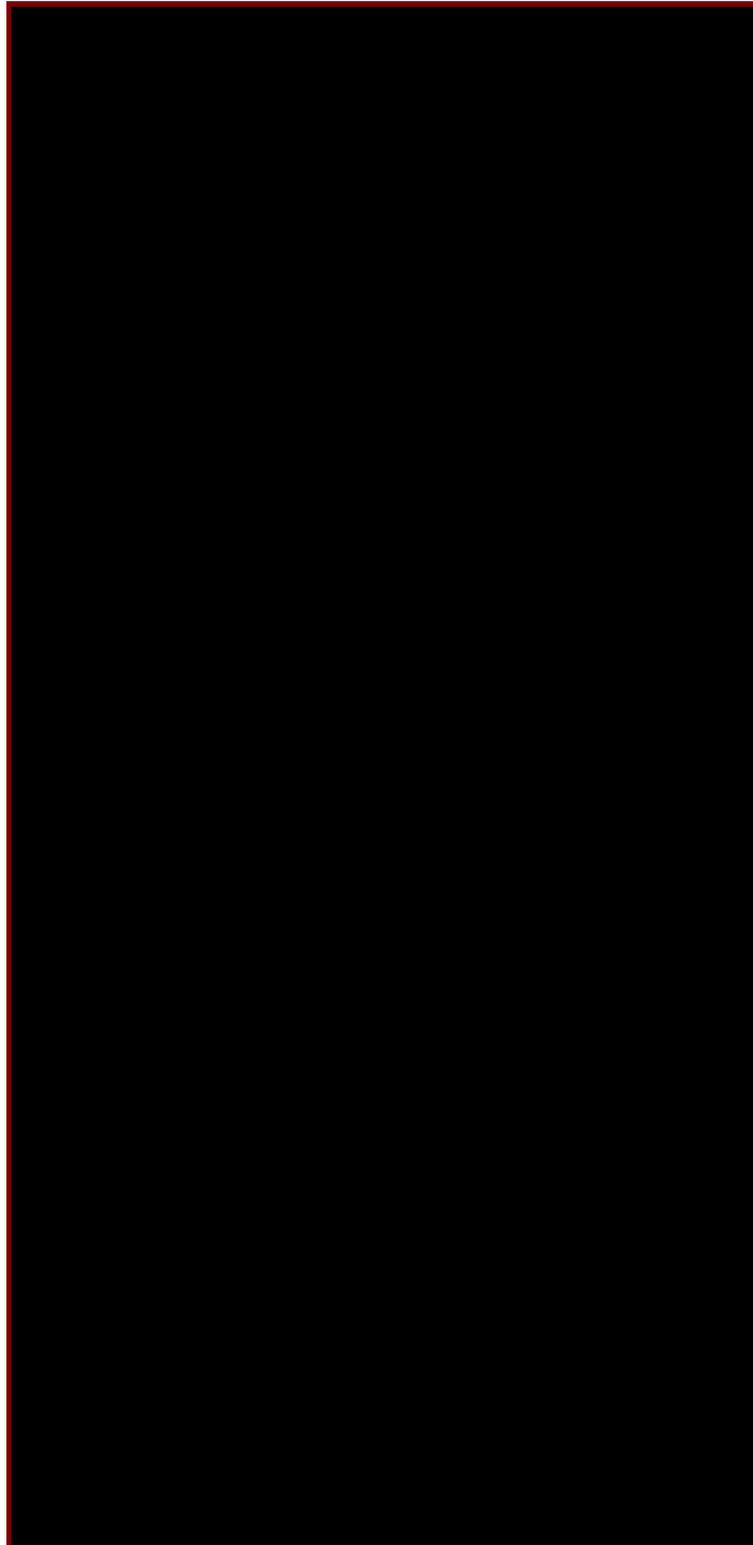
Fibrosis had a mean score of 1.25 which indicates very little fibrotic capsule formation. This indicated that the lesion created was not excessive which could lead to scar formation and encapsulation rather than healthy tissue ingrowth.

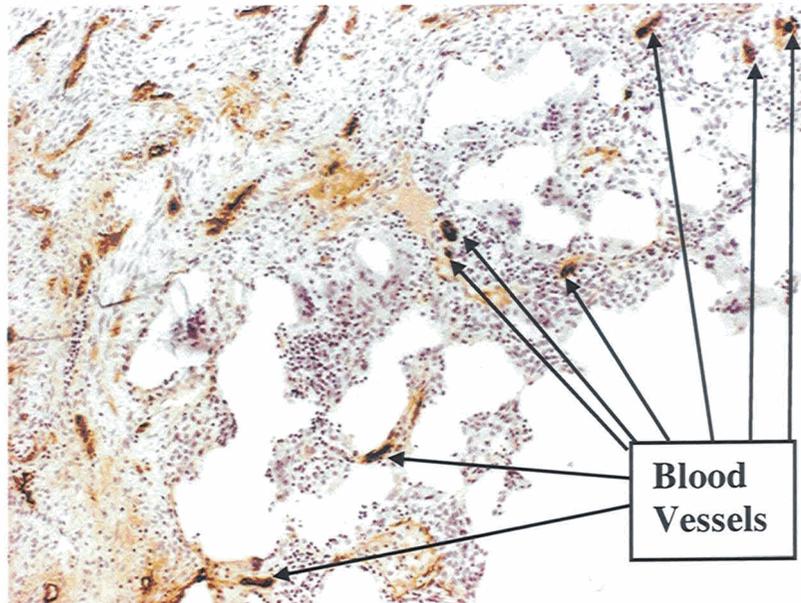
Necrosis had a mean score slightly under 2 which indicates little necrosis was found. This is probably a reflection of the good vascular supply throughout the matrix.

The one tube (AR1264) that showed patency with the RSG assay at 100 mmHg had the lowest ingrowth score and is believed to be due to the large growing myoma present in the uterus (refer to section 2.8.8.6). It is believed that such a patient would require a hysterectomy, as was the case with this patient, and not typically be a candidate for the Adiana Procedure.

The second tube (AR1440) that showed patency with the HSG and RSG assay contained minimal ingrowth captured within the pores of the matrix. This may have been due to over pressurization of the tubes during the HSG procedure, histological processing or a reflection of insufficient ingrowth. There was possible evidence of tubal occlusion by the existence of tubal distention in the segment distal to the matrix. Tubal distention indicates a condition where the lumen is round and appears to be distended or expanded when viewed through a microscope. This phenomenon is an observational one that is determined qualitatively and is not precisely defined. This phenomenon has been observed both proximal and distal to the matrix and







**Figure 2.9:** Example of intense immunostaining (brown stain) for factor viii, a marker for endothelial cells. Endothelial cells comprise the walls of blood vessels, therefore this stain identifies blood vessels. Of note, there are numerous blood vessels within the ingrowth in the Matrix pores, indicating healthy ingrowth with adequate nutritional supply.

#### 2.7.8.8 Individual Patients

Results from the individual tubes were remarkably similar. Ingrowth was generally space filling and included healthy ingrowth that extended throughout the Matrix.

Data from each of the individual implant studies are included in the following pages.

Individual tubes are described below with the following format: Each of the following pages includes data from a single patient. If only one tube was treated, no data will be shown for the non-treated tube. On each page, the study number and patient information is presented, followed by three pictures showing the Matrix. These are the first full section of Matrix (proximal), middle slice of Matrix, and last full section of Matrix (distal). The ingrowth parameters and total ingrowth score for that tube is also presented. All pictures were taken at 40X with the exception of AR1298 which was taken at 20X. Because of the longitudinal profile of the Matrix, a lower magnification was needed to get the whole Matrix in the picture

Pages 432-474 have been removed.

## **2.7.9 Conclusions**

### **Patient Tolerance of Procedure**

The patients appeared to tolerate the procedure well. Pain scores were lower during insertion of the Delivery Catheter and RF treatment than during insertion of the hysteroscope. The 24 hour period following the procedure generally had extremely low perceived pain, and the reported pain disappeared within the first hour and a half. During the 12 week wearing phase of the study, pain, nausea, and other symptoms were not elevated over pre-procedure levels.

### **Access Rate**

The overall access rate was 90 % but Pivotal Pre-2 accounted for most of the failed accesses (5 of 7 tubes that were attempted could not be accessed). A 5mm hysteroscope is normally used for catheter placement but in this study only a 10mm hysteroscope was available. The use of the larger hysteroscope prevented adequate access to the tubal ostium and resulted in a loss of catheter guidance. Later in the study, at this site with the same clinician but using a 5mm hysteroscope, there were no access problems (11 successful of 11 attempted).

### **Tubal Occlusion: HSG and RSG**

Sixty-three out of the sixty-five tubes treated and previously diagnosed patent by the pre-Adiana procedure HSG were assessed non-patent by HSG at time of hysterectomy for a 97% HSG tubal occlusion rate. Of the sixty-two tubes assessed by the more rigorous retrograde SG, sixty tubes were assessed non-patent at 50 mmHg and 59 tubes non-patent at 100 mmHg. Both tubes identified as open on HSG were also open by RSG.

Pages 432-474 have been removed.

slight amounts, which is probably a result of the abundant vascular supply.

- During histology examination, it appeared that on two occasions matrices were located within the tubal wall of the fallopian tube. Whether this observation is due to histology artifact, patient disease or procedure/device is unclear.

### **Adverse Events**

There were no serious adverse events during the course of this study.

## 2.8 Access Studies

### 2.8.1 Overview

During the course of clinical investigations, two factors which appeared to strongly influence the ability of the Delivery Catheter to access the fallopian tube were identified. These factors were device configuration (catheter design) and patient population (disease state).

During Cytc's clinical work, early studies were performed to evaluate tubal access on prototype devices. In addition, access rates were a component of all hysterectomy studies (Peri-Hysterectomy and Pre-Hysterectomy), and have been discussed and analyzed in the respective sections herein (Section 2.5, 2.6, 2.7). Overall access rates of all hysterectomy studies as a group are analyzed below.

Additionally, Cytc performed a study specifically analyzing only Delivery Catheter access utilizing the current design in a patient population reasonable close to the intended target population. These results are most indicative of the expected catheter performance in the proposed investigational trial.

### 2.8.2 Pooled Analysis; All Hysterectomy Access Results

Cytc analyzed all Peri-Hysterectomy [REDACTED] studies and Pre-Hysterectomy [REDACTED] studies to determine overall access rates. In all these studies, access rates were determined during acute Delivery Catheter placement, and are simply number of successful tubes divided by the number of tubes attempted. These studies are discussed in detail in other sections.

The observed access rate in the treated hysterectomy population including all attempted tubes was 91%, (336 of 369). This includes all Peri-Hysterectomy studies (128 patients and 253 tubes attempted) as well as the Pre-Hysterectomy studies (65 patients and 116 tubes attempted). It is important to note that this pooled analysis includes several versions of the Delivery Catheter.

**Table 2.14:** Study Tubal Access Rates

Study	# of patients	# of available tubes	# of tubes accessed	% of tubes accessed
[REDACTED]	62	124	105	85%
[REDACTED]	58	113	111	98%
[REDACTED]	8	16	15	94%
[REDACTED]	23	44	40	91%
[REDACTED]	42	72	65	90%
Totals	193	369	336	91%

### 2.8.3 Healthy Patient Access Study

The access rate as discussed above was felt to be influenced by the disease conditions that existed in the patient population for these protocols (i.e. with indications for elective hysterectomy). For this reason, Cytc undertook a different study that was designed to investigate the Access rate in a patient population reasonably close to [REDACTED]

The Healthy Patient Access Study recruited patients whom were seeking elective tubal ligation. Immediately prior to a scheduled laparoscopic tubal ligation, the Adiana Procedure was performed *except* there was NO RF energy delivery and NO Matrix delivery. The endpoint of the study was simply to determine that the catheter was placed at the correct position in the fallopian tube based on visual observation and that the PDA contact was satisfied on the [REDACTED]

[REDACTED] as the study site Principal Investigator. The study was conducted in accordance with the Food and Drug Administration's guideline, "Good Clinical Practice: Consolidated Guideline", effective May 9, 1997.

The protocol was approved by the local institutional Human Subjects Review Boards (Ethics Committee) and patients signed Informed Consent forms. Subjects were recruited from patients seeking an elective tubal ligation.

[REDACTED]

[REDACTED] there were two different catheter models utilized. The [REDACTED] for improved handling. The second half of this study employed a Nitinol core for catheter, [REDACTED]

Out of a total of 60 attempts in 28 patients (there were multiple attempts in four tubes), there were 30 attempts with the [REDACTED] catheter and 30 attempts with the [REDACTED] catheter.

Table 2.15 below summarizes results from both models.

**Table 2.15: Delivery Catheter Model Results**

[REDACTED]	Construction	Tubes attempted	Tubes Successful	Rate
[REDACTED]	[REDACTED]	30	25	83.3 %
[REDACTED]	[REDACTED]	30	27	90.0 %

One patient recruited and treated in the study presented with a small nulliparous uterine cavity and extremely small fallopian tubes. Both tubes were access failures.

Based on the results of this study, both numeric success rates and feedback from two investigators, the [REDACTED] catheter was felt to be an improvement [REDACTED]

[REDACTED]

[REDACTED] a study was conducted to evaluate device access rate and demonstrate ease of use of a smaller diameter shaft catheter. The device evaluated [REDACTED] the current design) was reduced in size from 7 to 5 French (Fr). The catheter was evaluated in hysteroscopes having 5 Fr and 7 Fr working channels. As an experimental control the previously released Adiana catheter [REDACTED] was used with the larger 7 Fr hysteroscope.

Out of a total of 60 attempts in 15 patients (there were two attempts for each tube), there were 22 attempts with the [REDACTED] catheter and 38 attempts with the [REDACTED] catheter.

Table 2.16 below summarizes results for this study.

**Table 2.16** [REDACTED] Results

Delivery Catheter Model	Shaft OD	Tubes attempted	Tubes Successful	Rate
[REDACTED]	7 Fr	22	20	91 %
[REDACTED]	5 Fr	38	38	100 %

Several conclusions were drawn from this study. First, the smaller shaft diameter catheter demonstrated an access rate of 100% and this access rate showed that a 7 Fr or 5 Fr working channel in the hysteroscope is acceptable for good catheter performance. Second, clinicians were very satisfied with the device ease of use, as was evident with the positive qualitative feedback on catheter placement and visualization during the procedure.

**SECTION BREAK**

## **Appendix 8**

### **In Growth Scoring System**

Pages 482 - 484 have been removed.

## **V. PIVOTAL CLINICAL TRIAL**

**V. A. ABSTRACT**

**SYNOPSIS**

<b>Name of Sponsor/Company:</b>	<b>CYTYC SURGICAL PRODUCTS</b>
<b>Name of Finished Product:</b>	<b>THE ADIANA TRANSCERVICAL STERILIZATION SYSTEM</b>
<p><b>Criteria for evaluation:</b></p> <p><b><u>Efficacy:</u></b>          The primary endpoint of the study was the pregnancy rate during the one-year Wearing Follow-up Period. This endpoint was evaluated for all patients who underwent successful bilateral treatment, demonstrated tubal occlusion (by HSG) at the end of the Waiting Period, and were evaluable for the one year primary endpoint. This study was powered to have an 80% chance of stating the true failure rate is less than 5%, with a 95% confidence. This would yield a minimum effectiveness rate of 95% (1-failure rate).</p> <p>Comparisons of the 12-month rates to other pregnancy prevention methods (historical controls) were conducted, including comparisons to the results published in the CREST Study (Peterson, et al; Collaborative Review of Sterilization, 1996) as well as results from other sterilization device and procedure studies described in the literature since publication of the CREST study.</p> <p>In addition, an analysis is provided to address the difference in the age of the populations in CREST as compared to the EASE population.</p> <p><b><u>Secondary Endpoints:</u></b>          Device Placement Rate          Patient satisfaction and comfort with the placement procedure          Patient satisfaction and comfort with device wearing</p> <p><b><u>Safety:</u></b>          Safety of the device placement procedure          Safety of device wearing</p>	
<p><b><u>Statistical Methods:</u></b>          The primary endpoint was the pregnancy rate during the 12-month wearing period, and is summarized with descriptive statistics including sample size, frequency counts, percentages, and 95% one-sided confidence intervals based on life-table methods. Additionally the pregnancy rate was determined for the 24- and 36-month time points utilizing the same life-table methods.</p>	



Comparisons of the 12-month rates to other pregnancy prevention methods (historical controls) were conducted, including comparisons to the results published in the CREST Study as well as results from other sterilization device and procedure studies described in the literature since publication of the CREST study. Due to the differences in study size between CREST and the EASE trial (and between the EASE trial and the individual method sub-populations in CREST) comparisons were made based on an analysis of the *differences in the point estimates* and the confidence interval of those differences. In addition to comparing the Adiana System to each of the methods individually, a comparison also was made to all CREST-reported methods combined and all 'comparable' CREST-reported methods combined (comparable methods excluded post-partum salpingectomy since the Adiana System cannot be used post-partum, and unipolar coagulation since this method is rarely utilized clinically.)

Finally, an analysis was conducted to compare the one-year age stratified pregnancy prevention rates in the EASE study to the similarly age stratified results reported in the CREST study. This analysis also considered the two- and three-year Adiana System pregnancy failure rates by age. A one-year, age-corrected Adiana failure rate was established based upon a weighted average of the age stratified EASE study data.

## SUMMARY – CONCLUSIONS

### Efficacy Results:

Of the 770 enrolled patients, 645 had treatment attempted and 611 achieved bilateral placement success (94.7%). Of these patients, 604 were evaluated for occlusion by HSG and 570 patients demonstrated bilateral occlusion. Thus, 88.4% of the patients in whom treatment was attempted achieved final treatment success and were able to begin reliance on the Adiana System for pregnancy prevention.

During the one-year follow-up period, there were six pregnancies: three were attributable to physician error (misinterpretation of HSG results) and the remaining three were due to method failure. Excluding failures attributed to known HSG misinterpretations, the one-year pregnancy prevention rate (derived from life-table methods) is 99.5%, with a single-sided, lower confidence bound of 99.0%. The one-year pregnancy prevention rate including all pregnancies for the Adiana System is 98.9% with a single-sided, lower confidence bound of 98.2%. Both of these outcomes exceed the pre-planned threshold set for demonstration of efficacy in the primary endpoint.

Results of the comparison of the pregnancy prevention rates observed for the Adiana System users to the six methods described within the CREST study show that the Adiana System is statistically comparable at one, two, and three years to the combined results from all methods reported in the CREST study. The Adiana System also was shown to be generally equivalent to methods reported since the publication of the CREST study. Additionally, an analysis of Adiana System pregnancy failure rates stratified by age shows a trend that is similar to that

observed in the CREST study and does not indicate an unexpectedly large age influence.

Patients overwhelmingly reported satisfaction with the Adiana System throughout long-term follow-up and more than 16,000 patient-months of device wearing. The low incidence of reported symptoms, along with the mild severity of the majority of reported symptoms, indicates that the Adiana Procedure and the wearing of the devices are well-tolerated and accepted by patients.

**Safety Results:**

Adverse events have been reported for all 645 Intent-to-Treat patients through the one-year Wearing Period. While not all patients have completed the full five year, long-term follow-up portion of the study, adverse events have been collected through March 1, 2007 for the 645 intent-to-treat patients; the total device exposure for this population is equivalent to over 16,000 patient-months.

The majority of adverse events reported on the day of the procedure were anticipated and minor in nature. None of the events required significant intervention other than medication and all but one (back pain) resolved within a mean duration of three days; the mean duration for back pain was nine days (Note: the duration of back pain reported in the EASE trial is comparable to that reported in the literature for hysteroscopic procedures). Additionally, procedure- or device-related adverse event rates reported on the day of the procedure were comparable to those reported in the published literature.

On the day of the procedure, there were no unanticipated or device-related serious adverse events. One serious adverse event, however, was procedure-related. This event was hyponatremia and it occurred as a result of fluid overload. (The patient was treated conservatively with Lasix and released the same day with no resulting medical sequelae.) There were no other occurrences of fluid overload reported in the trial. Additionally, there was one other report of a minor adverse event associated with a treatment procedure that involved a "sheared-off" Introducer tip that was left within the fluid of the endometrial cavity of the patient and was later expelled without incident. No injury was experienced by the patient and no medical or surgical intervention was required.

There were no uterine or tubal perforations reported during the Adiana treatment procedures. There were also no reports of aberrant burns, nor other injuries related to the delivery of RF energy and Matrix placement within the fallopian tubes. Additionally, there were no reports of excessive pain or bleeding.

Over the course of the trial thus far, 49 serious adverse events have been reported in 41 patients; no patients have died. In addition to the event of hyponatremia that was procedure-related, three additional events were considered device-related (two ectopic pregnancies and one endometrial polyp resection). Of these four procedure- or device-related serious adverse events, two were resolved with medication (hyponatremia with Lasix<sup>®</sup>, and one ectopic pregnancy with Methotrexate), and the remaining two required surgical intervention (an

ectopic pregnancy salpingectomy and the endometrial polyp resection). It should be noted that hyponatremia and ectopic pregnancy events are known complications of hysteroscopic sterilization procedures. Thus, these events were not unexpected, had a low incidence rate, and did not represent an unknown or unreasonable risk to the patient. The observed ectopic pregnancy rate was within the range expected for a post-sterilization population.

During the course of follow-up, the most commonly reported adverse events were headache, dysmenorrhea, and menorrhagia/metrorrhagia. Ten patients reported SAE's that occurred secondary to menorrhagia or dysmenorrhea or to treatment of the complaint. The DSMB determined one of these events to be possibly device-related and the remaining nine to be neither device- nor procedure-related. During the follow-up period, surgical interventions were performed in thirteen patients (inclusive of some of the ten SAE's noted above) with primary complaints of menorrhagia/dysmenorrhea or metrorrhagia: four patients were treated by endometrial ablation; seven by hysterectomy; and two by both endometrial ablation and hysterectomy.

A histological analysis of explanted tissue obtained from eight of the ten total patients who have undergone elective hysterectomy procedures during study follow-up showed the biocompatibility of the implant, the capability to provide total occlusion of the fallopian tube by tissue ingrowth into the pores of the implant, and the presence of a normal foreign body reaction indicating a normal biocompatible implant response at an average implant period of 3.1 years.

The remaining reports of adverse events potentially related to the device throughout the course of the Wearing Period were generally mild in nature, required minimal intervention, and were resolved quickly. Most importantly, throughout the entire course of the study there have been no reports of excessive discomfort, acute pain, or bleeding associated with wearing of the Adiana device. There have been no reported allergic or adverse reactions to the implants, no signs of infection related to the implants, and no need for implant removals.

**Conclusion:**

The results of this study demonstrate that the Adiana System is highly safe and effective for pregnancy prevention. Further, the required treatment procedure has a high degree of placement success; patients overwhelmingly reported satisfaction with the Adiana Procedure; and remained satisfied with the Adiana System throughout short and long-term follow-up including more than 16,000 patient-months of device wearing.

Date of the report: August 1, 2007

## **V. B. PROTOCOL**

Pages 492-500 have been removed.