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Question 15: Appendix 15 contains your report on a series of *in vitro* experiments to assess the feasibility of the Adiana procedure using various delivery catheter and electrode configurations. The results presented in Appendix 15 states that treatment with a 6 mm probe for 60 seconds at 64 °C results in mean epithelial ablation rate of 78.5%, with average lesion lengths and depths being 5.14 mm and 0.385mm, respectively. In section 4.3.3.3 of Volume 1 you have summarized the results of these studies; however, the values presented for epithelial ablation rate (93%) and lesion depth (0.514 mm) are not in agreement with those presented in Appendix 15. Please comment on the differences in epithelial ablation rate and lesion depth between these two sections of the module. In addition, please provide full reports on each of the studies presented in Appendix 15.

The results presented in Appendix 15 of Module 1 include data from 12 separate 'studies' performed in 69 patients between 8/28/1998 and 1/01/2001 under [REDACTED]. Within that broad range of development studies, there were 19 fallopian tubes in which a 64/60 time temperature treatment was evaluated.

In section 4.3.3.3 of Volume 1, we performed a meta analysis of ALL *In Vitro* results, at the 64/60 time temperature parameter. This included:

- [REDACTED]
- [REDACTED]

Note: This meta analysis *excluded* any data points that utilized devices or treatments that were not representative of the final device configuration. For example, different treatments, or 'masked' electrodes were excluded. These special configurations are described in the reports in Appendices 15 and 33.

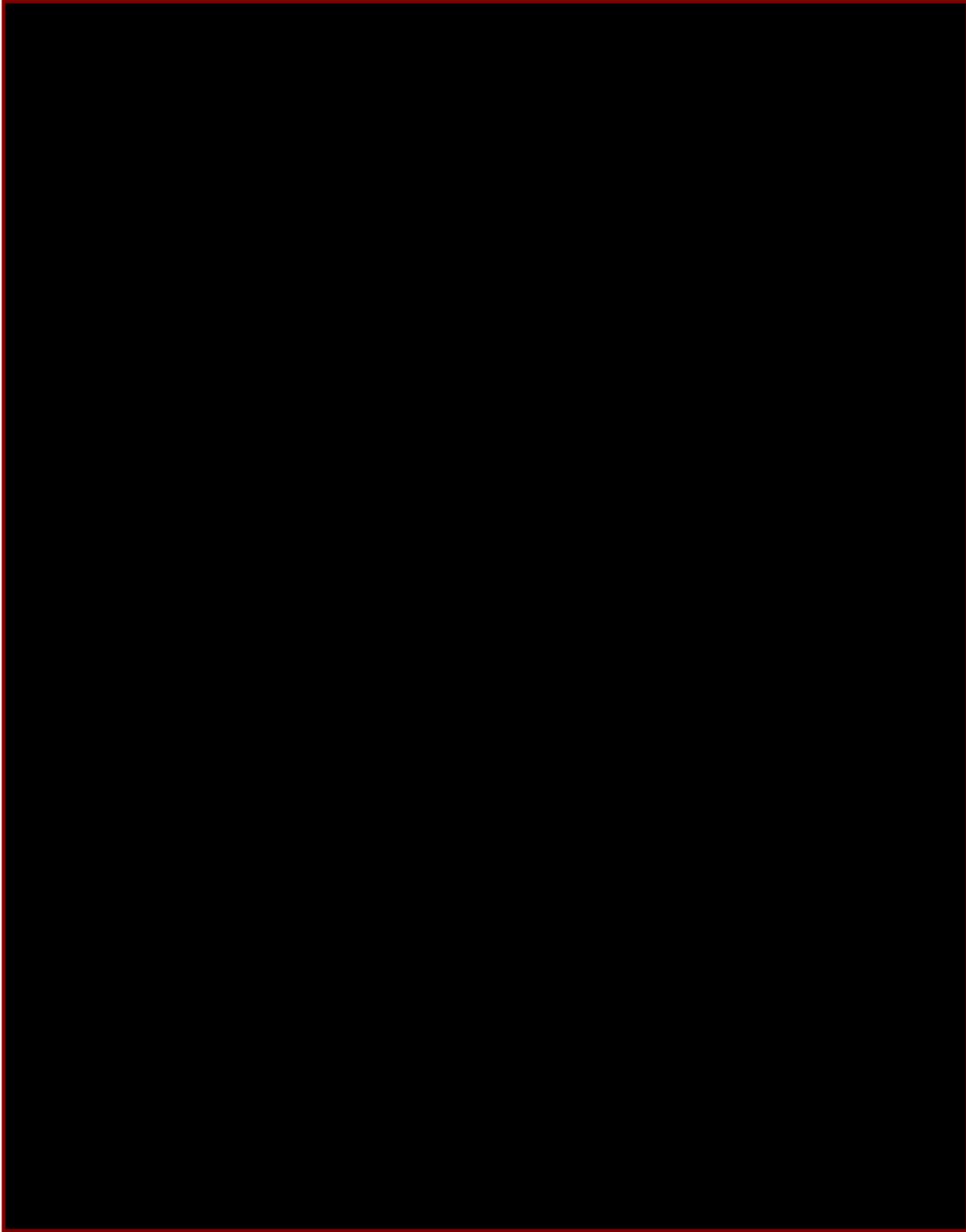
There are some minor differences in the methods used within these studies. [REDACTED] utilized hematoxylin and eosin stain (H&E) for studies 1, 2, 3 and 6. As work in tissue histology progressed, a better understanding of the impact on various processing methodologies on the ease of interpretation was developed. Later studies (specifically Studies 14 & 15 in [REDACTED] and Studies [REDACTED] utilized only NBT staining.

In evaluating these human tissue histology experiments, it is important to recognize that all women were undergoing hysterectomy for clinical indications. Exclusion criteria included gross pathologies of the fallopian tube (e.g. diagnosed

adenomyosis) but all patients had underlying disease processes. The impact of these disease processes on the application of RF energy (and indeed in the Pre-Hysterectomy ingrowths studies) was unknown. However, we believe that this remains the best model for achieving human implant histology.

The apparent difference in ablation rate is most likely due to underlying disease states and due to histological staining and identification of cellular destruction. As described in the reports, data was read and reviewed by two experienced reviewers, and we believe this was not a factor in the variability of this data.

Appendices 15 and 33 in Module 1 contain the full reports for the studies described therein. Internally, the term "Study" was used to describe a single day, or sequential days, in which a number of patients were recruited, treated, and data collected. Multiple 'studies' were done under the single Protocol number (i.e. [REDACTED]). There are no separate reports for any one 'study'.



Note that AR 637 and 639 used Formalin fixation which was not analyzed for lesion depth.

Question 16: Section 4.3.3.3 of Volume 1 states that the mean epithelial ablation rate (93%) had a range of ablation rates from 35 to 100%. This section also reported that the mean lesion depth was 0.514 ± 0.097 mm, and ranged from 0.334 to 0.732 mm. Please provide additional information on the impact of lower epithelial ablation rates and shallower lesions on possible device effectiveness during the 3 month waiting period and for long term success of the device.

The Adiana mechanism does not require 100% epithelial ablation nor uniform and specific lesion depth to create tubal occlusion. The healing response to a broad range of superficial lesions is adequate to cause tissue in-growth into the Matrix architecture.

Earlier in product development, animal studies were performed to evaluate the impact of lower epithelial ablation rates and shallower lesions on device effectiveness. In one particular study, 4 rabbit tubes were treated with a control or standard energy application, 4 rabbit tubes were treated with no energy application and 8 rabbit tubes were treated with low energy application to purposely create inferior lesions. Immediately following treatment Matrices were placed in all tubes and the animals sacrificed after three weeks.

At explant, oviducts were excised from the animals and evaluated for patency via a dye exclusion test. A cannula connected to a syringe containing 0.2% methyl blue in isotonic saline was ligated into the ovarian end of the fallopian tube. A side arm provided a fluid filled connection to a pressure transducer. Fluid was infused until it reached the Matrix and the tube dilated. Pressure was maintained at 50, 100 and 150 mm HG for 1 minute while observing for visual evidence of fluid passing the Matrix into the uterine horn. All tubes treated with inferior and control lesions were demonstrated not patent. Three of 4 tubes treated with no energy were shown to be patent. We concluded that 'inferior lesions' which included lower levels of epithelial ablation were still efficacious and created tubal occlusion.

(This study was not the subject of a formal report, but was collected in laboratory notebooks which are retained on file at Cytec.)

Pre-pivotal Hysterectomy studies included two basic models: Peri-Hysterectomy or In-vitro studies which allowed examination of acute RF lesion morphology, and Pre-Hysterectomy studies which examined tissue in-growth and occlusion.

Histological data obtained in the Pre-Hysterectomy model included tissue in-growth response 3 months after the RF treatment and Matrix implant.

It was not feasible to know specifically, on a 'per tube basis', what type of lesion was created during the pre-hysterectomy in-growth studies. (Since the RF lesions are healed after three months.) The same control parameters were utilized in these pre-hysterectomy studies (i.e. 64°C/60 seconds). During In Vitro and Peri studies we observed a range of epithelial ablation with these fixed treatment parameters, and it is therefore reasonable to assume that given the same patient population (patients seeking elective hysterectomy) that similar lesions were created during the Pre-Hysterectomy studies.

Utilizing the same RF treatment parameters, the Pre-Hysterectomy implant results show robust tissue ingrowth in virtually all women. Since it is reasonable to assume that a range of lesions (with a range of epithelial ablations) were created in these patients, the results of these studies show that such treatments are adequate.

Specifically, Module 4, Section 2.7 reviews the results of treating 42 women with the Adiana Procedure 3 months before their scheduled hysterectomy. All tubes treated were patent prior to the procedure and all but two were non-patent at the end of the study as assessed by hysterosalpingography (HSG).

In evaluating these human tissue histology experiments, it is important to recognize that all women were undergoing hysterectomy for clinical indications. The impact of disease processes on the resulting epithelial ablation rate and mean lesion depth was unknown. However, we believe that this remains the best model for obtaining acute human histology.

It is expected that in the target patient population, epithelial ablation rates and mean lesion depths will be more uniform creating a homogeneous lesion resulting in an effective device during the 3 month waiting period and for long term success of the device. Clinical results, from the EASE clinical trial, are included in Module 4 of this PMA, and show that the device is effective in preventing pregnancies in a large population of women using these lesion control parameters.

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**IV. D. 3. PERI-HYSTERECTOMY STUDIES
(HYSTERECTOMY IMMEDIATELY AFTER
TREATMENT)**

2.5 Peri-Hysterectomy Studies

2.5.1 Overview, Study Design and Number of Subjects

After verification of device performance in bench, in vitro and animal testing, evaluation in human clinical studies was undertaken. After completion of In Vitro studies in which serosal temperature monitoring was performed to show that treatment was safe, further studies were performed in patients during hysterectomy procedures.

There were a total of 120 patients whom were treated in 13 individual 'studies'. These individual studies [REDACTED] were performed in series to evaluate multiple device and procedure parameters. Each study protocol is discussed below. Copies of the reports for these studies, [REDACTED] can be found in Appendices 2 and 6 (respectively).

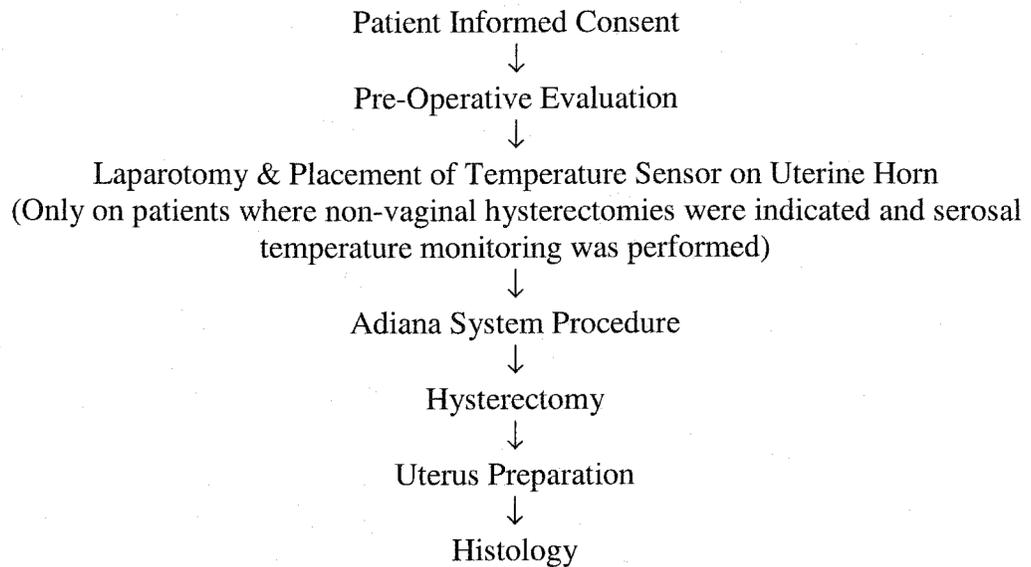
In addition, Peri-Hysterectomy studies were performed to evaluate any potential impact of the proximal Band Spacing change to the Delivery Catheter (as described in Module 1). These studies, in which eight patients were treated, were performed under Protocol [REDACTED]. Results of these studies have previously been discussed (Module 1, Section 4.2.3.3.3). A copy of the final report for this study, R0117, is included in Appendix 7.

2.5.2 Study Protocol [REDACTED]

In total for study protocol [REDACTED], 62 patients were treated in 8 Peri-Hysterectomy studies. The studies were initiated on [REDACTED] and the last study was performed on [REDACTED]. These studies were performed in pre-menopausal women scheduled to undergo elective hysterectomy for benign conditions at the [REDACTED]. The protocol was approved by the local Ethics Committee, and all patients provided Informed Consent for this study. [REDACTED] was the Principal Investigator.

Immediately prior to the scheduled hysterectomy, treatment with the Adiana System was performed. The patient then received the scheduled hysterectomy.

The following flowchart depicts the sequence of events:



Each time a new RF control parameter (i.e. time, temperature) was clinically evaluated, a minimum of the first six patients underwent the Adiana Procedure with serosal temperature monitoring. This involved placement of a needle thermocouple probe just under the surface of the serosa on the uterine horn to measure temperature. If no significant serosal temperature rise [REDACTED] was observed in these patients, it was considered safe to proceed without serosal temperature monitoring in the remaining patients.

2.5.2.1 General Protocol

Each patient was prepared for their hysterectomy using either a vaginal or abdominal technique, based on standard institution practice. In addition, the patient was prepared for a standard operative hysteroscopy. Once the uterus was distended with nonconductive fluid (glycine) the tubal ostia were identified in the hysteroscopic image. The Adiana system was then used as follows:

- The Delivery Catheter was removed from the sterile packaging and inspected.
- The Delivery Catheter was connected to the RF Generator using the catheter cable.
- The Delivery Catheter was placed into the working channel in the hysteroscope.
- While observing the hysteroscopic image, the Delivery Catheter was advanced into the uterine cavity.
- The Delivery Catheter was placed into the tubal ostium to the proper depth.
- RF energy was applied, and the tissue heated to a pre-determined temperature for a pre-determined time. (See Table 2.1 below)

- The standard Adiana Matrix was then delivered.

During RF energy delivery, continuous wattage and temperature measurements from both the catheter and serosal probes (when applicable) were recorded for the duration of the application.

During the device use, physician comments on device handling, ease of use and clinical observations were recorded.

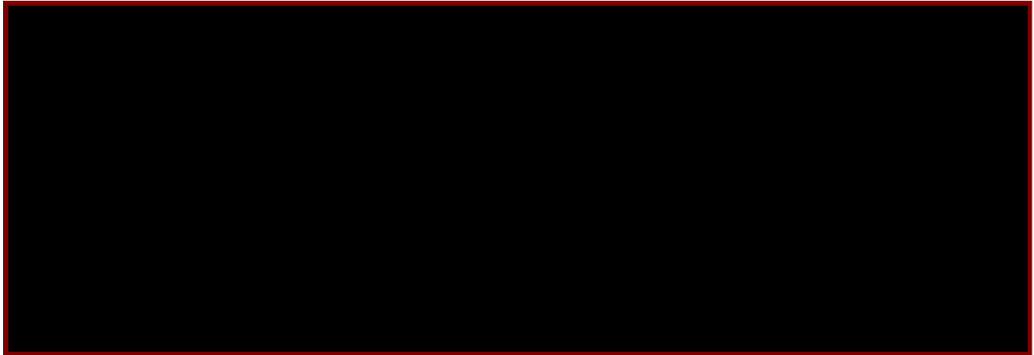
After both tubes were treated (or only one tube depending on tubal access conditions) the patients then underwent their hysterectomy.

Over the course of all Peri-Hysterectomy studies, there were several RF control parameters which were evaluated. As shown below, these varied from 52 to 64°C and from 45 to 120 seconds:



2.5.2.2 Methods





Histology Evaluation

Each fallopian tube was evaluated according to the following criteria:

- Uniformity and completeness of epithelial destruction
- Depth and uniformity of the thermal lesion
- Tubal lesion length
- Position of Matrix within the lesion



Stage 1

Stage 1 studies occurred early in the development cycle, and were part of the iterative process of optimizing device configuration and operating limits. The table below summarizes the results obtained:

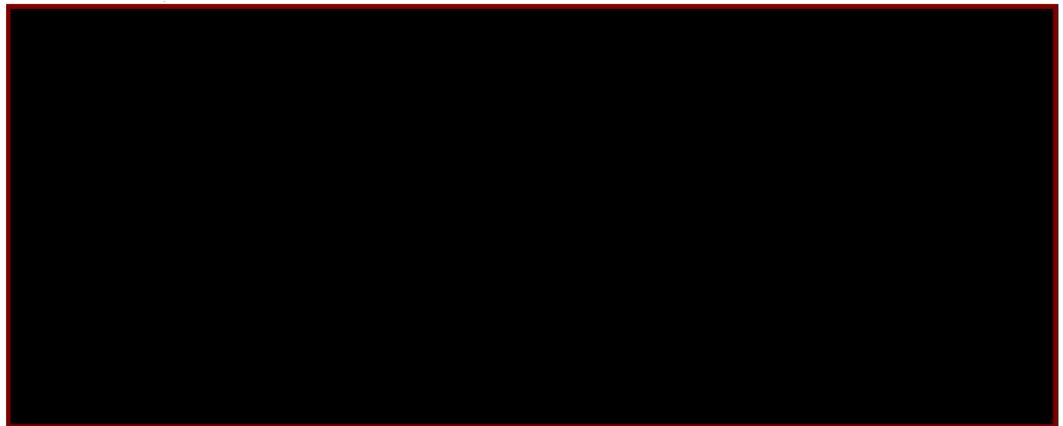


In total, during Stage 1 studies, there were 51 fallopian tubes treated in 31 patients, for an overall Tubal Access success rate of 82%.

Stage 2

The second stage involved verification testing of the final time and temperature settings (64°C for 60 seconds), electrode length of 6mm and electrode diameter of 0.047". Stage 2 also involved verification testing of the new Adiana RF generator to ensure that it provided the same performance characteristics as compared to the Radionics Generator used in the early studies. (Equivalency testing was also performed as part of Hardware and Software verification protocols, and in In-Vitro studies. All Equivalency Testing results for the Adiana RF Generator were collected within Studies 7 and 8.)

There were a total of 31 patients enrolled in the Stage 2 phase, with a total of 54 tubes treated at 64°C/60sec. These stage 2 studies were performed from [REDACTED]. (Note that results from the 2 tubes treated using 64°C / 60 seconds in Stage 1 are also included in the analysis section.)



2.5.2.4 Review of Study Objectives

There were 6 major objectives relating to safety and acute device performance in the Peri Hysterectomy Studies:

- Ability to apply RF energy in a controlled manner achieving a desired lesion on the surface of the fallopian tube without excessive fallopian tube damage or thermal injury to other organs.
- Ability to position the catheter into both tubal ostia using hysteroscopic techniques.
- Ability to release the Matrix from the Delivery Catheter.
- Ability to release the Matrix such that the Matrix is implanted in the area of the fallopian tube in which the RF lesion was formed.

- Ability of the Matrix to maintain position in the fallopian tube.
- Verification testing of the Aiana RF Generator as compared to the [REDACTED]

Each of these objectives is reviewed below.

Objective 1: Ability to apply RF energy in a controlled manner achieving a desired lesion on the epithelial surface of the fallopian tube without excessive fallopian tube damage or thermal injury to other organs

Acute treatment parameters were assessed for all treatments at 64°C/60 seconds. The table below details the results obtained in 54 individual tubes. (Serosal monitoring was performed on 11 tubes in 7 patients.) Results of all Stage 2 studies are shown in the following table, and a discussion of the individual results follows:

Table 2.4: Stage 2 Results

Endpoint	Evaluation Method	Results For Stage 2 Treatments At 64°C/60 Seconds (±SD)
Max. Lesion Depth	Histological Evaluation (Using NBT Only)	Average maximum lesion depth: 0.56mm ± 0.10mm
Lesion Length	Histological Evaluation	Average lesion length: 5.44mm ± 1.73mm
Epithelial Ablation	Histological Evaluation: Average Percent of Epithelial Ablation	Average Percent Ablation: 93%± 7%.
Serosal Temperature	Thermocouples placed on the serosa of the uterus.	Peak serosal temperature: 41.7°C Average temperature rise: 1.8°C

Serosal Temperatures



Overall, including all temperature-time combinations, peak serosal temperature was monitored in 40 tubes in 24 patients in the Peri-Hysterectomy studies. There were four different temperature-time combinations, from 52 °C for 45 seconds to 64 °C for 60 seconds. Overall, peak serosal temperature only exceeded 44°C in both tubes in a single patient (44.5 °C and 45.4 °C). These two tubes were in a patient treated at 56 °C /45 seconds. It was postulated that this was due to the misapplication of the

thermocouple needle probe used to monitor temperature. This probe is intended to be inserted into the tissue, just under the serosal surface. Due to the tight confines within the operative field, it is felt that the needle may have been placed too deeply and therefore too close to the catheter electrodes. Careful analysis of these two lesions, specifically analyzing lesion depth, has shown that the lesion created during the RF treatment were normal (for that temperature-time combination), and that the average maximum lesion depth was within normal ranges (0.26mm and 0.27mm). The patient's treatment was unremarkable.

Lesion Depth

The Adiana RF treatment is intended to ablate the epithelium, but also to limit the depth of the lesion in order to prevent necrosis or damage out to the serosa. Histological analysis was employed to determine the degree of cell death. Samples stained with H&E were examined for disruption of nuclei, while samples stained with NBT were examined for viability. Each cross section through a given segment of the treatment region was analyzed, and the maximum depth of cell damage was determined. This maximum depth was then averaged over the length of the lesion.

[REDACTED]

(Other measurements such as lesion length and % epithelial ablation were found not to vary based on staining technique.) There were 25 tubes in which NBT stain was used, and 29 in which H&E was used.

Treatment parameter of 64°C/60 seconds created an average maximum lesion depth of 0.56mm \pm 0.10mm in a total of 25 treated tubes which were stained with NBT (range 0.43 – 0.81mm). Overall, including the H&E stained samples, the average maximum lesion depth was found to be 0.47mm \pm 0.16mm. In no case did any lesions extend to the serosa.

Lesion Length

The histology of the tissue was examined for thermal damage. Samples stained with H&E were examined for disruption of nuclei, while samples stained with NBT were examined for viability. Analysis of both methods showed similar results, therefore the numbers were pooled. The lesion length is the total distance between the first slide that shows thermal damage and the last slide that shows thermal damage.

In a total of 54 tubes in 31 patients, the average lesion length for treatment parameter of 64°C/60 seconds was 5.44mm \pm 1.73mm.

Epithelial Ablation

One criterion for effective RF treatment is the ability to destroy the layer of epithelial cells that line the fallopian tube.

Under microscopic analysis, each slide is analyzed for ablated epithelium using morphometric software which allows the operator to trace a detailed circumference. Average Percent of Epithelial Ablation involves the evaluation of the percentage of the luminal circumference that is free of residual epithelium in each section showing lesion. This percentage is then averaged over the entire length of the lesion.

In a total of 54 tubes in 31 patients, the percent of epithelial ablation for treatment parameter of 64°C/60 seconds was 93% \pm 7%, with a range of 72-100%.

Objective 2: Ability to position the catheter into both tubal ostia using hysteroscopic techniques

One measurement of the delivery catheter's control and ease of use is Tubal Access Rate. Tubal Access Rate is calculated as the percentage of successful placements of the catheter into the fallopian tube. For the 62 patients treated (124 available tubes) in this study, there were 105 successful placements of the catheter into the fallopian tube, resulting in a Tubal Access Rate of 85%.

For Stage 1, there were 31 patients treated (62 available tubes) with 51 successful placements of the catheter into the fallopian tube, resulting in a Tubal Access Rate of 82%. For Stage 2, there were 31 patients treated (62 available tubes) with 54 successful placements of the catheter into the fallopian tube, resulting in a Tubal Access Rate of 87%.

Objective 3: Ability to release the Matrix from the Delivery Catheter

During Stage 1, there were two Matrix release failures, and a total of 49 properly released matrices out of a total of 51 attempts. These two failures occurred in the early peri studies, with early development catheters.

Catheter modifications were successfully implemented and there were no Matrix release failures during Stage 2, with a total of 54 successful placements.

Objective 4: Ability to release the Matrix such that the Matrix is implanted in the area of the fallopian tube in which the RF lesion was formed

Matrix positioning within the targeted lesion was evaluated by histology. Since this acute protocol did not allow for tissue integration into the matrix, there was no ingrowth to anchor the matrix in place and therefore measurements of the alignment of the lesion and matrix were difficult to interpret. However, since the lesion is only quantifiable in an acute setting

(healing eliminates the lesion after several weeks) this was the only study in which lesion and matrix alignment could be investigated clinically.

The lengths and depths recorded may also exhibit minor inaccuracies due to tissue collection and process variables. For example, fixation/processing-related tissue shrinkage due to formalin fixation will cause the tissue to shrink and may create inaccuracies in measurements of lengths and depths. Another possible measurement inaccuracy involves linear sectioning of curved/tortuous fallopian tube lumens that result in oblique versus transverse sectional cuts. Another possible measurement inaccuracy involves serial tissue block reconstruction. Several blocks of tissue typically capture the lesion and matrix and tissue from distal and proximal sides of the block may be lost during tissue processing, under representing lesion and matrix length.

Matrix position was measured by comparing the proximal end of the matrix to the proximal end of the lesion and comparing the distal end of the matrix with the distal end of the lesion. The measurement would be a positive value if the matrix were located within the lesion and negative if placed outside the lesion.

In Stage 2 studies, the average distance from the proximal edge of the lesion to the proximal end of the matrix was 2.02mm, and the average distance from the distal end of the matrix to the distal end of the lesion was 0.45mm. For all studies, include Stage 1 and 2, these distances were 1.60 and 0.75 mm respectively.

During histological examination, it appeared that on 4 occasions a portion the distal matrix was within the tubal wall of the fallopian tube and on 1 occasion the matrix was placed completely within the tubal wall. Subsequent investigation has revealed that histological processing can create artifacts that appear to show the matrix within the wall of the tube, but in actual fact are due to the plane of histological sectioning creating this perception. Distal and proximal misplacements are, therefore, not considered significant. In the one case where it appears that the entire device was placed outside the true lumen, the device was still within the tube. It is unclear what might have caused this observation, however the fact that the patient had significant underlying disease which required a hysterectomy cannot be ruled out as a contributing factor. Nonetheless, device features have been incorporated to reduce the risk of this occurrence.

Objective 5: Ability of the matrix to maintain position in the fallopian tube

During Stage 2, all matrices were identified by histology within the fallopian tubal lumen with the exception of one as discussed above in Objective 4.

During Stage 1, there was considerable work performed on perfecting the technical aspects of tissue removal, dissection and processing. Until processing methods were perfected, complete samples were not always taken of the entire fallopian tube. This led to instances where the matrix was not identified in subsequent microscopic analysis. In total, there were four instances where the matrix could not be identified within the fallopian tube by histology. In one case the matrix was visually identified on dissection, but subsequently lost during processing, in another case the matrix and lesion were not delivered into the tube due to operator error, and in the last two cases the matrix was inadvertently lost during histology preparation.

Objective 6: Verification testing of the Adiana RF Generator as compared to the [REDACTED]

The Adiana RF Generator was developed for use with the Adiana delivery catheter. It was designed to deliver equivalent dosimetry with a comparable temperature-feedback profile as the [REDACTED] generator used previously.

This study was performed in a total of 31 patients in order to validate the use of the Adiana RF Generator when compared to the commercially available [REDACTED] generator. Results in these 31 patients included 54 tubes. The values for lesion length, depth, and % epithelial ablation obtained with the Adiana RF Generator were comparable to those obtained with the [REDACTED] generator. Note that lesion depth includes only samples analyzed using NBT stain.

Table 2.5: Adiana RF Generator Equivalency Study (\pm SD with number of samples for each measurement)

Parameter	Adiana RF Generator	[REDACTED] generator
Maximum Average Lesion Depth (NBT Only) (mm)	0.52mm \pm 0.08mm, n=9	0.58mm \pm 0.11mm, n=16
Lesion Length (mm)	5.80mm \pm 1.97mm, n=27	5.04mm \pm 1.40mm, n=27
% Epithelial Ablation	95% \pm 6%, n=27	92% \pm 8%, n=27

2.5.2.5 Conclusions for Study [REDACTED]

The study was separated into two stages. The first stage involved the investigation of how varying temperature/time parameters and electrode length/diameter dimensions impacted lesion creation and serosal temperature rises. This allowed the selection of one temperature/time and electrode configuration that safely creates an acceptable lesion. The selected

temperature/time was 64°C/60 seconds and the selected electrode dimensions consisted of a bipolar, 4 band electrode array 6mm long with a 0.047” diameter.

The second stage involved verification testing of the final 64°C/60s setting. It was demonstrated at this setting that lesions could be generated reproducibly, that treatment with the Aiana delivery catheter caused no risk to adjacent organs or structures, and that matrix delivery was reliably obtained.

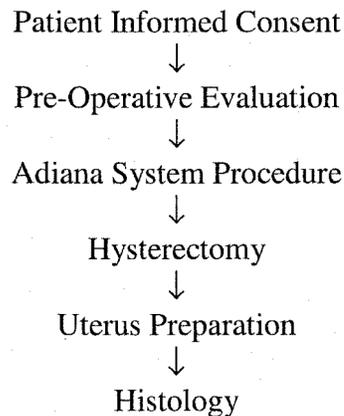
During the course of this Peri Hysterectomy Study there were no patient complications or adverse clinical events due to either the Aiana System or the Aiana Procedure. [REDACTED] can be found in Appendix 2.

2.5.3 Study Protocol P0083

In total for study [REDACTED] 58 patients were treated in a total of 5 Peri-Hysterectomy studies. The studies were initiated on [REDACTED] and the last study was performed on [REDACTED]. These studies were performed in pre-menopausal women scheduled to undergo elective hysterectomy for benign conditions at the [REDACTED]. The protocol was approved by the local Ethics Committee, and all patients provided Informed Consent for this study. [REDACTED] was the Principal Investigator.

Immediately prior to the scheduled hysterectomy, treatment with the Aiana System was performed. The patient then received the scheduled hysterectomy.

The following flowchart depicts the sequence of events:



The primary objective of this study was to evaluate the acute safety and efficacy performance of two catheter modifications in a hysterectomy patient population.



The second catheter modification (FA011) involved a new handle design and reduction in the outside shaft diameter from 7 French to 5 French to allow for a wider use of available hysteroscopes. This change was submitted to FDA under [REDACTED]

2.5.3.1 General Protocol

The general protocol was similar to the study protocol described in section 2.5.2.1 for protocol [REDACTED]. Energy treatment parameters of 64°C for 60 seconds, as discussed in the previous sections, remained the same throughout the study. Serosal temperature monitoring was not performed under this protocol since earlier studies had established the safety of RF energy delivery within the intramural portion of the fallopian tube.

2.5.3.2 Methods

Uterus preparation and formalin processing was similar to the study protocol [REDACTED] as described in section 2.5.2.2. Cryogenic processing was not utilized in this study.

Study Objectives and Methods

The primary objective of this study was to evaluate the acute safety and efficacy performance of the device modifications in a hysterectomy patient population.

Objective and subjective measurements included:

- Delivery System Control; the ability to position the catheter into both tubal ostia using hysteroscopic techniques. Evaluated with a physician questionnaire during the procedure. Physician answered either satisfactory or unsatisfactory.
- Release Procedure Positioning; the ability to release the matrix such that the matrix is deposited in the area of the fallopian tube in which the lesion was formed. This was evaluated with a

physician questionnaire during the procedure. The physician answered either satisfactory or unsatisfactory.

- Histological evaluation method:
 - Lesion depth
 - Lesion length
 - Percent epithelium ablated
 - Matrix position in relation to lesion
 - It is important to note that these acute studies do not allow the matrix to permanently fix in place with tissue ingrowth and that tissue manipulation during the surgery and subsequent tissue processing may inadvertently move the matrix from its initial placement. Also worth noting is the tissue shrinkage that occurs during tissue fixation/processing related to formalin fixation may also inadvertently move the non-shrinking matrix relative to the lesion.

2.5.3.3 Results

Catheters [REDACTED] were evaluated separately and are discussed independently in this section. [REDACTED] was clinically tested in Peri Study [REDACTED] [REDACTED] was clinically tested sequentially in 4 individual studies, Peri Studies [REDACTED]

- Delivery System Control: In all procedures, Delivery System Control was found satisfactory for [REDACTED]
- Release Procedure Positioning:
 - In all procedures for catheter [REDACTED] Release Procedure Positioning was found satisfactory by the physician.
 - Four individual studies were performed sequentially for [REDACTED] over a period of several months. Once the individual study was performed, results were analyzed and, if necessary, engineering or manufacturing modifications to the catheter were made to address issues observed from the study. For [REDACTED] version, there were eleven unsatisfactory release procedures observed in the first 56 attempts for studies 10 and 11. Modifications were made to the device and the delivery catheter performed satisfactorily in the following 33 release attempts in studies [REDACTED]
- Histology was captured and analyzed for all 12 patients treated with device [REDACTED] Histology analysis for [REDACTED] includes results representing the final catheter design. The final design

was used in studies 12 and 13 representing 17 patients. Results are shown in the table below:



The studies concluded that:

- The lesion was not observed beyond the uterine serosa in any of the treatments.
- For [REDACTED], all tubes presented matrix within the lesion. For [REDACTED] definitive thermal lesions could not be easily identified in two tubes. Lesion at the location of the matrix was not ruled out, but difficult to identify. [REDACTED] two matrices were not observed in the thermal lesion zone. It was felt that this was possibly due to artifact induced by the surgical hysterectomy process as discussed above in section 2.5.2.4 (under Objective 4).

2.5.3.4 Conclusions for Study Protocol [REDACTED]

The primary objective of this study was to evaluate the acute safety and efficacy performance of device modifications in a hysterectomy patient population. The modifications evaluated were as follows:

- Catheter electrode sheath modifications [REDACTED]
- New handle design and reduced catheter shaft diameter [REDACTED]

Acute performance of the two devices was found to be satisfactory. Review and analysis of the histology demonstrated acceptable matrix positioning and lesion results. No lesions were identified beyond the serosal lining of the uterus.

During the course of this Peri Hysterectomy Study there were no patient complications or adverse clinical events due to either the Adiana System or the Adiana Procedure.

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