

While the preliminary comparison shown in Table 8-17 is instructive, a more precise way to evaluate the relative performance of two methods is to compare the *difference between their point estimates and the confidence intervals associated with that difference*. This evaluation is particularly valuable when, as in the CREST and Adiana studies, there are substantial sample size differences associated with reported outcomes for each individual method. Thus, this approach was used to compare the Adiana method (total population as well as US and OUS populations) to the other methods presented in the CREST study. Results of this analysis are presented in Tables 8-18, 8-19, and 8-20, in which, respectively, the total population, the US population, and the OUS population within the Adiana study are compared to each of the CREST study methods. A detailed explanation of the statistical methods used to perform this analysis is provided in Appendix 13.1.7.

In each of the comparison tables (8-18 through 8-20), the difference in point estimates between the Adiana method and each individual method reported in the CREST study are shown; these failure rate differences are presented along with their associated two-sided 95% confidence interval ranges. Within the sampling error, when the confidence interval range associated with the difference between methods includes zero, this suggests that the Adiana and CREST failure rates are statistically comparable.

Results of the comparison of the confidence interval differences of the Adiana total population to each of the CREST methods show that the Adiana method is statistically comparable to bipolar coagulation, silicone rubber band application, interval partial salpingectomy, spring clip application, all methods combined, and all “comparable methods” combined (Table 8-18). The Adiana method is not statistically comparable to the post-partum salpingectomy or the unipolar coagulation methods; however, these two methods are not clinically relevant for comparison as the Adiana method cannot be performed in the post-partum time period, and the unipolar coagulation method is rarely utilized clinically due to the relatively high complication rate. (Note that “comparable methods” includes all methods except post-partum salpingectomy and unipolar coagulation.)

Results of the comparison of the confidence interval differences between the Adiana US and OUS populations to the CREST methods show that the failure rates in these two Adiana populations are statistically comparable to the failure rates for each of the CREST-reported methods individually, for all of the methods combined, and for all of the “comparable methods” combined; see Tables 8-19 and 8-20, respectively. (Note that “comparable methods” includes all methods except post-partum salpingectomy and unipolar coagulation.)

**Table 8-18: Differences in One-Year Failure Rates, Comparison Between the Total Adiana Population and Individual Methods Reported in the CREST Study**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+10.2	+1.5 to +18.9
Unipolar Coagulation	+10.1	+1.4 to +18.8
Bipolar Coagulation	+8.5	-0.3 to +17.3 <sup>1</sup>
Silicone Rubber Band Application	+4.9	-4.1 to +13.9 <sup>1</sup>
Interval Partial Salpingectomy	+3.5	-8.4 to +15.4 <sup>1</sup>
Spring Clip Application	-7.4	-18.3 to +3.5 <sup>1</sup>
All Methods	+5.3	-3.4 to +14.0 <sup>1</sup>
Comparable Methods <sup>2</sup>	+3.3	-5.4 to +12.1 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

**Table 8-19: Differences in One-Year Failure Rates, Comparison Between the US Adiana Population and Individual Methods Reported in the CREST Study**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+8.3	-0.5 to +17.0 <sup>1</sup>
Unipolar Coagulation	+8.2	-0.6 to +16.9 <sup>1</sup>
Bipolar Coagulation	+6.6	-2.3 to +15.4 <sup>1</sup>
Silicone Rubber Band Application	+3.0	-6.1 to +12.0 <sup>1</sup>
Interval Partial Salpingectomy	+1.6	-10.4 to +13.5 <sup>1</sup>
Spring Clip Application	-9.3	-20.3 to +1.6 <sup>1</sup>
All Methods	+3.4	-5.4 to +12.1 <sup>1</sup>
Comparable Methods <sup>2</sup>	+1.4	-7.4 to +10.2 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically



**Table 8-20: Differences in One-Year Failure Rates, Comparison Between the OUS Adiana Population and Individual Methods Reported in the CREST Study**

	Difference in Failures/1000	95% CI Range of Difference
Post Partum Partial Salpingectomy	+18.3	-7.6 to +44.2 <sup>1</sup>
Unipolar Coagulation	+18.2	-7.7 to +44.1 <sup>1</sup>
Bipolar Coagulation	+16.6	-9.3 to +42.5 <sup>1</sup>
Silicone Rubber Band Application	+13.0	-13.0 to +39.0 <sup>1</sup>
Interval Partial Salpingectomy	+11.6	-15.5 to +38.7 <sup>1</sup>
Spring Clip Application	+0.7	-26.0 to +27.4 <sup>1</sup>
All Methods	+13.4	-12.5 to +39.3 <sup>1</sup>
Comparable Methods <sup>2</sup>	+11.4	-14.5 to 37.3 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

Overall, the more precise comparison between the Adiana method and the methods reported in the CREST study indicate that there are no statistically significant differences between the Adiana method and all CREST-reported methods combined, and that, with the exception of post-partum salpingectomy and unipolar coagulation, there are no statistically significant differences between the Adiana method and any of the individual methods. In the case of the two methods for which statistically significant differences were observed, neither comparison is clinically relevant as the Adiana method cannot be performed in the post-partum time period and the unipolar coagulation method is rarely utilized.

### 8.8.1 Analysis of Efficacy Based on Age

Age is a recognized factor in fertility rates: in general, fertility decreases as age increases. Given this, it is important to consider how the Adiana System's pregnancy prevention rates might be influenced by patient age. To evaluate this, the one-, two-, and three-year pregnancy failure rates were stratified by age using the categorical breakdowns described in the CREST study and then analyzed statistically. Additionally, a correction to the overall one-year Adiana pregnancy failure rate was determined to explicitly account for age as a factor in pregnancy.

The one-year Adiana pregnancy failure rates are presented in Section 8.8 and the two- and three-year rates are presented in Section 8.10; these rates, respectively, are 1.08%, 1.82%, and 1.82% (alternatively, as point estimates for failures in 1000 patients, these correspond, respectively, to 10.8, 18.2, and 18.2).

Table 8-21 presents a tabulation of the one-, two-, and three-year failure rates for the Adiana System by age category. The age stratification used in this table matches the one described within the CREST study (18-27 years of age, 28-33 years of age, and



34-44 years of age); for comparative purposes the proportion of patients in each age category for the Adiana and CREST-reported methods also are included.

**Table 8-21: Age Stratification of Adiana Pregnancy Failure Rates with Comparisons to CREST Methods**

	1-Yr Rates		Patient Distribution		Long-Term Adiana Rates	
	Adiana	CREST <sup>1</sup>	EASE %N <sup>2</sup>	CREST %N <sup>2</sup>	2-Yr	3-Yr
All Patients	1.08%	0.55%	100.0%	100.0%	1.82%	1.82%
Age Categories <sup>3</sup>						
18-27	2.26%	1.25%	24.2%	32.8%	3.52%	3.52%
28-33	1.12%	1.00%	47.9%	35.4%	2.20%	2.20%
34-44 <sup>4</sup>	0.00%	0.46%	27.9%	31.8%	0.00%	0.00%

<sup>1</sup> Results for all methods combined.

<sup>2</sup> %N refers to the proportion of subjects in each age category by study. The median age in the EASE trial was 31 years; the median age in the CREST study was 30 years.

<sup>3</sup> The age categories were selected to match the ones described within the CREST study.

<sup>4</sup> No pregnancies were reported within this age category for the Adiana System.

While the proportion of patients within each age category differed between the EASE and CREST studies, the one-year pregnancy failure rates showed essentially the same trend in lower rates with increasing patient ages. It is important to recognize that while the rates for all patients are numerically different between the Adiana System and the CREST-reported methods, as was presented in Section 8.8, the rates are not statistically different and thus, the methods are comparable.

The long-term analysis indicates that while a similar trend for lower rates with increasing age is observed, no numerical differences from two-year to three-year prevention rates were observed. Additionally, across the one-, two-, and three-year Adiana System pregnancy failure rates, the logrank p-value was 0.0961, which implies that the rates are equal, although there is a slight trend that indicates otherwise.

For the Adiana one-year pregnancy failure rate, an age-corrected value was determined using a weighted average based on the raw failure rates by age category and the proportion of subjects within each category. As shown in Table 8-21, the one-year rate is 1.08%. When adjusted for age, this rate becomes 1.14%.

Overall, while age is an acknowledged factor in fertility, 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. Finally, the age-corrected failure rate is not substantially greater than the un-adjusted rate, further indicating that while age is a factor, it does not substantially affect the pregnancy prevention outcomes demonstrated in this study.



### 8.8.2 Comparison to Cumulative Pregnancy Rates Published Since the CREST Study

A Medline literature search was performed for years 1996 through March 2007. All publications identified through key word searches for ‘female sterilization’, ‘female tubal ligation’, ‘male sterilization’, and ‘vasectomy’ were included. A total of 296 abstracts were reviewed in an effort to identify appropriate recent additional control groups to the CREST study, the designated efficacy control for the EASE Clinical Trial. All controlled trials were considered. The results of the literature search identified five publications containing cumulative pregnancy rates for comparable sterilization methods. These included: three papers that contained results from the pivotal ESSURE clinical trial (Kerin, Carignan et al. 2001; Cooper, Carignan et al. 2003; Kerin, Cooper et al. 2003); and two papers that contained data related to the Filshie Clip (Dominik, Gates et al. 2000) (Sokal, Gates et al. 2000). A complete report of the literature search performed, as well as a listing of all reviewed publications can be found in Appendix 13.1.8.

Both Essure and the Filshie Clip are methods that were reported after the CREST study concluded. Currently, no reports in the literature contain cumulative pregnancy prevention rates for the Essure method, but two publications have investigated the long-term efficacy of the Filshie Clip when delivered laparoscopically.<sup>3,4</sup>

Because long-term pregnancy prevention rates published for the Essure method are limited, a detailed comparison to the Adiana System is not entirely possible. It is, however, somewhat useful to note the experience reported in the pivotal trial conducted to evaluate the Essure method. In this study, no pregnancies were reported in the 439 patients that were followed for the first year. With this result, the 95% lower confidence bound would appear to correlate with an effectiveness claim of 99.24%. That number is contained in Essure’s Summary of Safety and Effectiveness Data.<sup>5</sup>

However, Essure’s promotional literature consistently states that the device is 99.93% effective at one-year follow-up.<sup>6</sup> When making this marketing claim, the sponsor of the ESSURE study, Conceptus has been permitted to use their ‘point estimate’ for the results from the ESSURE clinical trial which, in this instance, should be 100.0% (i.e., no failures in 439 patients). We hypothesize that the company wanted to

<sup>3</sup> Dominik R, Gates D, Sokal D, Cordero M, Lasso de la Vega J, Remes Ruiz A, et al. Two randomized controlled trials comparing the Hulka and Filshie Clips for tubal sterilization. *Contraception*. 2000 Oct 1;62(4):169-75.

<sup>4</sup> Sokal D, Gates D, Amatya R, Dominik R. Two randomized controlled trials comparing the tubal ring and filshie clip for tubal sterilization. *Fertil Steril*. 2000 Sep 1;74(3):525-33.

<sup>5</sup> Summary of Safety and Effectiveness Data, Page 19, Table 7. See: <http://www.fda.gov/cdrh/pdf2/p020014b.pdf>

<sup>6</sup> Essure Patient Brochure, Page 10. See: [http://www.essure.com/Portals/0/Skins/Conceptus\\_Skin/PDFs/patient\\_info\\_booklet\\_eng.pdf](http://www.essure.com/Portals/0/Skins/Conceptus_Skin/PDFs/patient_info_booklet_eng.pdf)

indicate to the public that there was a small chance of failure.<sup>7</sup> For that reason, Conceptus has stated that they are 99.93% effective at one year, 99.86% effective at two years, and 99.80% effective at three years. There does not appear to be a statistical basis or derivation for this claim and no studies have been reported in the literature to substantiate these rates.

Assuming that a similar use of the “point estimate” from the EASE study with the Adiana System is allowed in marketing materials (using Essure as a predicate), then the Adiana System has a one-year pregnancy prevention rate of at least 98.92%. By limiting the number of patients who were lost to follow-up, the claim might be increased slightly, perhaps to 99.0%. Given this, a comparison between the Adiana System and the Essure method indicates that the two techniques have a one-year pregnancy prevention rate that differs by less than one percentage point.

A more thorough comparison between the Adiana System and the Filshie Clip (delivered laparoscopically) can be made since long-term pregnancy prevention rates with the Filshie Clip have been reported in the literature. Specifically, in order to evaluate this method relative to the Adiana System, an analysis was conducted to compare the one-year pregnancy prevention rates for the two methods. As a preliminary evaluation, similar to the evaluation conducted with the CREST-reported methods, the two-sided 95% confidence limits of the observed rate for the methods were compared; this analysis allowed for the relative performance of the two sterilization methods to be determined. The one-year failure rates and two-sided 95% confidence interval efficacy ranges are ordered by decreasing efficacy and are summarized in Table 8-22.

**Table 8-22: Filshie Clip versus Adiana System, One-Year Failures**

	Failure per 1000 patients		95% CI <sup>1</sup>
	<u>Point Estimate</u>	<u>95% CI</u>	<u>Efficacy Range</u>
Filshie Clip as reported in Dominik, et al.	1.9	-2.7 to 6.5	99.35 – 100
Filshie Clip as reported in Sokal, et al.	2.5	-2.1 to 7.1	99.29 – 100
Adiana (US)	8.9	0.2 to 17.5	98.25 – 99.98
Adiana (Total)	10.8	2.2 to 19.4	98.06 – 99.78
Adiana (OUS)	18.9	0.0 to 44.8	95.52 - 100

<sup>1</sup> Two-sided confidence interval derived with life-table methods.

While this analysis is instructive, a more precise method of evaluating the one-year efficacy results requires comparing the difference between point estimates and the confidence intervals of that difference for the Filshie Clip relative to the Adiana method. This analysis was conducted using the results from the two publications that investigated one-year pregnancy prevention rates for the clip and the total Adiana population as well as the US and OUS populations; the results are presented in Tables

<sup>7</sup> Private communication from former Conceptus executives.



8-23, 8-24, and 8-25 for the three Adiana populations, respectively. A detailed explanation of these statistical methods is provided in Appendix 13.1.7. As previously stated, when the confidence interval range associated with the difference between methods includes zero, the Adiana and Filshie Clip failure rates are suggested to be statistically comparable.

**Table 8-23: Differences in One-Year Failure Rates, Comparison between the Total Adiana Population and the Filshie Clip**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Filshie Clip as reported in Dominik, et al.	+8.9	-0.8 to +18.6 <sup>1</sup>
Filshie Clip as reported in Sokal, et al.	+8.3	-1.4 to +18.0 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest that, within sampling error, the Adiana and Filshie Clip failure rates are statistically comparable

**Table 8-24: Differences in One-Year Failure Rates, Comparison between the US Adiana Population and the Filshie Clip**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Filshie Clip as reported in Dominik, et al.	+7.0	-2.8 to +16.7 <sup>1</sup>
Filshie Clip as reported in Sokal, et al.	+6.4	-3.4 to +16.1 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest that, within sampling error, the Adiana and Filshie Clip failure rates are statistically comparable

**Table 8-25: Differences in One-Year Failure Rates, Comparison between the OUS Adiana Population and the Filshie Clip**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Filshie Clip as reported in Dominik, et al.	+17.0	-9.3 to +43.3 <sup>1</sup>
Filshie Clip as reported in Sokal, et al.	+16.4	-9.9 to +42.7 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest that, within sampling error, the Adiana and Filshie Clip failure rates are statistically comparable

Overall, the one-year pregnancy prevention rate for the Adiana System is statistically comparable to the Filshie Clip. Specifically, this result is true for the comparison of prevention rates between the Filshie Clip and the total Adiana population, the US



Adiana population, and the OUS Adiana population. Additionally, while two different studies investigated the prevention rates for the Filshie Clip, the Adiana System is comparable to the rates obtained in both studies. Thus, the Adiana System's one-year pregnancy prevention rate is comparable not only to the methods described in the CREST study (with the exceptions of post-partum salpingectomy and unipolar coagulation in the analysis of the total Adiana population), but also to the Filshie Clip. In regard to the Essure method, a similar approach to the efficacy claim made by Essure indicates that the two methods differ in one-year pregnancy prevention rates by less than one percentage point and therefore are not substantially dissimilar.

## 8.9 Statistical/Analytical Issues

### 8.9.1 Handling of Dropouts or Missing Data

Of the 570 patients who were determined to have bilateral tubal occlusion and allowed to rely on the Adiana System for pregnancy prevention, 17 were not evaluated for the one-year primary efficacy endpoint (see listing in Appendix 13.2.4). The reasons why these patients were not included in the one-year efficacy analysis are as follows:

#### Tubal patency determined after HSG review:

Three patients who had been determined to be bilaterally occluded by the investigator and were relying on the Adiana System for pregnancy prevention were found to have possible tubal patency during review of HSG's by the Core Lab. These patients were instructed by the investigator to discontinue reliance on the Adiana System prior to their reaching the primary one-year endpoint. None of these three patients has experienced a pregnancy and all three are still enrolled in the study and being followed for safety endpoints only.

#### Withdrawn from study:

Two relying patients elected to withdraw from the study during the one-year follow-up period. One patient withdrew following an endometrial ablation procedure for metrorrhagia immediately following determination of bilateral tubal occlusion. The second patient withdrew after her six month follow-up visit due to personal obligations and a busy work schedule as a licensed vocational nurse. Both patients were aware of the risks associated with the study and understood that they could return to the clinical site for medical attention should a pregnancy or complication occur.

#### Terminated from the study by the investigator for protocol non-compliance:

One relying patient was terminated by an investigator for significant protocol non-compliance due to narcotic medication use. The last point of contact with this patient

was at her 9-month follow-up visit. The patient was terminated from the study and has had no contact with the clinical site since that visit.

#### Lost to follow-up

Eleven relying patients were lost to follow-up during the one-year efficacy follow-up period. Clinical sites lost contact with six of these patients immediately following determination of bilateral tubal occlusion status. Three patients were followed through the six month follow-up visit, and the remaining two patients were followed through their nine-month visit. Multiple attempts to contact and locate these patients were made over many months.

It is important to note that of the 17 patients not included in the efficacy analysis, three remain in the study and are being followed for safety endpoints; therefore, only 14 of the 570 relying patients in this study have unknown one-year pregnancy prevention status. The one-year primary endpoint compliance rate of 97.5% for the EASE trial compares favorably to the one year compliance rates seen in the Essure pivotal clinical trial (96.9%)<sup>8</sup> and the CREST study (89.2%).

Additionally, two patients who chose to withdraw from the study are still believed to be local to the clinical site and able to return for follow-up should a pregnancy or complication occur. Of the remaining twelve patients, it should be noted that four were followed through the six month visit and two were followed through the nine-month visit. Multiple attempts were made by the clinical sites to locate and follow these patients (detailed documentation from the clinical sites is provided in Appendix 13.2.4).

Patients are made aware that medical treatment is provided for by the clinical site should a pregnancy or complication occur. Clinical results to date have shown that patients who have moved or are at a great distance from their original clinical site and who have become pregnant have immediately notified the clinical site of the pregnancy. For these reasons, the sponsor believes it is highly likely that should any of the lost to follow-up patients become pregnant, they would contact the clinical site. Thus, the observed one-year pregnancy prevention rate determined for the Per Protocol population is believed to be a true reflection of the one-year clinical results for the EASE trial.

#### **8.9.2 Data Monitoring**

Clinical data from the EASE trial have been reviewed by the Data Safety Monitoring Board (DSMB) at two separate meetings. The first meeting was held in Chicago, Illinois on [REDACTED]. The purpose of this meeting was to review current

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<sup>8</sup> Summary of Safety and Effectiveness Data, Page 19, Tables 6 & 7. See: <http://www.fda.gov/cdrh/pdf2/p020014b.pdf>



safety and efficacy data from the EASE clinical trial and answer the following question:

*Do the study's pregnancies represent a risk exceeding that described in our protocol and informed consent and previously communicated to participants?*

The sponsor representatives reviewed the trial protocol including the informed consent followed by a full review of the trial's results. Each of the failures was discussed in detail and the DSMB members were provided an opportunity to discuss the results and share their opinions, with the sponsor representatives providing clarification when requested.

The findings of the DSMB were as follows:

- The study's protocol and informed consent have adequately conveyed the risk of pregnancy and ectopic pregnancy to study participants. The current results do not present a risk that exceeds the risks conveyed by the original informed consent.
- It is important for the study to be completed without disruption (i.e., alarming patients and/or investigators) to determine the effectiveness of the device.
- Investigators should be reminded that study participants require follow up, but no communication of an increased risk to patients is indicated at this time.
- The review group should meet in approximately six months and review two year data to reconsider the threshold for informing participants of increased or unanticipated risks.
- Based on the current failure rates, including pregnancies attributable to management errors and method failures and considering ectopic pregnancies, outcomes appear to be within the range of failure rates for other sterilization methods.

The detailed summary from this DSMB meeting is included in Appendix 13.5.

A second DSMB meeting was held in Chicago, Illinois on [REDACTED]. The purpose of this meeting was to review current safety and efficacy data from the EASE clinical trial as well as the following specific items:

- The review of serious adverse events
- To garner an opinion from reviewers on all SAE's listed as "related" or "possibly related" to the Adiana Procedure or device use by the study investigators, of concern by the sponsor, or of concern by the reviewers
- To review hysterectomy cases over the duration of the study follow-up through February 28, 2007 in the context of a measurable outcome against the general population.
- To broadly review outcomes in terms of adverse events (numbers, classifications, potential concerns)

The DSMB members reviewed and discussed all SAE's and gave a consensus opinion on the degree of procedure or device-relatedness when the reviewers' opinions disagreed with that of the investigator reporting the event. The DSMB members had no significant concerns about the number, type, or degree of procedure or device-relatedness of the SAE's observed in the EASE clinical trial to date. Additionally, the panel unanimously agreed that the study hysterectomy rate of 1.5% falls within normal observed rates in the general population based on published literature. The detailed summary from this DSMB meeting is included in Appendix 13.5.

### **8.9.3 Multicenter Studies**

The EASE clinical trial was conducted under a common protocol for each study site with the intention of pooling the data for analysis. In order to evaluate the appropriateness of pooling data across clinical sites, an analysis of variance (ANOVA, for continuous data) or Cochran-Mantel-Haenszel test (for categorical data) with a factor of stratification as described below was conducted for demographic characteristics and pre-operative factors. The analysis specifically considered the appropriateness of pooling data based on differences in demographics (age, height, weight, gravidity, and parity) and geographic location of the study (US and OUS).

Three stratification analyses were performed for each baseline demographic variable. The first involved a stratification of US versus OUS clinical sites; results of this analysis are presented in Table 8-26. The second and third analyses involved stratification of the US clinical sites, and stratification of the OUS clinical sites; results of these analyses are presented in Tables 8-27, and 8-28, respectively.

In terms of height, weight, gravidity, and parity, baseline demographic differences (p-value less than 0.10) between the US and OUS populations were noted for each of the variables with the exception of gravidity. Additionally, non-homogeneity in baseline demographics was observed for weight and gravidity amongst the US sites, and for gravidity amongst the OUS sites. These results are neither unexpected nor substantive given the different populations from which the patients were drawn. Further, the variability in the baseline demographic data is believed to lend robustness to the study outcome and represents the Adiana System being applied to the complete range of patients expected to use the procedure once approved. The differences seen in these variables are therefore not believed to be clinically meaningful, to have significant impact on the study results, or to prohibit the pooling of data across clinical sites.

In terms of patient age, the comparison showed significant differences between the US and OUS populations, as well as within each of these populations. The difference in mean age between the US and OUS populations was small (1.3 years) with the OUS population being slightly younger than the US population (mean age of 30.5 years vs. 31.8 years, respectively). The mean patient age for the US clinical sites ranged from 27.6 to 41.5 years, and from 27.7 to 32.4 years in the two OUS clinical sites.

To determine whether age is a significant predictor of outcome success, and thus a factor in the appropriateness of pooling the data across sites, a logistic regression was performed. The independent factors were US/OUS and age, with occlusion and pregnancy outcome as the dependent variables. The results of the pooling analyses for US and OUS sites are presented in Table 8-29; the US results are presented independently in Table 8-30 and the OUS results are shown in Table 8-31.

The results demonstrate that age is not a predictor of bilateral occlusion success; however, it is a factor in pregnancy outcome. Age is known to impact the risk of pregnancy in sterilization studies and specifically was observed in the CREST study where different relative risks were reported in three different age groups of women. As a result, the impact of age on pregnancy outcome was taken into consideration when interpreting the efficacy evaluations in this study (please refer to section 8.8.1). Differences in age, however, did not prohibit the pooling of data across clinical sites.

The consistency of the final HSG results and the one year pregnancy prevention rate were analyzed using a logistic regression model with a factor of stratification (as performed above); this analysis was conducted in order to validate that the primary efficacy data could be pooled in order to achieve common statistical and clinical conclusions.

In comparing the US and OUS clinical sites, the analyses show that there is no significant non-homogeneity in either bilateral occlusion or pregnancy outcomes (Table 8-32). Additionally, the stratification analysis of the US centers shows homogeneity between the sites; there is no extreme responding center in terms of outcome success (Table 8-33).

Different from the evaluation of US sites, however, the stratification analysis of the OUS sites showed non-homogeneity in the bilateral occlusion and pregnancy outcomes (Table 8-34). In the US, 14 investigative centers were included in the analysis, whereas in the OUS, only two sites participated in the study and were analyzed. Given this, it is likely that the observed non-homogeneity is merely a consequence of population differences. Therefore, a further stratified analysis was performed using all sixteen clinical sites in order to determine whether either of the two OUS sites was an extreme responding center in regard to outcome success; see Tables 8-35 and 8-36 for complete details.

The additional stratification analysis confirmed that pregnancy outcome results for the OUS clinical sites were statistically comparable to those observed at US clinical sites; however, the bilateral occlusion outcomes were not comparable. The results indicated that the reason for the non-homogeneity in bilateral occlusion outcomes was due to exceptionally good, rather than especially poor, results at one of the two sites. Specifically, the Australian center had 100% bilateral occlusion success in 66 patients. This result was reviewed in conjunction with the associated patient demographics and no correlation could be found to account for the increased occlusion success rate. Moreover, eight other clinical sites had greater acute procedural success rates than were observed at this OUS site, indicating that the occlusion success was not driven by a high acute treatment success. Therefore, the success rate at this site does not appear to have an identifiable clinical cause and the results are subsequently not considered to fall outside the expectations of normal clinical practice. As such, it is appropriate to pool the efficacy data across sites for analysis.

#### **8.9.4 Delivery Catheter Multiversion Poolability**

During the course of the study, two versions (version 1.0 and version 1.5) of the Adiana Delivery Catheter were utilized. (The difference between the versions involved changes to the handles and catheter shafts; there were no changes to the energy delivery mechanism or to the implanted Matrix.) To assess the appropriateness of pooling data from patients whose procedures were conducted using different versions of the Adiana Delivery Catheter, a comparison of the final HSG results and the one year pregnancy prevention rates was conducted using a logistic regression model with a factor of version.

The comparison of the Delivery Catheters demonstrated non-homogeneity in procedure time and bilateral placement success; see Table 8-37. Note that no pre-access procedures were conducted with the version 1.5 catheter; therefore, the Delivery Catheters were compared either across all procedures — regardless of whether or not a pre-access protocol was followed — or across specific procedures in which a pre-access protocol was not implemented.

Despite the differences in procedure times and bilateral placement successes, the comparison indicated no significant differences in final HSG results or one year pregnancy prevention rates. Given this, the different catheters are not relevant to the analysis of efficacy and the data from patients whose procedures were conducted using the version 1.0 and version 1.5 Delivery Catheters were appropriately pooled.

**Table 8-37: Pooling Analysis of Device Version**

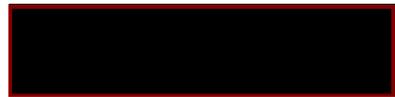
	N	Mean	STD	Median	Minimum	Maximum	p-value
<b>Procedure Time (min:sec)</b>							
Version 1.0	340	14:05	7:49	11:42	5:15	50:35	<0.001 <sup>a</sup>
Version 1.5	310	9:31	5:22	7:44	4:36	44:11	
<b>Procedure Time (min:sec) – with <i>Pre-access</i></b>							
Version 1.0	119	15:56	6:38	13:36	6:21	41:32	NA <sup>a</sup>
Version 1.5	0	.	.	.	.	.	
<b>Procedure Time (min:sec) – without <i>Pre-access</i></b>							
Version 1.0	221	13:05	8:14	10:35	5:15	50:35	<0.001 <sup>a</sup>
Version 1.5	310	9:31	5:22	7:44	4:36	44:11	
		Yes	No				p-value
<b>Bilateral Placement</b>							
Version 1.0	315 (92.1%)	27 (7.9%)					0.073 <sup>b</sup>
Version 1.5	296 (95.5%)	14 (4.5%)					
		Bilateral Occlusion	Unilateral Occlusion Right	Unilateral Occlusion Left	Both Patent	Equivocal	p-value
<b>Final HSG Result (3 Months or Reevaluation)</b>							
Version 1.0	295 (94.2%)	7 (2.2%)	11 (3.5%)	0 (0.0%)	0 (0.0%)		0.893 <sup>b</sup>
Version 1.5	275 (94.5%)	4 (1.4%)	9 (3.1%)	1 (0.3%)	2 (0.7%)		
		Yes	No				p-value
<b>Pregnancy During First 12 Months</b>							
Version 1.0	2 (0.7%)	293 (99.3%)					0.361 <sup>b</sup>
Version 1.5	4 (1.5%)	271 (98.5%)					

<sup>a</sup> P-value from an analysis of variance, with factor of device version.

<sup>b</sup> P-value from a logistic regression, with factor of device version.

Note: Final HSG was dichotomized to success (bilateral occlusion) and failure (non-bilateral occlusion) for the analysis.

SOURCE: BARMSTRONG\adiana\ease3\i\_pool3 (Jul 5, 2007 09:05)



### 8.9.5 Overall Conclusion of Poolability Analyses

In order to evaluate the appropriateness of pooling the clinical data across sites within and outside the US, several statistical comparisons of intrinsic and extrinsic factors were made. Specifically, comparisons were conducted between US and OUS data in general, in addition to independent comparisons within US sites and within OUS sites. The evaluated parameters included patient demographics (age, height, weight, gravidity, and parity), efficacy outcomes (final HSG results and one year pregnancy prevention rates), and Adiana Delivery Catheter Systems (versions 1.0 and 1.5).

Overall, although some non-homogeneity was seen in the baseline demographic data, with the exception of age, the differences are not clinically meaningful; the impact of age on pregnancy outcome is considered explicitly in the efficacy analyses. Further, a review was conducted of the demographic characteristics (age, gravidity, parity, weight, and height) for the six patients who became pregnant by one-year post-implantation. This evaluation indicated that no trends were observed that would raise a concern about the poolability of the data; see Table 8-38. Thus, the observed variation in baseline demographics is not sufficient to preclude data pooling, but rather lends robustness to the clinical results. Additionally, the differences in demographics indicate that the enrolled population is generally representative of US patients who would potentially use the Adiana System once approved.

**Table 8-38: Baseline Demographics of Patients with Pregnancies During First 12 Months**

<u>Patient ID</u>	<u>Age</u>	<u>Gravidity</u>	<u>Parity</u>	<u>Weight (lbs)</u>	<u>Height (in)</u>
[REDACTED]	26	5	4	99.5	66
[REDACTED]	32	3	3	134	67
[REDACTED]	34	1	1	132	64
[REDACTED]	29	3	2	270	65
[REDACTED]	24	3	3	146.6	66
[REDACTED]	22	3	3	126.6	61

Logistic regression analyses of the final HSG results and the one year pregnancy prevention rates indicate that the US and OUS populations are statistically comparable. Although the analyses revealed one extreme responding center in terms of bilateral occlusion success, the result from this OUS site does not preclude data pooling as it appears that the results do not have an identifiable clinical cause and, therefore, are within the expected range for treatment outcomes.

Finally, analyses of the two utilized Delivery Catheters show comparable results. While differences in procedure times and bilateral placement successes were observed, use of the different catheters did not affect final HSG results or one year



pregnancy prevention outcomes. This analysis therefore confirms the acceptability of pooling data from patients whose procedures used either version of the Delivery Catheter.

In conclusion, the analysis of subject demographics, efficacy outcomes, and Delivery Catheter systems across sites indicates the appropriateness of pooling the data in order to analyze the common treatment effect of the Aiana System.

### 8.10 Analysis of Long-term Follow-up Efficacy

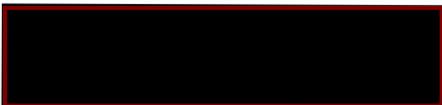
As of March 1, 2007, 16,080 patient months of wearing have been accrued in the EASE clinical Trial (this includes 13,401 months in the US and 2,679 months in the OUS). A preliminary summary of cumulative pregnancy prevention rates is given in Table 8-39. The results shown in this table are incomplete since not all patients currently have reached each of the long-term follow-up endpoints: 512 patients have 18-month results; 321 patients have 24-month results; and 133 patients have 36-month results. Once the datasets are complete (i.e., all possible patients have reached each endpoint), the cumulative results are likely to be different from what appears in the summary table; however, it is not expected that the complete results will substantially alter the interpretation of the long-term follow-up efficacy rates presented herein.

**Table 8-39: Summary of Long-Term Follow-up Efficacy Results**

	US	OUS	Total
<b>Number of Subjects Evaluated for 18-Month Efficacy Endpoint</b>	<b>412</b>	<b>100</b>	<b>512</b>
New Pregnancy at 18 Month Endpoint			
Yes	2	0	2
No	410	100	510
95% CI <sup>1</sup> for % No	(98.0 , 100)	(96.0 , 100)	(97.9 , 100)
<b>Number of Subjects Evaluated for 24-Month Efficacy Endpoint</b>	<b>273</b>	<b>48</b>	<b>321</b>
New Pregnancy at 24 Month Endpoint			
Yes	0	1	1
No	273	47	320
95% CI <sup>1</sup> for % No	(97.5 , 100)	(93.1 , 100)	(97.2 , 100)
<b>Number of Subjects Evaluated for 36-Month Efficacy Endpoint</b>	<b>133</b>	<b>0</b>	<b>133</b>
New Pregnancy at 36 Month Endpoint			
Yes	0	0	0
No	133	0	133
95% CI <sup>1</sup> for % No	(97.5 , 100)	(93.1 , 100)	(97.2 , 100)
<b>Total Patient Months Wearing as of March 1, 2007<sup>2</sup></b>	<b>13401</b>	<b>2679</b>	<b>16080</b>

<sup>1</sup> One-sided confidence interval derived with life-table methods. A total of 570 subjects that relied on the device were included in the analysis.

<sup>2</sup> Patient months of wearing derived using 570 subjects that relied on device.



Two-Year Pregnancy Prevention Rates

An analysis was performed that compared the two-year pregnancy prevention rates for the Adiana System to each of the other methods presented in the CREST study. The two-year failure rates and two-sided 95% confidence interval efficacy ranges for the six methods reported in the CREST study along with the Adiana results (total, US, and OUS) are presented in Table 8-40.

**Table 8-40: CREST Methods: Two-Year Failures**

	Failure per 1000 patients		95% CI <sup>1</sup>
	<u>Point Estimate</u>	<u>95% CI</u>	<u>Efficacy Range</u>
Post Partum Partial Salpingectomy	3.9	0.8 to 7.0	99.30 – 99.92
Unipolar Coagulation	2.3	0.0 to 4.8	99.52 – 100
Bipolar Coagulation	4.6	1.8 to 7.4	99.26 – 99.82
Silicone Rubber Band Application	7.6	4.6 to 10.6	99.54 – 98.94
Interval Partial Salpingectomy	15.1	3.1 to 27.1	97.29 – 99.69
Adiana (US)	14.8	2.9 to 26.7	97.33 – 99.71
Adiana (Total)	18.2	6.2 to 30.2	96.98 – 99.38
Spring Clip Application	23.8	16.1 to 31.5	96.85 – 98.39
Adiana (OUS)	34.0	0.0 to 72.8	92.72 - 100
All Methods	8.4	6.7 to 10.1	98.99 – 99.33
Comparable Methods <sup>2</sup>	10.5	8.6 to 12.5	98.75 – 99.14

<sup>1</sup> Two-sided confidence interval derived with life-table methods.

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

While this comparison is instructive, it is not necessarily the most precise means of comparing methods, especially when the population sizes are substantially different. Therefore, as was done with the one-year efficacy results (see Section 8.8), an analysis of the difference between point estimates and the confidence intervals of that difference was performed for *each* method versus the Adiana method. This analysis was conducted using the total Adiana population as well as the US and OUS populations; the results are presented in Tables 8-41, 8-42, and 8-43, respectively. A detailed explanation of these statistical methods is provided in Appendix 13.1.7. As previously stated, within the sampling error, when the confidence interval range associated with the difference between methods includes zero, the Adiana and CREST failure rates are suggested to be statistically comparable.

Results of the one-year failure rate comparison described in Section 8.8 demonstrated that the total population who utilized the Adiana System is statistically comparable to the population that used each of the CREST methods with the exceptions of post-partum salpingectomy and unipolar coagulation. (Comparisons to either of these methods, however, are not clinically relevant as the Adiana System can not be performed post-partum and the unipolar method is rarely utilized.) The results also showed that the US and OUS Adiana population failure rates (considered independently) are comparable to each of the CREST methods without exception.



In the analysis of two-year pregnancy prevention, the total Adiana population rates are comparable to each of the CREST methods with the exceptions of post-partum salpingectomy, unipolar coagulation, and bipolar coagulation. Despite these exceptions, the Adiana System is statistically comparable to the combined results from all methods as well as the combined results from “comparable methods” reported in the CREST study. (Note that “comparable methods” includes all methods in the CREST study with the exceptions of post-partum partial salpingectomy and unipolar coagulation.) Additionally, it is possible that, once two-year endpoint data have been obtained for all patients, the analysis between the Adiana System and the bipolar coagulation method will show the pregnancy prevention rates to be statistically comparable (as they were for the one-year endpoint). The US component of the total Adiana population demonstrated two-year pregnancy prevention rates that are comparable to all but the unipolar coagulation method; the OUS component showed rates that are comparable to all methods without exception.

**Table 8-41: Differences in Two-Year Failure Rates, Comparison to CREST Study (Adiana Total)**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+14.3	+1.9 to +26.7
Unipolar Coagulation	+15.9	+3.7 to +28.1
Bipolar Coagulation	+13.6	+1.3 to +25.9
Silicone Rubber Band Application	+10.6	-1.8 to +23.0 <sup>1</sup>
Interval Partial Salpingectomy	+3.1	-13.9 to +20.1 <sup>1</sup>
Spring Clip Application	-5.6	-19.8 to +8.6 <sup>1</sup>
All Methods	+9.8	-2.3 to +21.9 <sup>1</sup>
Comparable Methods <sup>2</sup>	+7.7	-4.5 to +19.8 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically



**Table 8-42: Differences in Two-Year Failure Rates, Comparison to CREST Study (Adiana US)**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+10.9	-1.4 to +23.2 <sup>1</sup>
Unipolar Coagulation	+12.5	+0.3 to +24.7
Bipolar Coagulation	+10.2	-2.1 to +22.5 <sup>1</sup>
Silicone Rubber Band Application	+7.2	-5.1 to +19.5 <sup>1</sup>
Interval Partial Salpingectomy	-0.3	-17.2 to +16.6 <sup>1</sup>
Spring Clip Application	-9.0	-23.2 to +5.2 <sup>1</sup>
All Methods	+6.4	-5.6 to +18.4 <sup>1</sup>
Comparable Methods <sup>2</sup>	+4.3	-7.8 to +16.4 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

**Table 8-43: Differences in Two-Year Failure Rates, Comparison to CREST Study (Adiana OUS)**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+30.1	-8.8 to +69.0 <sup>1</sup>
Unipolar Coagulation	+31.7	-7.2 to +70.6 <sup>1</sup>
Bipolar Coagulation	+29.4	-9.5 to +68.3 <sup>1</sup>
Silicone Rubber Band Application	+26.4	-12.5 to +65.3 <sup>1</sup>
Interval Partial Salpingectomy	+18.9	-21.7 to +59.5 <sup>1</sup>
Spring Clip Application	+10.2	-29.4 to +49.8 <sup>1</sup>
All Methods	+25.6	-13.2 to +64.4 <sup>1</sup>
Comparable Methods <sup>2</sup>	+23.5	-15.4 to +62.3 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

Three-Year Pregnancy Prevention Rates

Similar to the analysis conducted using the two-year rates, a comparison was made between the Adiana System three-year pregnancy prevention rates and each of the other methods presented in the CREST study. The three-year rates and two-sided 95% confidence interval efficacy ranges for each of the six CREST-reported methods along with the Adiana System results (total, US, and OUS) are presented in Table 8-44.



**Table 8-44: CREST Methods: Three-Year Failures**

	Failure per 1000 patients		95% CI <sup>1</sup>
	<u>Point Estimate</u>	<u>95% CI</u>	<u>Efficacy Range</u>
Post Partum Partial Salpingectomy	4.6	1.2 to 8.0	99.20 – 99.88
Unipolar Coagulation	2.3	0.0 to 4.8	99.52 – 100
Bipolar Coagulation	6.7	3.2 to 10.2	98.98 – 99.68
Silicone Rubber Band Application	8.3	5.2 to 11.4	98.86 – 99.48
Interval Partial Salpingectomy	15.1	3.1 to 27.1	97.29 – 99.69
Adiana (US)	14.8	2.9 to 26.7	97.33 – 99.71
Adiana (Total)	18.2	6.2 to 30.2	96.98 – 99.38
Spring Clip Application	29.1	20.5 to 37.7	96.23 – 97.95
Adiana (OUS)	34.0	0.0 to 72.8	92.72 - 100
All Methods	9.9	8.0 to 11.8	98.82 – 99.20
Comparable Methods <sup>2</sup>	12.6	10.4 to 14.7	98.53 – 98.96

<sup>1</sup> Two-sided confidence interval derived with life-table methods.

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

As was conducted using the one- and two-year pregnancy prevention rates, an analysis of the difference between point estimates and the confidence intervals of that difference was performed for *each* method versus the Adiana method using the three-year rates. This analysis was performed for the total Adiana population as well as the US and OUS populations; the results are presented in Tables 8-45, 8-46, and 8-47, respectively.

In the analysis of three-year pregnancy prevention, the total Adiana population rates are comparable to each of the CREST methods with the exceptions of post-partum salpingectomy and unipolar coagulation. (Note that while the two-year analysis indicated that the total Adiana population rates are not comparable to the rates for the bipolar coagulation method, the three-year results are comparable [as are the one-year results presented in Section 8.8]. It therefore is likely that, as more patients complete the two-year endpoint, the results for the comparison at that point between the Adiana System and the bipolar coagulation method may change.) The US component of the total Adiana population demonstrated three-year pregnancy prevention rates that are comparable to all but the unipolar coagulation method – this observation also was made for the two-year endpoint analysis; the OUS component showed rates that are comparable to all methods without exception



**Table 8-45: Differences in Three-Year Failure Rates, Comparison to CREST Study (Adiana Total)**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+13.6	+1.1 to +26.1
Unipolar Coagulation	+15.9	+3.7 to +28.1
Bipolar Coagulation	+11.5	-1.0 to +24.0 <sup>1</sup>
Silicone Rubber Band Application	+9.9	-2.5 to +22.3 <sup>1</sup>
Interval Partial Salpingectomy	+3.1	-13.9 to +20.1 <sup>1</sup>
Spring Clip Application	-10.9	-25.6 to +3.8 <sup>1</sup>
All Methods	+8.3	-3.8 to +20.4 <sup>1</sup>
Comparable Methods <sup>2</sup>	+5.6	-6.5 to +17.8 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

**Table 8-46: Differences in Three-Year Failure Rates, Comparison to CREST Study (Adiana US)**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+10.2	-2.2 to +22.6 <sup>1</sup>
Unipolar Coagulation	+12.5	+0.3 to +24.7
Bipolar Coagulation	+8.1	-4.3 to +20.5 <sup>1</sup>
Silicone Rubber Band Application	+6.5	-5.8 to +18.8 <sup>1</sup>
Interval Partial Salpingectomy	-0.3	-17.2 to +16.6 <sup>1</sup>
Spring Clip Application	-14.3	-29.0 to +0.4 <sup>1</sup>
All Methods	+4.9	-7.2 to +17.0 <sup>1</sup>
Comparable Methods <sup>2</sup>	+2.2	-9.9 to +14.3 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically



**Table 8-47: Differences in Three-Year Failure Rates, Comparison to CREST Study (Adiana OUS)**

	<u>Difference in Failures/1000</u>	<u>95% CI Range of Difference</u>
Post Partum Partial Salpingectomy	+29.4	-9.6 to +68.4 <sup>1</sup>
Unipolar Coagulation	+31.7	-7.2 to +70.6 <sup>1</sup>
Bipolar Coagulation	+27.3	-11.7 to +66.3 <sup>1</sup>
Silicone Rubber Band Application	+25.7	-13.2 to +64.6 <sup>1</sup>
Interval Partial Salpingectomy	+18.9	-21.7 to +59.5 <sup>1</sup>
Spring Clip Application	+4.9	-34.8 to +44.6 <sup>1</sup>
All Methods	+24.1	-14.8 to +63.0 <sup>1</sup>
Comparable Methods <sup>2</sup>	+21.4	-17.4 to +60.3 <sup>1</sup>

<sup>1</sup> Lower and Upper Confidence Limits which include zero suggest, that within sampling error, the Adiana and CREST failure rates are statistically comparable

<sup>2</sup> Excludes post-partum salpingectomy, which is non-comparative, and unipolar, which is rarely utilized clinically

To provide a more comprehensive evaluation of the two- and three-year pregnancy prevention rates observed in the EASE trial, a literature review was conducted to obtain rates for methods published since the CREST study was completed. Unfortunately, no further analysis can be conducted, as none of the published literature for comparable sterilization methods contains two- or three-year cumulative pregnancy prevention rates.

**8.10.1 Conclusions of Long-term Follow-up Efficacy Analyses**

Pregnancy prevention rates for the total population of patients who used the Adiana System were reviewed at two, and three years post-procedure. These rates also were compared individually to six other methods reported in the CREST study, as well as to all of the methods combined, and to all of the “comparable methods” combined. (Comparable methods excluded post-partum salpingectomy since the Adiana System can not be used post-partum, and unipolar coagulation since this method is rarely utilized clinically.) In addition to evaluating the prevention rates for the total Adiana population relative to the CREST-reported methods, individual comparisons of the US and OUS Adiana populations to the methods in the CREST study also were conducted.

In the analysis of two-year pregnancy prevention, the total Adiana population rates are comparable to each of the CREST methods with the exceptions of post-partum salpingectomy, unipolar coagulation, and bipolar coagulation. Despite these exceptions, the Adiana System is statistically comparable to the combined results from all methods as well as the combined results from comparable methods reported in the CREST study. Additionally, it is possible that, once two-year endpoint data is obtained for all patients, the analysis between the Adiana System and the bipolar coagulation method will show the pregnancy prevention rates to be statistically comparable. The US component of the total Adiana population demonstrated two-



year pregnancy prevention rates that are comparable to all but the unipolar coagulation method; the OUS component showed rates that are comparable to all methods without exception.

In the analysis of three-year pregnancy prevention, the total Adiana population rates are comparable to each of the CREST methods with the exceptions of post-partum salpingectomy and unipolar coagulation. (Note that while the two-year analysis indicated that the total Adiana population rates are not comparable to the rates for the bipolar coagulation method, the three-year results are comparable [as are the one-year results presented in Section 8.8].) The US component of the total Adiana population demonstrated three-year pregnancy prevention rates that are comparable to all but the unipolar coagulation method; the OUS component showed rates that are comparable to all methods without exception

Overall, the long-term follow-up analyses based on three-year data indicate that the pregnancy prevention rate for users of the Adiana System is comparable to all other methods (combined), to all comparable methods (combined), and, generally, to each of the individual CREST-reported methods with the exceptions of post-partum salpingectomy and unipolar coagulation. At three-years, the rate for the OUS component of the Adiana EASE study was comparable to each of the CREST methods and the US component was comparable to all but the unipolar coagulation method.

### **8.11 Analysis of Secondary Endpoints**

Secondary endpoints to be evaluated in this study include the following:

- Device placement rate
- Patient satisfaction and comfort with the placement procedure
- Patient satisfaction and comfort with device wearing
- Safety of the device placement procedure
- Safety of device wearing

Device placement rates have been presented and discussed previously in Section 8.3. Safety of the device placement procedure is presented in Section 9.2.3.2 and Safety of device wearing is presented in Sections 9.2.3.3 through 9.2.3.6. The remaining secondary endpoints are discussed in the following two sections.

#### **8.11.1 Patient Satisfaction and Comfort with the Placement Procedure**

Patient satisfaction and comfort with the acute device placement procedure was determined by verbal questionnaire immediately following the procedure and at 48 hours post-placement. Patients were asked about their overall satisfaction with the Adiana Procedure, as well as the incidence and severity of specific symptoms (e.g.; cramping, pelvic pain, spotting, bleeding, abnormal discharge, dysuria, nausea/vomiting, shoulder/back pain, and headache). Tables 11.2.6.1.1 through 11.2.6.2.2 and 11.2.9.1.1 through 11.2.9.2.2 summarize these findings for the US, OUS, and Total data groupings for both the ITT and PP populations.

Of the 645 ITT patients in the study, the majority (68%) reported only minor or no discomfort during the Adiana treatment procedure. Approximately 23% of patients reported being somewhat uncomfortable, and 9% reported being very uncomfortable. When asked at which point the discomfort was the most during the procedure, most of the patients who experienced discomfort reported that it was towards the middle of the procedure. Overall, more than 80% of patients reported that any discomfort or pain experienced during the procedure was the same as or less than they expected.

The symptoms of note experienced by patients immediately post-procedure included mild-moderate cramping (49%), mild spotting (42%), and mild bleeding (17%). When asked to rate the amount of pain experienced following the procedure (using a visual analog scale of 0-100, with 0 representing "no pain" and 100 representing "worst pain imaginable"), the mean score reported was 5.9.

By 48 hours following the procedure, 98.4% of ITT patients had returned to normal activities, with the great majority doing so within one day of the treatment procedure. Additionally, 98% of patients reported that they tolerated the procedure well to excellent, with 91% also reporting that discomfort experienced in the first 48 hours following the procedure was the same as or less than expected, or even none at all. Symptoms of note reported during the first 48 hours following the procedure included

mild-moderate cramping (35%) and mild spotting (58.7%). Overall, 96.8% of patients reported being satisfied with their experience at 48 hours following the procedure.

The need for analgesia during the immediate post-procedure time period was also evaluated. Results are presented for the US, OUS, and Total data groupings for both the ITT and PP populations in tables 11.2.7.1.1 through 11.2.7.2.2. Findings show that the Adiana Procedure was well-tolerated with only minimal post-procedural analgesia required by the majority of patients. The only use of intravenous narcotic or NSAID analgesia was immediately post-procedure and prior to discharge, with only 4.8% of patients requiring intravenous narcotic analgesia, and 3.1% receiving intravenous NSAIDs. The remaining use of analgesics were oral medications and consisted of narcotic medications in 17.7% of patients, and non-narcotic medications (NSAIDs, acetaminophen, salicylates) in 41.7% of patients.

When the above procedural and immediate post-procedure results were compared between the ITT and PP populations, no significant differences were noted. However, when comparing the US versus the OUS data for these populations, it was observed that in general the OUS patients reported experiencing less discomfort during and after the procedure; experienced fewer and less severe symptoms following the procedure; and required less analgesia post-procedure than the US patients. These results are believed to be a result of cultural differences.

### **8.11.2 Patient Satisfaction and Comfort with Device Wearing**

Patient satisfaction and comfort with device wearing were determined by verbal questionnaire during periodic follow-up contacts throughout the Waiting and Wearing Periods. Patients were asked about their overall satisfaction with the Adiana Procedure and comfort in wearing the device, as well as the incidence and severity of specific symptoms (e.g.; cramping, pelvic pain, spotting, bleeding, abnormal discharge, dysuria, nausea/vomiting, shoulder/back pain, and headache).

#### Waiting Period

Over the course of the Waiting Period, the majority of ITT patients reported that they did not experience the pre-defined, study-related symptoms, or only had mild severity of some symptoms. The incidence and severity of symptoms that were reported did not differ significantly from baseline rates reported at screening. Additionally, the mean duration of menses and periodicity of menses did not change significantly.

During the three-month Waiting Period, approximately 67.0% of patients (reported on a monthly basis) did not have any complaints of dysmenorrhea. On average, approximately 30% of patients reported having mild to moderate dysmenorrhea each month, and approximately 3% had severe symptoms. This rate appears to be within

the normal expected population based rate.<sup>9</sup> Medications taken for dysmenorrhea during the Waiting Period did not differ significantly in type or usage as those reported being taken for dysmenorrhea at the time of baseline screening (see tables 11.2.12.1.1 through 11.2.12.2.2).

Throughout all evaluation time points during the Waiting Period, 95% or more of the ITT patients consistently reported being satisfied with the Adiana device and greater than 99% of patients reported “good” to “excellent” comfort with wearing of the device. No patients reported wearing of the device as “intolerable”. There were no requests for device removal due to discomfort.

For the Waiting Period, tables 11.2.10.1.1 through 11.2.10.3.2 summarize the one-week findings and tables 11.2.11.1.1 through 11.2.11.3.2 summarize the one-three month findings for the US, OUS, and Total data groupings for the ITT, PP, and SEO populations.

#### Wearing Period

Over the course of the one-year primary Wearing Period, the majority of PP patients continued to report not having any pre-defined, study-related symptoms, or only mild severity of some symptoms. The incidence and severity of symptoms that were reported did not differ significantly from baseline rates reported at screening. Additionally, the mean duration of menses and periodicity of menses varied slightly over the one-year course of wearing; however, they did not change significantly.

During the one-year Wearing Period, approximately 61 to 66% of patients (reported on a quarterly basis) did not have any complaints of dysmenorrhea. On average, approximately 31-35% of patients reported having mild to moderate dysmenorrhea, and approximately 2-4% had severe symptoms. The incidence and severity of dysmenorrhea during the one-year Wearing Period was slightly higher than that seen in the Waiting Period. This was not unexpected, as the start of the Wearing Period is the time point at which women discontinued alternative forms of birth control and began relying on the Adiana System for contraception. In the EASE clinical trial, 48.2% of the intent to treat subjects used hormonal contraception prior to sterilization, thus putting them at risk of recognizing menstrual changes post sterilization, perceived as a change in the menstrual cycle. It is also well described in the literature that menorrhagia (as defined as blood loss of greater than 80mL per cycle) is seldom either measured or a predictor of subsequent treatment.<sup>10, 11, 12, 13</sup>

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<sup>9</sup> Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care patients. *Obstet Gynecol.* 1996;87(1):55-58.

<sup>10</sup> Pitkin, J. Dysfunctional Uterine Bleeding. *BMJ* 2007;334:1110-1111

<sup>11</sup> Warner PE, Critchley HO, Lumbsden MA, et al. *Am J Obstet Gynecol.* 2004; 190(5): 1224-9

<sup>12</sup> Gentile GP, Kaufman SC, Helbig DW. Is there any evidence for a post-tubal sterilization syndrome? *Fertil Steril* 1998;69:179-86.

<sup>13</sup> Rulin MC, Davidson AR, Philliber SG, Graves WL, Cushman LF. Long-term effect of tubal sterilization on menstrual indices and pelvic pain. *Obstet Gynecol* 1993;82:118-21.

Likewise, the increase in use of medication for treatment of dysmenorrhea observed at the three-month Wearing Period follow-up is also most likely attributable to the cessation of hormonal birth control and the resulting increase in dysmenorrhea. As the Wearing Period progressed, use of medications for dysmenorrhea subsided to rates similar to or below those seen at baseline screening (see tables 11.2.15.1.1 and 11.2.15.1.2).

Over the course of the long-term follow-up Wearing Period (18, 24, and 36-months), a slightly increasing percentage of patients have reported changes to the duration of menses or length of their cycle at each follow-up time point. The types of changes reported have varied, with no obvious trends observed; thus, these are believed to be typical menstrual changes similar to those seen in the general population.<sup>14 15</sup>

During the long-term follow-up in the Wearing Period, more than 99% of PP patients remain satisfied with the Adiana device and greater than 99% of patients continue to report “good” to “excellent” comfort with wearing of the device. No patients reported wearing of the device as “intolerable”. There were no requests for device removal due to discomfort.

Tables 11.2.14.1.1 through 11.2.16.1.2 summarize the one-year primary Wearing Period findings, and tables 11.2.19.1.1 through 11.2.19.2.2 summarize the long-term (18, 24, and 36-month) findings for the US, OUS, and Total data groupings for the PP, and SEO populations.

When the above Waiting and Wearing Period results were compared between the ITT, PP, and SEO populations as appropriate, no significant differences were noted. Additionally, when comparing the US versus the OUS data for these populations, it was observed that the US patients had slightly different trends than the OUS patients in the incidence and severity of symptoms reported; however, none of the differences were significant.

In summary, the overwhelming majority of patients reporting satisfaction with the Adiana Procedure and comfort of wearing the devices throughout long-term follow-up, as well as the low incidence of reported symptoms and the mild severity of the majority of symptoms reported indicate that the Adiana Procedure and the wearing of the devices are well-tolerated and have high patient approval ratings.

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<sup>14</sup> Treloar A, Boynton R, Behn B, Brown B. Variation of the human menstrual cycle through reproductive life. *Int J Fertil* 1967;12:77-126.

<sup>15</sup> Ferrell RJ, Rodriguez KA, Gorrindo G, Holman, T et al. Monitoring reproductive aging in a 5-year prospective study: aggregate and individual changes in steroid hormones and menstrual cycle lengths with age.[see comment][erratum appears in *Menopause*. 2006 Jan-Feb;13(1):156; PMID: 16607112].

### 8.12 Efficacy Conclusions

Of the 770 patients enrolled in the EASE trial, 645 had treatment attempted (ITT population) and 604 had placement success on the initial treatment attempt (93.6%). Eight patients subsequently underwent a second treatment procedure and seven of the patients were treated successfully. Thus, 611 of the 645 patients in whom treatment was attempted achieved bilateral placement success (94.7%). Finally, 553 patients were successfully treated and evaluated for the one-year primary endpoint.

The median age of the 553 subjects successfully treated and evaluated at one year was 32 years. The subjects predominantly were Caucasian (76.1%) or Hispanic (14.6%), had gravidity greater than two (60.2%), and parity of two (47.4%) or more than two (34.7%). Additionally, the subjects had a mean weight of 161.0 lbs and a height of 64.6 inches. Subjects were enrolled across 14 sites in the US and 2 sites outside the US.

In this study, 652 device deployment procedures were attempted and 616 achieved acute procedural success (94.5%), which was defined as successful bilateral tubal access followed by successful bilateral RF treatment and Matrix placement. In 120 of the 652 procedures, a pre-access treatment protocol was utilized and acute procedural success rates were slightly better – but not statistically different – for the procedures performed with rather than without the pre-access treatment protocol (95.8% with versus 94.2% without,  $p = 0.66$ ). The average procedure time was approximately 11 minutes, with the shortest placement time being 4 minutes and 36 seconds. Procedures in which the pre-access treatment procedure was performed took an average of approximately 4 minutes longer than procedures in which pre-access was not performed. The majority of patients in the trial (53.0%) required only minimal sedation or analgesia, and no patients required intubation or the use of general anesthesia.

Of the 604 patients who had successful bilateral device placement and were evaluated for occlusion by HSG, 570 patients (94.4%) demonstrated bilateral occlusion (551 were bilaterally occluded at the three month evaluation and 19 were bilaterally occluded at the repeat six-month evaluation). 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.

The primary efficacy endpoint for the trial was the pregnancy prevention rate after one year of reliance on the Adiana System. This evaluation was defined statistically as a one-year pregnancy prevention rate greater than 95% at a one-sided 95% confidence level. This primary endpoint was evaluated for the Per Protocol population (i.e., all patients who underwent successful bilateral treatment, had demonstrated tubal occlusion [by HSG] at the end of the Waiting Period, and were evaluated for the one year primary endpoint).

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.

The pregnancy prevention rates observed for the total population of Adiana System users were compared to six methods described within the CREST study as well as to the combined rate from all six methods and the combined rate for the four “comparable methods”. (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.) This analysis indicated that, with the exceptions of post-partum salpingectomy and unipolar coagulation, there are no statistically significant differences between the Adiana System’s one-year prevention rates and any of the rates for the individual CREST-reported methods. After two years, the total Adiana population rates are comparable to each of the CREST methods with the exceptions of post-partum salpingectomy, unipolar coagulation, and bipolar coagulation. Additionally, after three years, the total Adiana population rates are comparable to each of the CREST methods with the exceptions of post-partum salpingectomy and unipolar coagulation. Finally, the Adiana System is statistically comparable at one, two, and three years to the combined results from all methods as well as to the combined results from all comparable methods reported in the CREST study.

Separate from the comparison to the CREST study, the Adiana System was compared to the Filshie Clip and the Essure method; both of these techniques were reported after the publication of the CREST study. This analysis showed that, by using a similar approach to the efficacy claim made by Essure, the two methods differ in one-year pregnancy prevention rates by less than one percentage point and therefore, generally are similar. In regard to the Filshie Clip, the analysis indicated the Adiana System is statistically comparable.

While age is an acknowledged factor in fertility, 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. Additionally, the age-corrected failure rate is not substantially greater than the un-adjusted rate, further indicating that while age is a factor, it does not substantially affect the pregnancy prevention outcomes demonstrated in this study.

For the secondary variables of patient satisfaction and comfort with the placement procedure and device wearing, patients overwhelmingly reported satisfaction with the Adiana System, from the initial placement procedure throughout long-term follow-up, and more than 16,000 patient-months of device wearing. Patients reported that pain experienced after discharge from the procedure was minimal and was treated with oral

analgesic medications. The low incidence of reported symptoms, along with the mild severity of the majority of reported symptoms, indicates that the Aiana Procedure and the wearing of the devices are well-tolerated and accepted by patients.

In conclusion, the results of this study demonstrate that the Aiana System is effective for pregnancy prevention and is statistically comparable to the majority of methods currently available. Further, the required treatment procedure occurs in a brief period of time and with a high degree of placement success. Patients reported few symptoms associated with device wearing and found the placement procedure to be well-tolerated.



**ADDITIONAL FDA REQUESTED EFFICACY TABLE  
PENDING  
TO BE INSERTED HERE**

## **V. D. 6. SAFETY RESULTS**

## 9. SAFETY EVALUATION

### 9.1 Extent of Exposure

All 645 patients in whom device placement was attempted (Intent-to-Treat population) are included in the safety analyses. Of the 645 ITT patients, 625 had at least one device implanted (a total of 1243 devices were implanted in 625 patients). The total device exposure for this patient population is equivalent to over 16,000 patient-months. The 625 patients who received implants are evaluated for safety at all follow-up time points for the duration of the clinical study (except for those patients who have voluntarily withdrawn or have been terminated from the study). The 20 patients who did not have any devices implanted were followed per protocol for safety data for either one week (no RF delivered and no devices placed) or three months (RF delivered, but no devices placed) post-procedure and then discontinued from the study.

All adverse events and other events related to safety reported from the time of enrollment until March 1, 2007, are included in the safety analyses.

### 9.2 Adverse Events

#### 9.2.1 Brief Summary of Adverse Events

Of the 645 patients in the Intent-to-Treat population, 642 reported one or more adverse events. These 642 patients reported a total of 15,119 adverse events as of March 1, 2007.

#### Severity

Of the total adverse events reported, 49.7% were classified as mild severity, 38.7% as moderate, and 11.6% as severe. It is important to note that classification of severity was made on an individual basis by each investigative site with no standardized reporting format utilized between sites. Thus, subsequent discussions of adverse events will focus on the frequency and types of interventions required and mean durations of reported events in order to standardize the presentation of adverse event severity, outcome and resolution.

#### Device or Procedure Relatedness

Of the total adverse events reported, 68.2% were not related to the device or treatment procedure and 5.7% were reported as having unknown device relatedness. The remaining 26.1% of events had some degree of device or procedure relatedness reported.

Twenty-one percent (21.0%) of adverse events were reported as being *possibly* device or procedure related. Of these, 25.4% required some form of medical intervention. One serious adverse event, determined to be possibly device-related by the DSMB, required in-patient surgery for resection of an endometrial polyp (Patient ID: [REDACTED]). Two additional adverse events required minor surgical, out-patient procedures:

Patient ID: [REDACTED] underwent a out-patient cone biopsy for CIN III which was negative; Patient ID: [REDACTED] underwent out-patient resection of an endometrial polyp.). Additionally, 25.3% of the events required treatment with medication. None of the remaining adverse events reported as *possibly* device or procedure related required medication, surgery or hospitalization (74.6%). These adverse events reported as *possibly* related had a mean duration of 4.8 days.

Only 3.9% of adverse events were reported as being *probably* related, and 1.2% as *definitely* related (5.1% total). Of these 5.1% of events that were reported as being *probably* or *definitely* related, 24.6% were treated with medication only (including two serious adverse events). One serious adverse event determined to be device-related by the DSMB (an ectopic pregnancy) required surgery; however, none of the remaining events reported as *probably* or *definitely* device or procedure related required medication, surgical intervention or hospitalization. Mean duration of resolution of the *probably* or *definitely* related events was 3.4 days.

The above adverse event information is summarized by US, OUS and Total populations in Table 11.3.1. Additionally, these data are also summarized by investigative site in Table 11.3.1.2.

#### Serious Adverse Events

There have been no deaths reported in the EASE clinical trial as well as no unanticipated, device-related serious adverse events. A total of 49 serious adverse events were reported in 41 patients. One of these events was related to the treatment procedure (hyponatremia) and three are considered as having some degree of relatedness to the device (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, and one ectopic pregnancy with Methotrexate), and the remaining two required surgical intervention (an ectopic pregnancy salpingectomy and the endometrial polyp resection). All serious adverse events are presented by patient indicating the type of event, time of onset following treatment, outcome, and device relatedness in Table 11.3.6. These events are also presented in narrative detail in section 9.3.2 and discussed in section 9.3.3.

### 9.2.3 Analysis of Adverse Events

#### 9.2.3.1 Pre-Procedure

Adverse events were reported from the time of patient enrollment into the study. Because of the *treatment window* scheduling requirement (refer to section 6.4.1), there was occasionally a delay between the time of enrollment and the device placement procedure. A total of 32 events in 29 patients were recorded during the pre-procedure period and are summarized in table 11.3.2.1

None of these events were of a nature to prevent the patient from undergoing the treatment procedure or to adversely impact the outcome of the treatment procedure or study follow-up. Fourteen (14) of these 32 events were resolved prior to the treatment procedure, and the remaining 18 were considered minor enough in nature so as to not contra-indicate the procedure and were resolved during follow-up.

There were two reports of serious adverse events during the pre-procedure time period. One involved a patient who was hospitalized for depression and a renal disorder (Patient ID: [REDACTED]). The event was resolved and the patient was successfully treated with the Adiana System. The other event involved a patient who was hospitalized for loss of consciousness and cardiac arrest following a drug overdose (Patient ID: [REDACTED]). The patient recovered from the event, but failed to complete the study screening requirements and was therefore not treated with the Adiana System. These events are detailed in Section 9.3.2.

### 9.2.3.2 Procedure day

Tables 11.3.2.2 and 11.3.4.1 summarize adverse events reported on the day of the treatment procedure. On the day of treatment, 624 patients reported a total of 1832 adverse events. The majority of these events were anticipated and minor in nature, and consisted of cramping – not related to menses (25%), spotting (24%), post-procedural bleeding (10%), pelvic pain (9%), back pain (6%), nausea (6%), and headache (4%). These rates are comparable to those reported in the published literature.<sup>16</sup> Of these events, 73.4% were reported as having some degree of device or procedure relatedness. However, none of these events required significant intervention other than medication (27.8% were treated with medication). All these events were resolved within a mean duration of 3.0 days, with the exception of back pain which had a mean duration of 9.0 days. Post-operative back pain following gynecologic procedures performed in the both the supine and the lithotomy position is reported in the literature due to flattening of the lumbar lordosis and added tension on the lumbosacral nerve roots. The duration of discomfort reported in the EASE trial does not appear to be greater than reported in the literature.<sup>17, 18</sup>

There were no unanticipated serious adverse events or device-related serious adverse events on the day of the procedure. There was one report of a serious adverse event related to the procedure. This was a case of hyponatremia in a patient, resulting from fluid overload during the procedure (Patient ID: [REDACTED]). 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. This event is discussed in detail in section 9.3.3.

There was one report of a minor adverse event resulting from a procedural error. The MedDRA coding classifies this event as a “medical device complication”; however, it is important to note that this event was not due to a complication with the Delivery Catheter itself, but rather the catheter introducer. (*Note; the introducer is an accessory supplied with the Adiana Delivery Catheter which protects the catheter from damage during hysteroscope insertion*). In this case, the physician did not remove the introducer after the Delivery Catheter was inserted. During the procedure the

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<sup>16</sup> <http://www.emedicine.com/med/topic3314.htm>

<sup>17</sup> Clarke AM, Stillwell S, Paterson ME, Getty CJ. Role of the surgical position in the development of postoperative low back pain. *J Spinal Disord.* 1993 Jun;6(3): 238-41

<sup>18</sup> Hirabayashi Y, Igarashi T, Suzuki H, Fukuda H, et al. Mechanical effects of leg position on vertebral structures examined by magnetic resonance imaging. *Reg Anesth Pain Med.* 2002; 27(4):429-32.

introducer was advanced into the hysteroscope such that the tip of the introducer was past the pivot valve. When the Delivery Catheter was removed, the physician closed the pivot valve, and the introducer was “sheared off”. The tip of the introducer was 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 (Patient ID: [REDACTED]). This event is discussed in detail in section 9.3.3.

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.

#### **9.2.3.3 One-Two Days Post-Procedure**

Events occurring within 48 hours following the treatment procedure are summarized in Tables 11.3.2.3 and 11.3.4.2. Fifty-two percent (52%) of the ITT population reported adverse events in this time period. These patients reported a total of 588 events which consisted primarily of anticipated and minor events such as spotting (20%), headache (14%), cramping – not related to menses (13%), pelvic pain (10%), back pain (8%), post-procedural bleeding (6%), and vaginal discharge (5%).

Of the commonly reported events noted above, 60.8% were reported as having some degree of device or procedure relatedness. However, none of these events required intervention other than medication (24.8% required treatment with medication). All these events were resolved within a mean duration of 2.4 days.

There were no serious adverse events, or other significant adverse events, reported in the 48-hour time period following the procedure.

#### **9.2.3.4 Three-Seven Days Post-Procedure**

Events occurring within 3-7 days following the procedure are summarized in tables 11.3.2.4 and 11.3.4.3. A total of 777 events were reported by 58% of the ITT patients. As was seen in the 48-hour post procedure time period, the vast majority of events reported in the remainder of the one-week post-procedure period continued to be complaints that were anticipated and minor in nature.

The incidence of headaches, pelvic pain, and back pain remained relatively the same at 14%, 10%, and 8% respectively; however, the other common complaints decreased: spotting (12%), cramping – not related to menses (9%),

and vaginal bleeding (4%). The incidence of vaginal discharge, as described by the patient increased slightly to (14%) as postoperative bleeding/spotting decreased.

Of the commonly reported events noted above, 47.9% were reported as having some degree of device or procedure relatedness. However, none of these events required intervention other than medication (23.7% were treated with medication). All these events were resolved within a mean duration of 2.6 days.

There was one serious adverse event reported within the 3-7 day post-procedure time period, which involved patient hospitalization for the treatment of gastroesophageal reflux disease (Patient ID: [REDACTED]). The investigative site reported device-procedural relatedness as “unknown” principally due to the proximity of this event to the treatment procedure, and the DSMB concurred with this determination. This event is discussed in detail in section 9.3.3.

There were no other significant adverse events reported in the one-week time period following the procedure. Additionally, there were no reported tubal infections or abscesses and no reports of excessive pain or bleeding.

#### **9.2.3.5 Eight Days Post-Procedure through Waiting Period**

Events occurring from the one-week post-procedure time point through the three-month Waiting Period follow-up are summarized in tables 11.3.2.5 and 11.3.4.4. During the Waiting Period, 593 patients reported a total of 5737 adverse events. The majority of these events were minor and anticipated in nature.

The most frequently reported events during the Waiting Period were dysmenorrhea (23%) and headache (17%). Although approximately 31% of the complaints of dysmenorrhea were reported to have some degree of device-relatedness this rate appears to be within the normal expected population based rate.<sup>19</sup> The mean duration of all dysmenorrhea complaints was only 2.4 days. Only 3% of the complaints of headache were considered device related and average duration of these events was 2.1 days. The rate and duration of these events also appears to be within the normal range.<sup>20</sup>

Less commonly reported complaints included back pain (9%), pelvic pain (6%), vaginal discharge (6%), cramping – not related to menses (4%), spotting

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<sup>19</sup> Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care patients. *Obstet Gynecol.* 1996;87(1):55-58

<sup>20</sup> Russell MB, Levi N, Saltyte-Benth J, Fenger K. Tension-type headache in adolescents and adults: a population based study of 33,764 twins. *European J Epidemiology.* 2006; 21(2):153-60,

(4%), and vaginal bleeding (3%). Of these specified events, 32.4% were reported as having some degree of device relatedness and 15.3% required treatment with medication. [REDACTED]

[REDACTED] The DSMB concluded that the event's device-procedural relatedness should be considered as "unknown" due to the proximity of this event to the treatment procedure. None of the remaining events required medication, surgery, or hospitalization (84.7%). These events had a mean duration of 3.7 days.

The low incidence of amenorrhea, menorrhagia, delayed menses, irregular menstruation, and polymenorrhea complaints reported during this time period (each  $\leq 1\%$ ) support the conclusion that the Adiana treatment procedure is not particularly disruptive of a woman's normal menstrual cycle. It is important to note that during the three-month Waiting Period, women must continue to rely on alternative forms of birth control.

Three serious adverse events were reported during the Waiting Period. As noted above, one patient underwent a diagnostic laparoscopy for persistent pelvic pain 89 days following the Adiana treatment procedure (Patient ID: [REDACTED])

[REDACTED] The DSMB concluded that the event's device-procedural relatedness should be considered as "unknown" due to the proximity of this event to the treatment procedure. The other two events were not device or procedure related and [REDACTED]

[REDACTED] These events are detailed in section 9.3.2 and discussed in section 9.3.3.

There were no other significant adverse events reported during the Waiting Period.

#### **9.2.3.6 Wearing Period**

Events occurring during the Wearing Period follow-up (or >90 days post procedure and onwards) are summarized in tables 11.3.2.6 and 11.3.4.5. As of March 1, 2007, 563 patients had reported a total of 6001 adverse events.

Most of the less commonly reported complaints that were noted in the Waiting Period decreased slightly in incidence during the Wearing Period: headache (12%), back pain (6%), pelvic pain (5%), vaginal discharge (4%), and cramping – not related to menses (2%). Of these events, only 13.6% were reported as having some degree of device relatedness. Approximately 50% of the events specified above were treated with medication. There were four reports of pelvic pain that required further intervention. One of these was a

serious adverse event that involved patient hospitalization for diagnostic evaluation (Patient ID: [REDACTED]). The other three were adverse events that required an outpatient surgical procedure (Patient ID: [REDACTED]). All of the events reported for the categories above resolved in a mean duration of 6.5 days.

Not surprisingly, the incidence of menses or bleeding-related adverse events increased during the Wearing Period: dysmenorrhea (26%), vaginal bleeding (5%), and menorrhagia (3%), and spotting (4%). Of these events, 27.6% were reported as having some degree of device relatedness and 26.8% required some form of medical intervention. Approximately 26% of these events were treated with medication. Additionally, surgical interventions were performed in thirteen patients 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. (Note: There have been a total of ten hysterectomy procedures performed during the follow-up period to date. These events are detailed in section 9.4.2). Adverse events related to menses or bleeding during the Wearing Period were resolved in a mean duration of 4.6 days.

The increase in menses and bleeding-related adverse events was not unexpected, as the start of the Wearing Period was the point at which women stopped using alternative birth control and began relying on the Adiana System for pregnancy prevention. In the EASE clinical trial, 48.2% of the intent to treat subjects used hormonal contraception prior to sterilization, thus putting them at risk of recognizing menstrual changes post sterilization, perceived as a change in the menstrual cycle. It is also well described in the literature that menorrhagia (as defined as blood loss of greater than 80mL per cycle) is seldom either measured or a predictor of subsequent treatment.<sup>21, 22, 23, 24</sup>

There were two serious adverse events reported during the Wearing Period that were determined to be related to the Adiana device. These both involved ectopic pregnancies that occurred in women relying on the Adiana System for pregnancy prevention (Patient ID: [REDACTED]). One woman was treated conservatively with methotrexate and subsequent salpingectomy at the time of her laparoscopic tubal sterilization. The second woman underwent

<sup>21</sup> Pitkin, J. Dysfunctional Uterine Bleeding. *BMJ* 2007;334:1110-1111

<sup>22</sup> Warner PE, Critchley HO, Lumsden MA, et al. *Am J Obstet Gynecol.* 2004; 190(5): 1224-9

<sup>23</sup> Gentile GP, Kaufman SC, Helbig DW. Is there any evidence for a post-tubal sterilization syndrome? *Fertil Steril* 1998;69:179-86.

<sup>24</sup> Rulin MC, Davidson AR, Philliber SG, Graves WL, Cushman LF. Long-term effect of tubal sterilization on menstrual indices and pelvic pain. *Obstet Gynecol* 1993;82:118-21.

laparoscopic treatment and surgical tubal sterilization. Both patients continue to be followed for safety endpoints and neither have had any further medical sequelae resulting from the ectopic pregnancies (see section 9.3.3 for further discussion).

An additional serious adverse event was reported during the Wearing Period which was determined to be *possibly* related to the Adiana device by the DSMB. This involved a patient who underwent elective hysteroscopy and polypectomy approximately 18 months following the treatment procedure (Patient ID: [REDACTED]). The DSMB agreed that the polyp had probably been present at the time of the Adiana Procedure but not identified; however, without definitive evidence they felt the event should be classified as “possibly device related”. The patient continues to rely on the Adiana System for contraception and remains satisfied with her contraceptive choice (see section 9.3.3 for further discussion).

The remaining serious adverse events that have been reported during the Wearing period have all been determined to be unrelated to the Adiana device or procedure by the DSMB. These events are presented in detail in section 9.3.2 and discussed in section 9.3.3.

It should be noted that throughout the course of the Waiting and Wearing Period follow-up, there have continued to be 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 implant, no signs of infection related to the implants, and no need for any implant removals.

#### **9.2.4 Listing of Adverse Events by Patient**

A complete listing of the unique adverse events as reported by the patient can be found in Appendix 13.2.6

### **9.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events**

#### **9.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events**

##### **9.3.1.1 Deaths**

There have been no deaths reported in the 770 patients enrolled in this study.

##### **9.3.1.2 Other Serious Adverse Events**

A listing of serious adverse events presented by patient and documenting outcome and final relationship to device or procedure conclusions is located in Table 11.3.6. Narratives detailing these events are presented in Section 9.3.2., and detailed individual case reports for each patient can be found in Appendix 13.3.3.

##### **9.3.1.3 Other Significant Adverse Events**

One additional significant adverse event is described for a patient who experienced a minor complication resulting from the treatment procedure (Patient ID [REDACTED]). A narrative describing this event is included in Section 9.3.2., and a detailed case report for this patient is presented in Appendix 13.3.3.

#### **9.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain other Significant Adverse Events**

As of March 1, 2007, there have been no deaths reported in the EASE clinical trial as well as no unanticipated, device-related serious adverse events. A total of 49 serious adverse events (SAE) have been reported in 41 separate patients. Additionally, there was one other significant adverse event which occurred during a treatment procedure that is detailed in the following section.

The Device Safety Monitoring Board (DSMB) reviewed all SAE's and made final conclusion regarding the relationship of each event to the Adiana treatment procedure and/or the use of the device. Of the 49 reported SAE's, one was related to the treatment procedure and three events were determined to have some degree of relationship to the Adiana device. Table 9-1 below summarizes the final procedure or device relatedness conclusions of the DSMB. A narrative of each event along with final conclusion is provided below. Additionally, detailed case reports for each of these patients can be found in Appendix 13.3.3.

**Table 9-1: Summary of Serious Adverse Event Procedure or Device Relatedness**

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<u>Relationship to Procedure of Device</u>	<u>Number of Events</u>
Procedure Related	1
Definitely Device Related	2
Possibly Device Related	1
Unknown if Device Related	2
Not Device Related	43

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**Procedure Related Events**

Of the 49 SAEs reported, one event was determined to be related to the treatment procedure. The patient experienced post-procedure hyponatremia as a result of the treatment procedure.

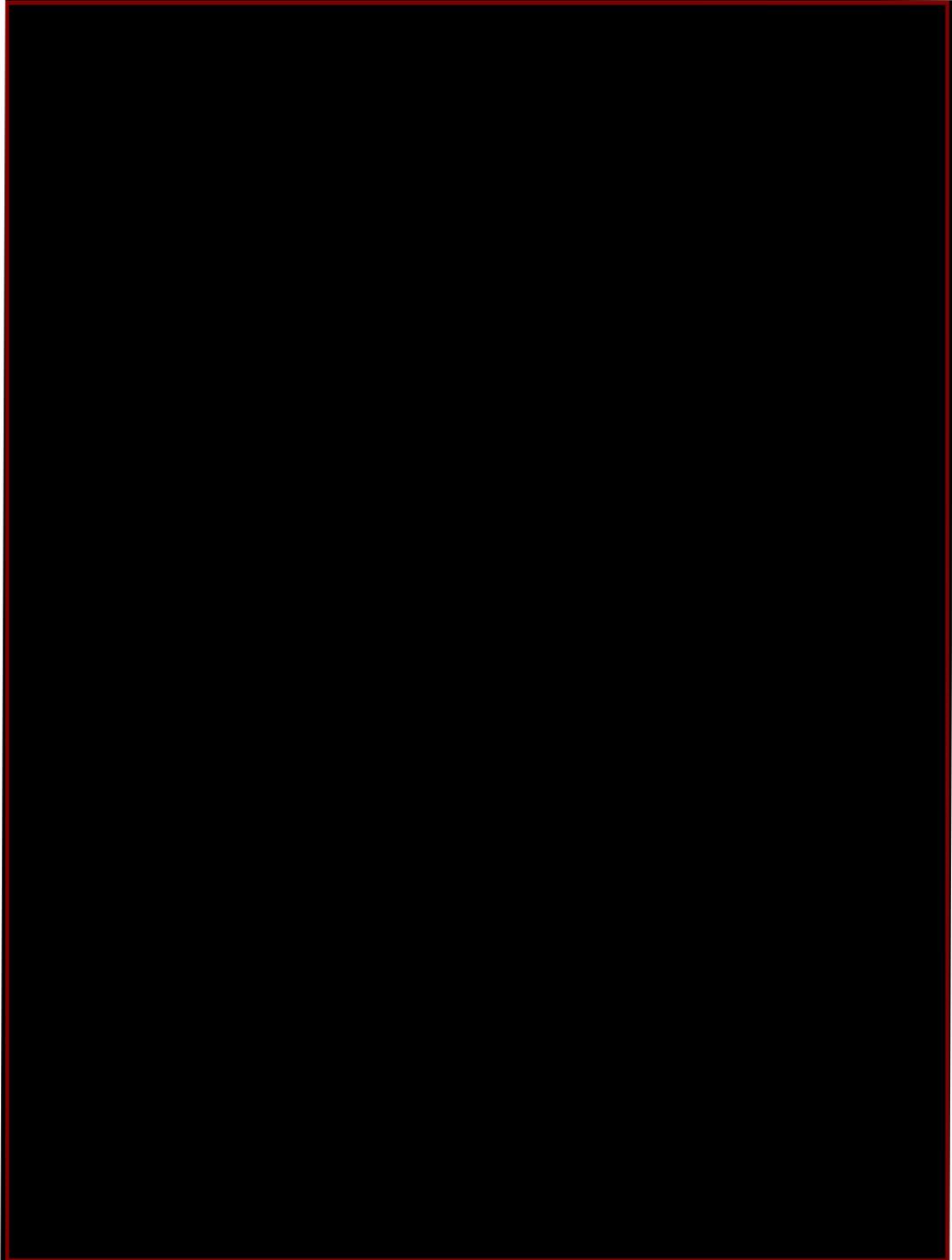
**Case Discussion:**



**Device Related Events**

Two of the 49 SAE's were ectopic pregnancies determined to be related to the use of the Adiana device.

**Case Discussions:**

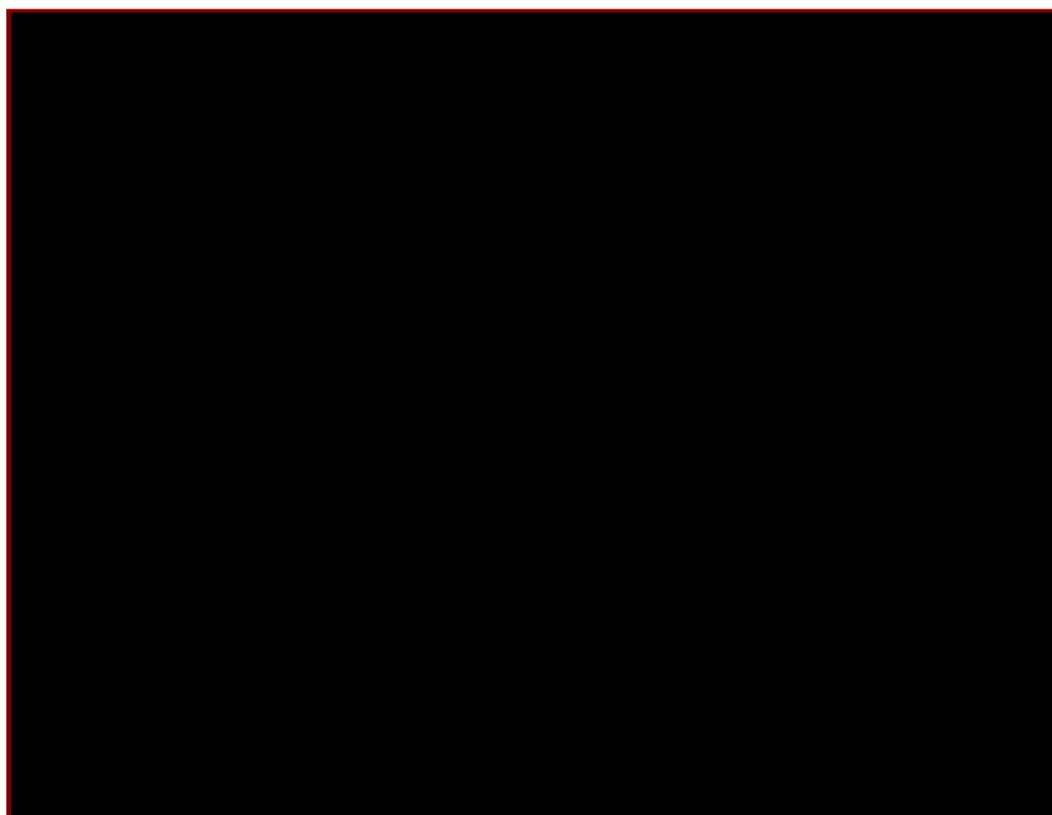


Final conclusion of this event was concurred by the sponsor and the DSMB.

**Possibly Device Related Events**

One case of persistent dysmenorrhea was evaluated and treated with polypectomy at 17 months post procedure. The investigator considered this event unrelated to the Aiana device. The DSMB agreed that the event was likely unrelated and that the polyp had probably been present at the time of the Aiana Procedure but not identified; however, without definitive evidence they felt the event should be classified as "possibly device related".

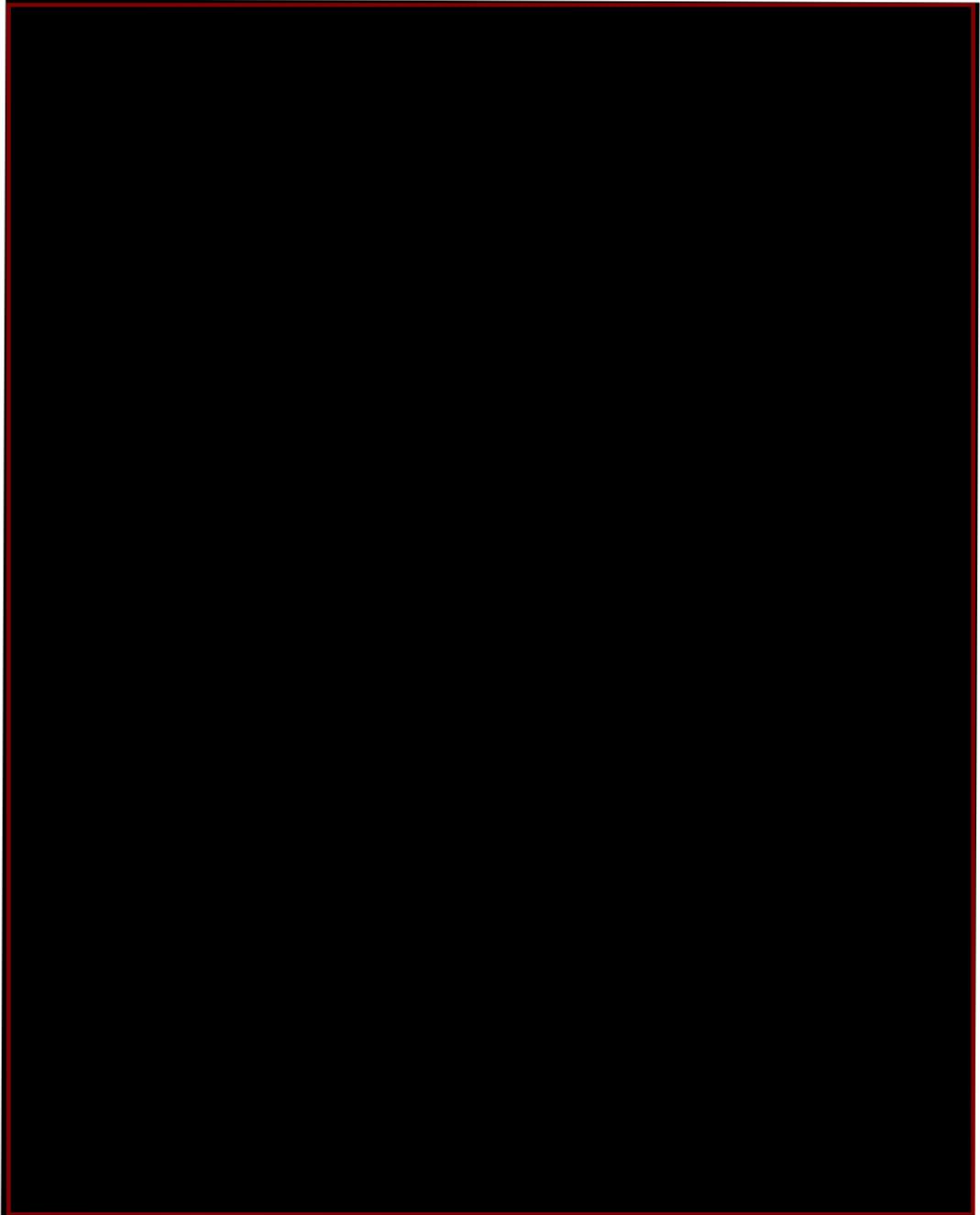
**Case Discussion:**



**Events Unknown if Related to Device or Procedure**

Two events occurred in patients within close proximity to the Aiana Procedure and were therefore classified as “unknown if related” by the DSMB. These included one case of persistent pelvic pain evaluated by laparoscopy 3 months post procedure and a patient hospitalization four days post procedure with GERD.

**Case Discussions:**





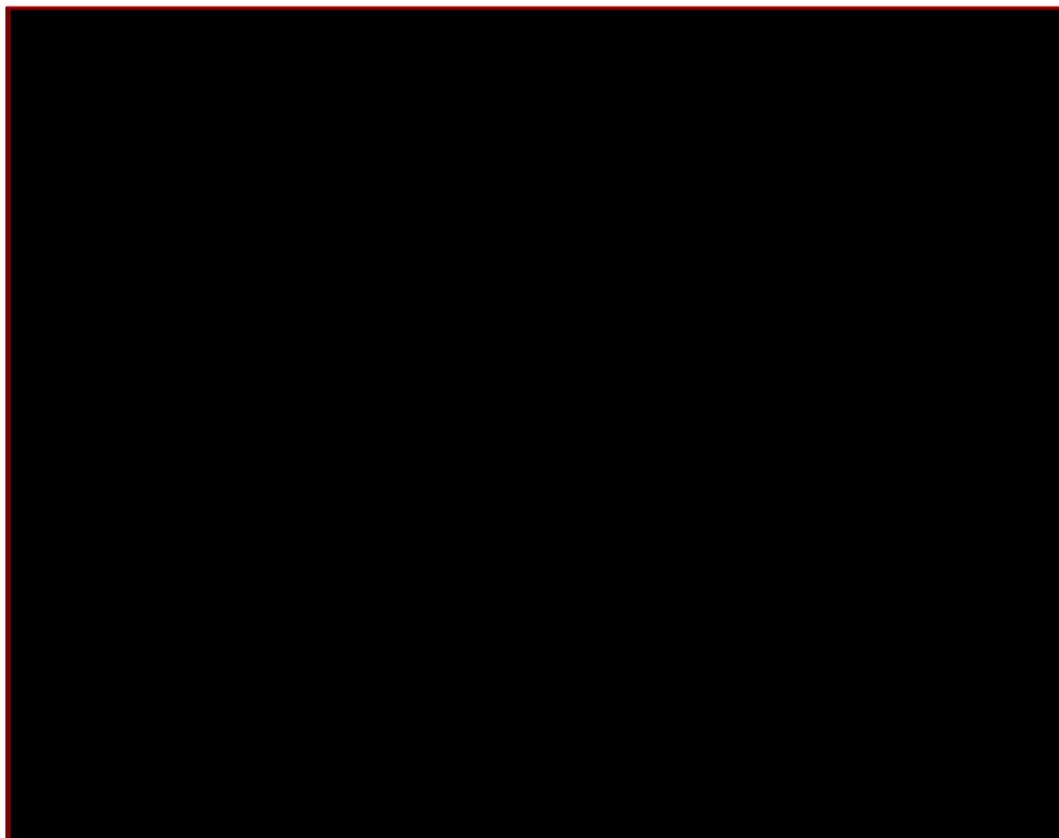
**Unrelated Events**

There are a total of 43 events that were determined to be unrelated to the device or treatment procedure (note: one of these events was described above for patient [REDACTED]). The remaining 42 events are presented in two categories: patients with events that occurred secondary to menorrhagia or dysmenorrhea are presented first, followed by the remaining patients with non-specific isolated events.

Ten patients reported SAE's that occurred secondary to menorrhagia or dysmenorrhea. One of these events was discussed above as a "possibly device related" event (patient [REDACTED]). The remaining nine patients who reported menorrhagia-related SAE's are described below based on the time period in which the event occurred following the treatment procedure.

- One patient experienced a menorrhagia-related SAE that occurred within one year of the Adiana Procedure.

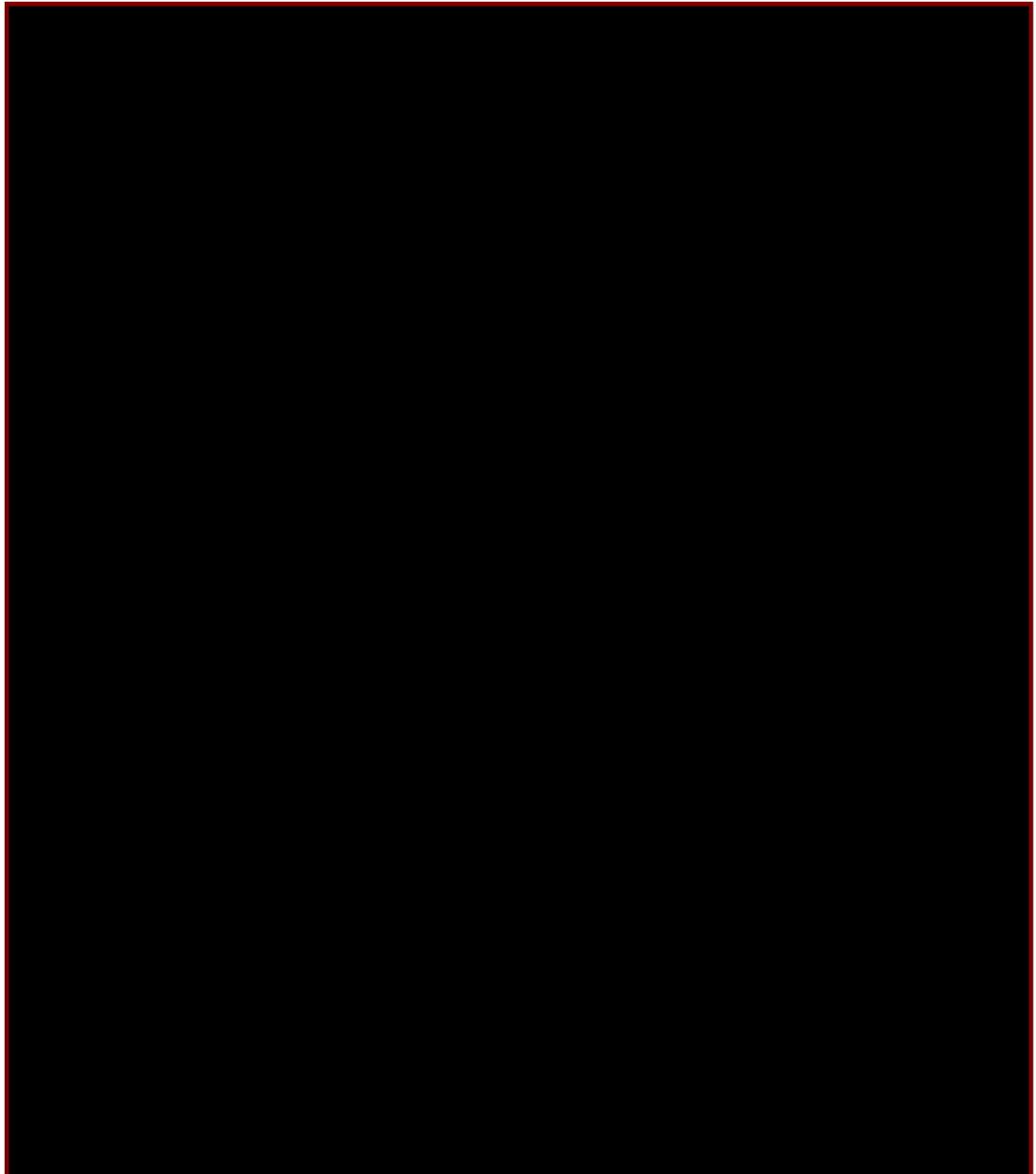
**Case Discussion:**





- Three patients experienced a menorrhagia-related SAE that occurred within the second year following the Adiana Procedure.

**Case Discussions:**



Conclusion

This event was reported by the investigator as unrelated to the procedure. Final conclusion of this event was concurred by the sponsor and the DSMB.



- Two patients experienced a menorrhagia-related SAE that occurred within the third year following the Adiana Procedure.

**Case Discussions:**

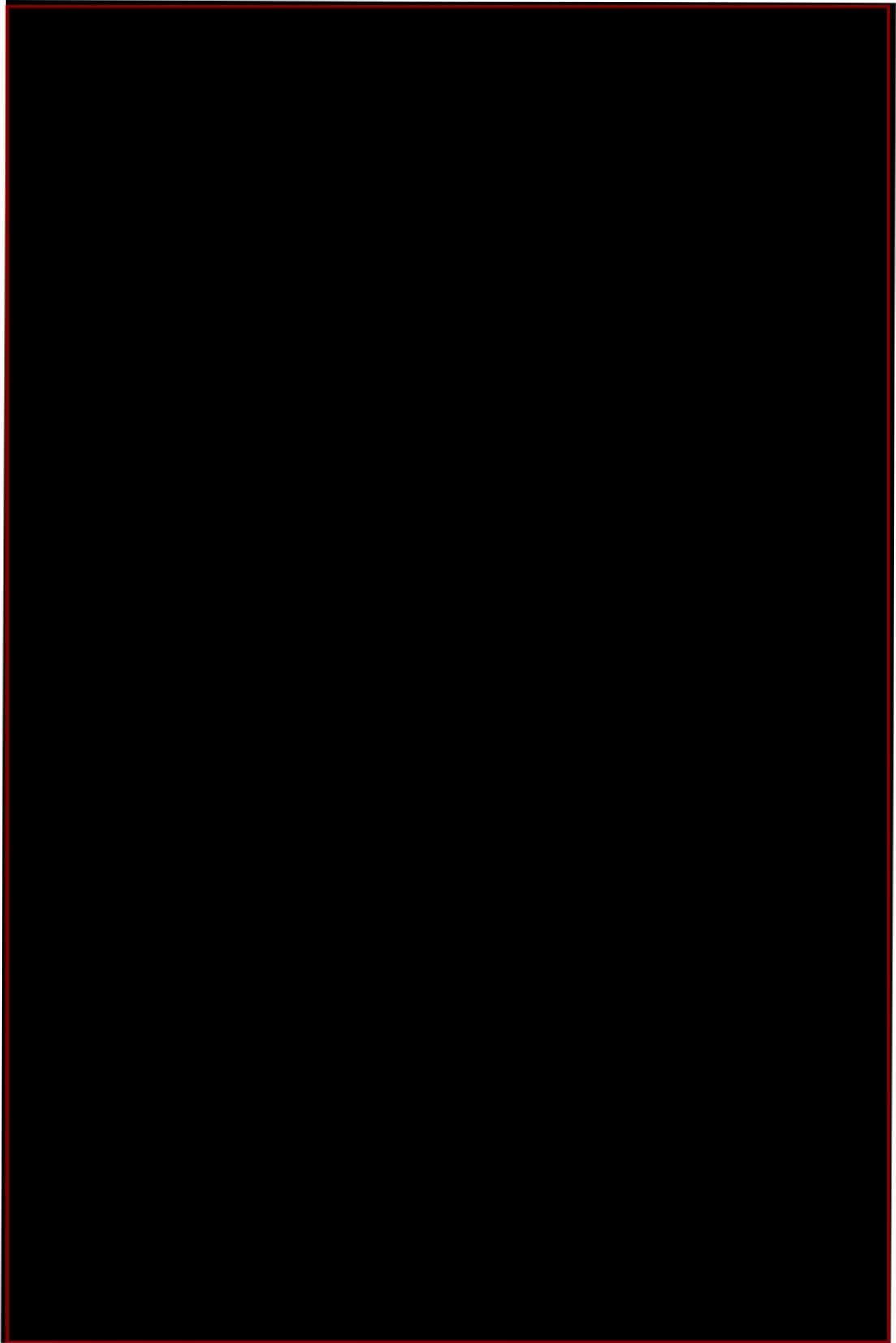




- Three patients experienced a menorrhagia-related SAE that occurred within the fourth year following the Adiana Procedure.

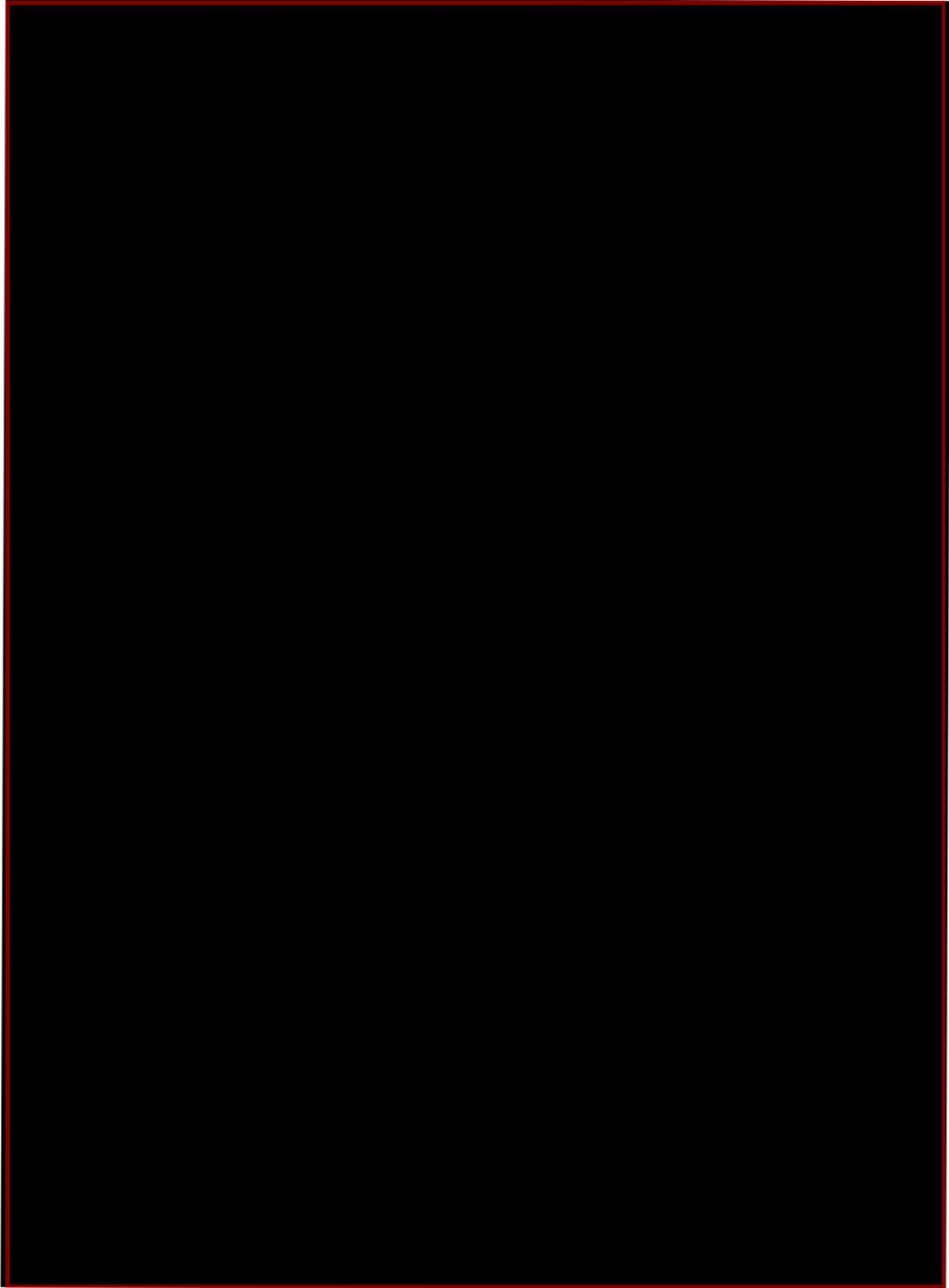
**Case Discussions:**

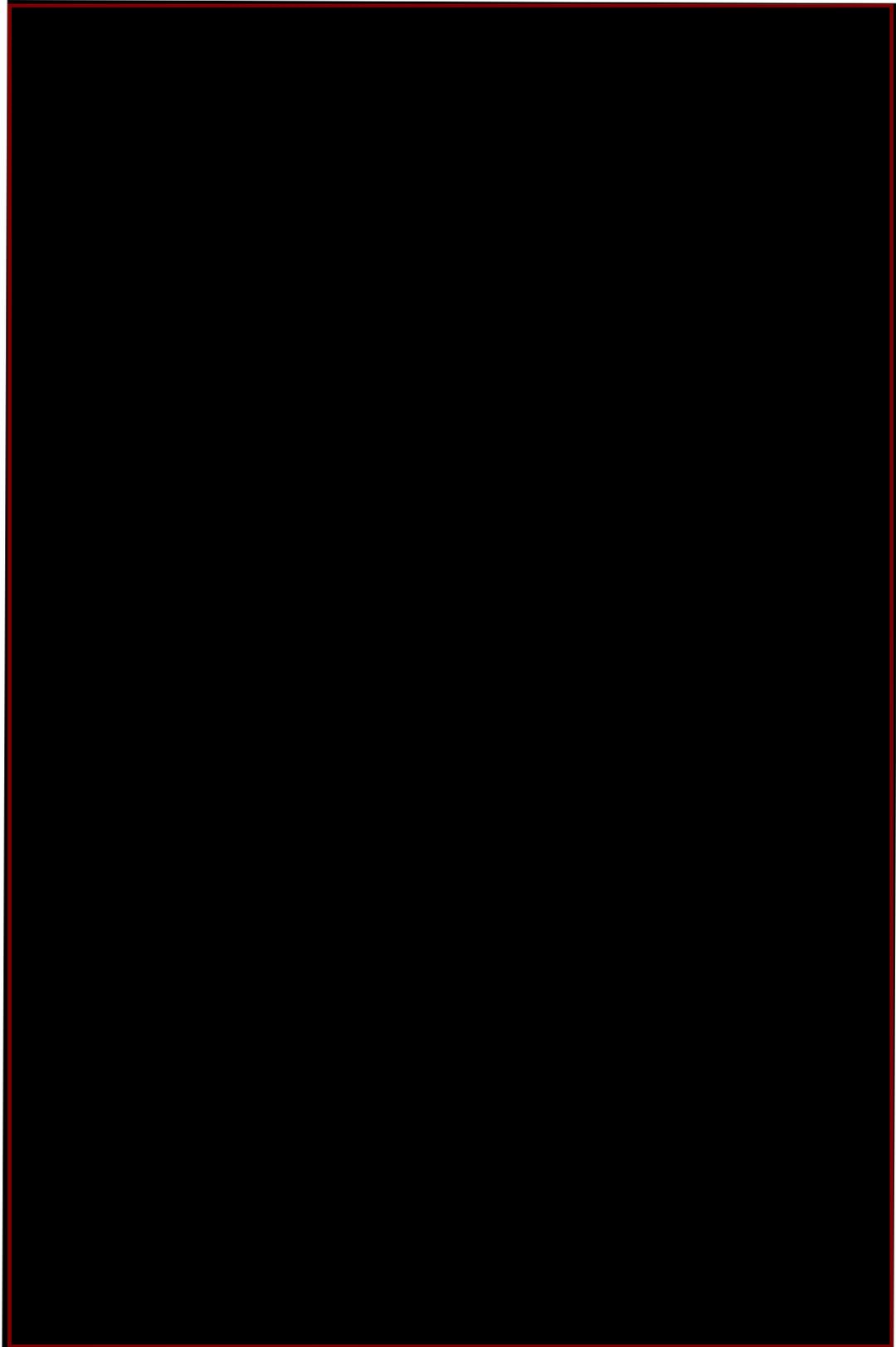


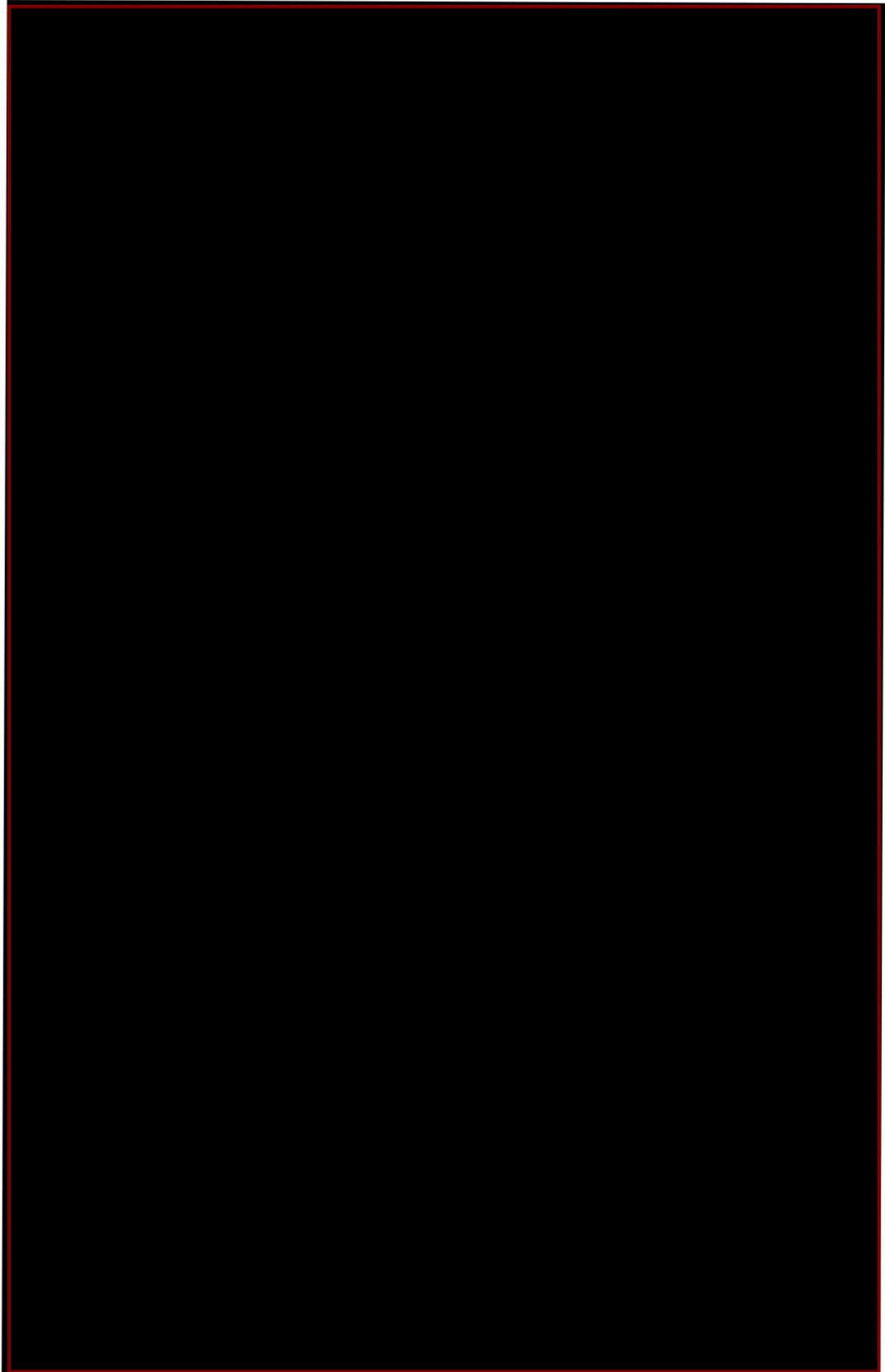


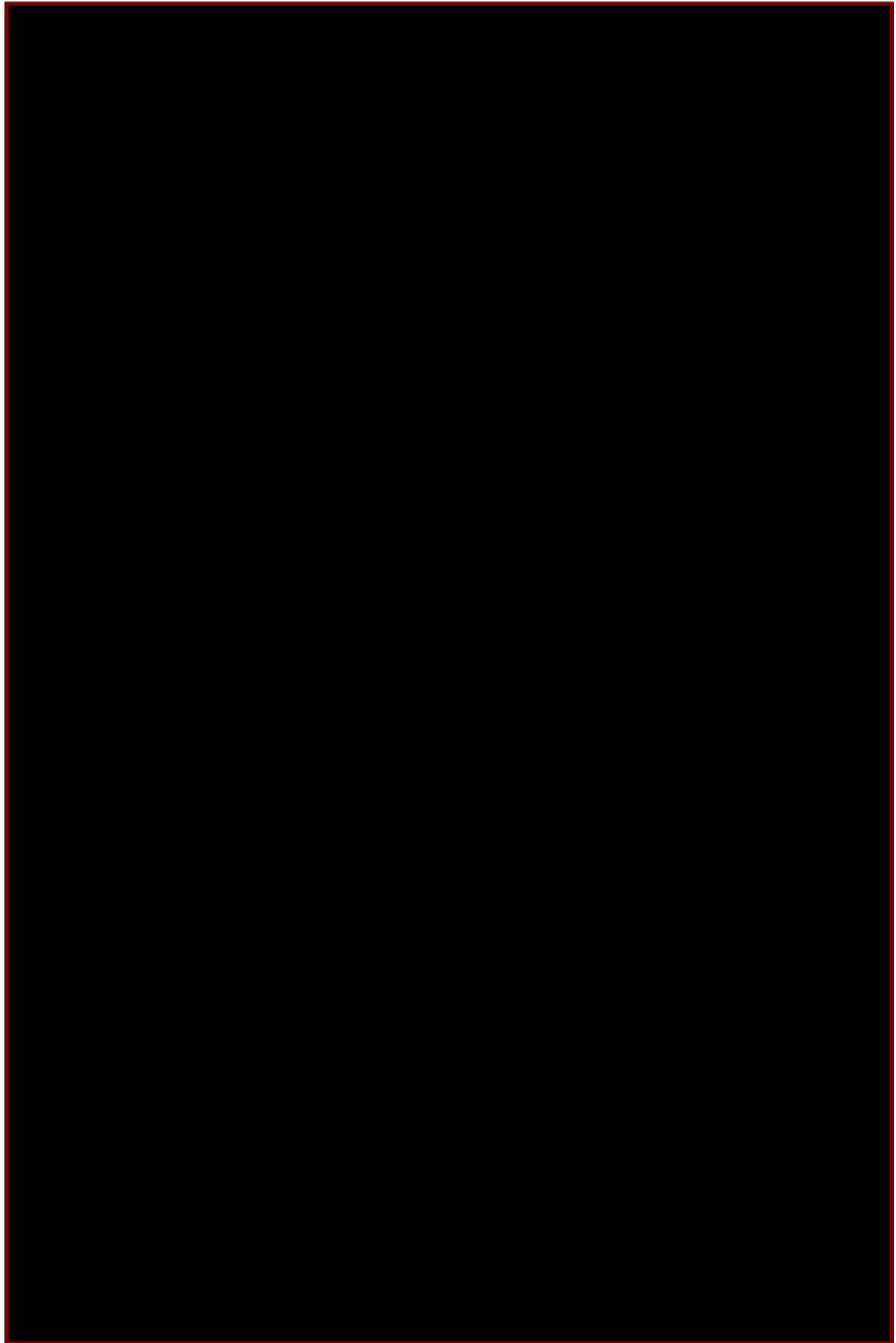
- The remaining 26 patients reported isolated SAE's that do not indicate any specific trend.

**Case Discussions:**

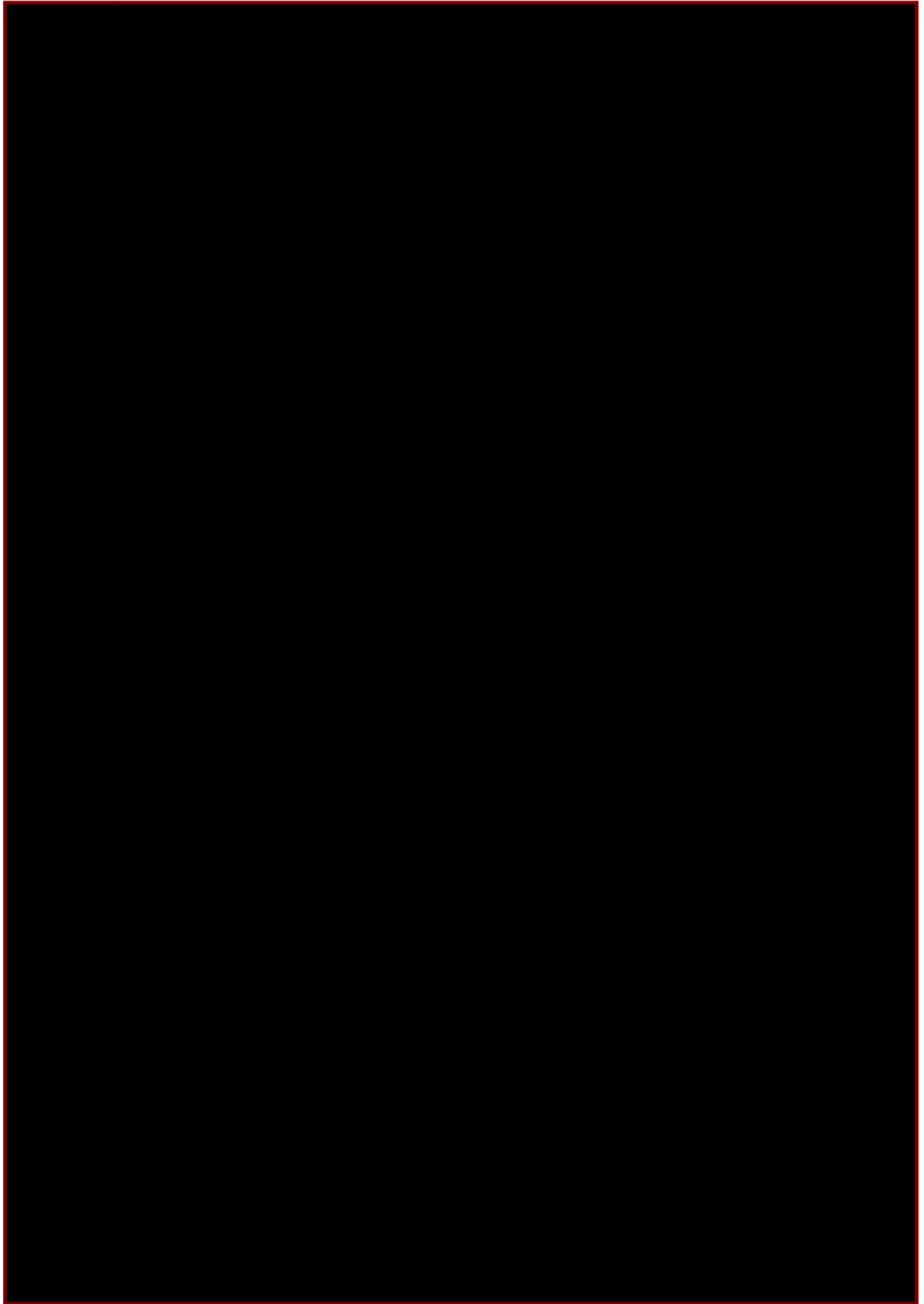


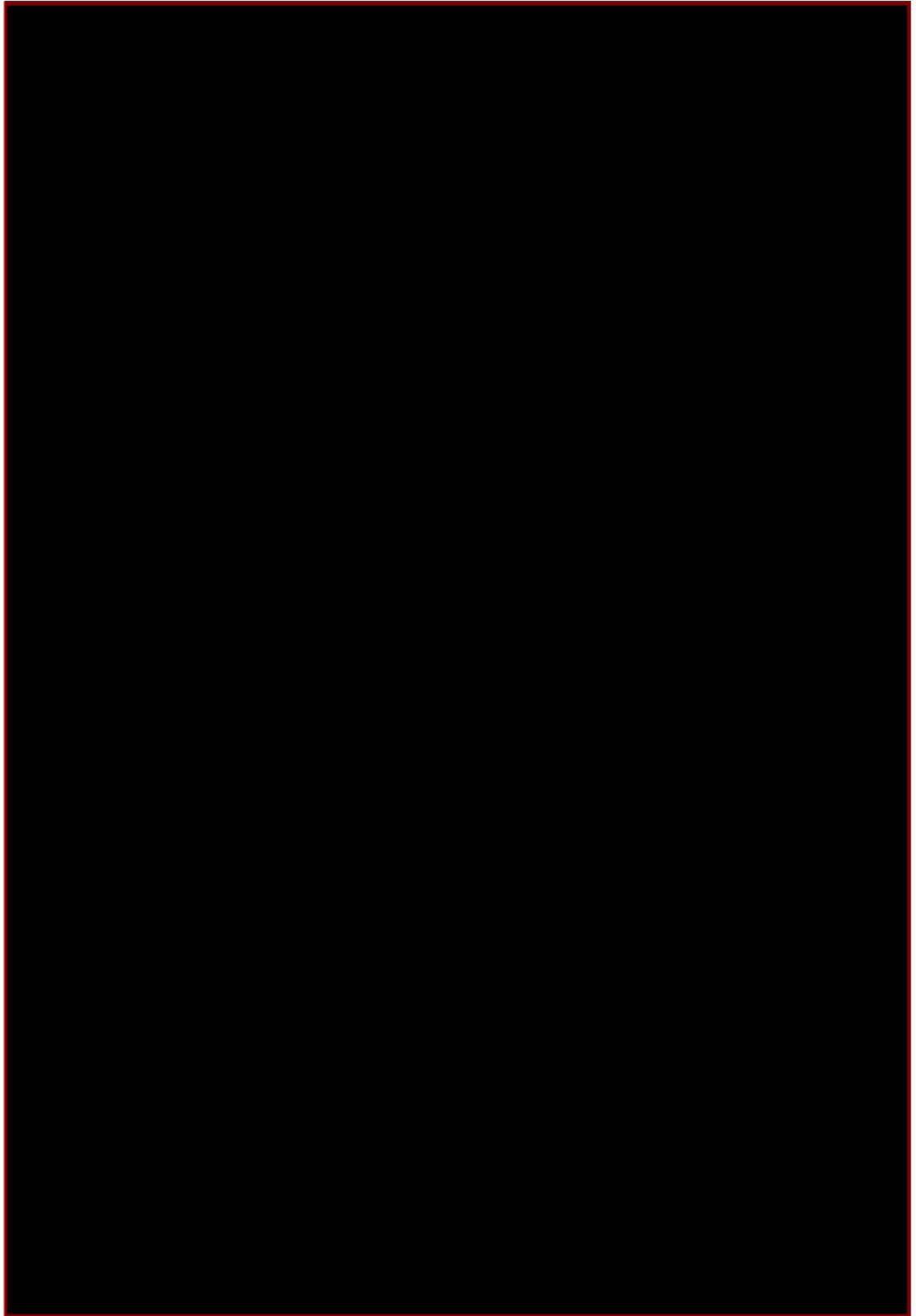


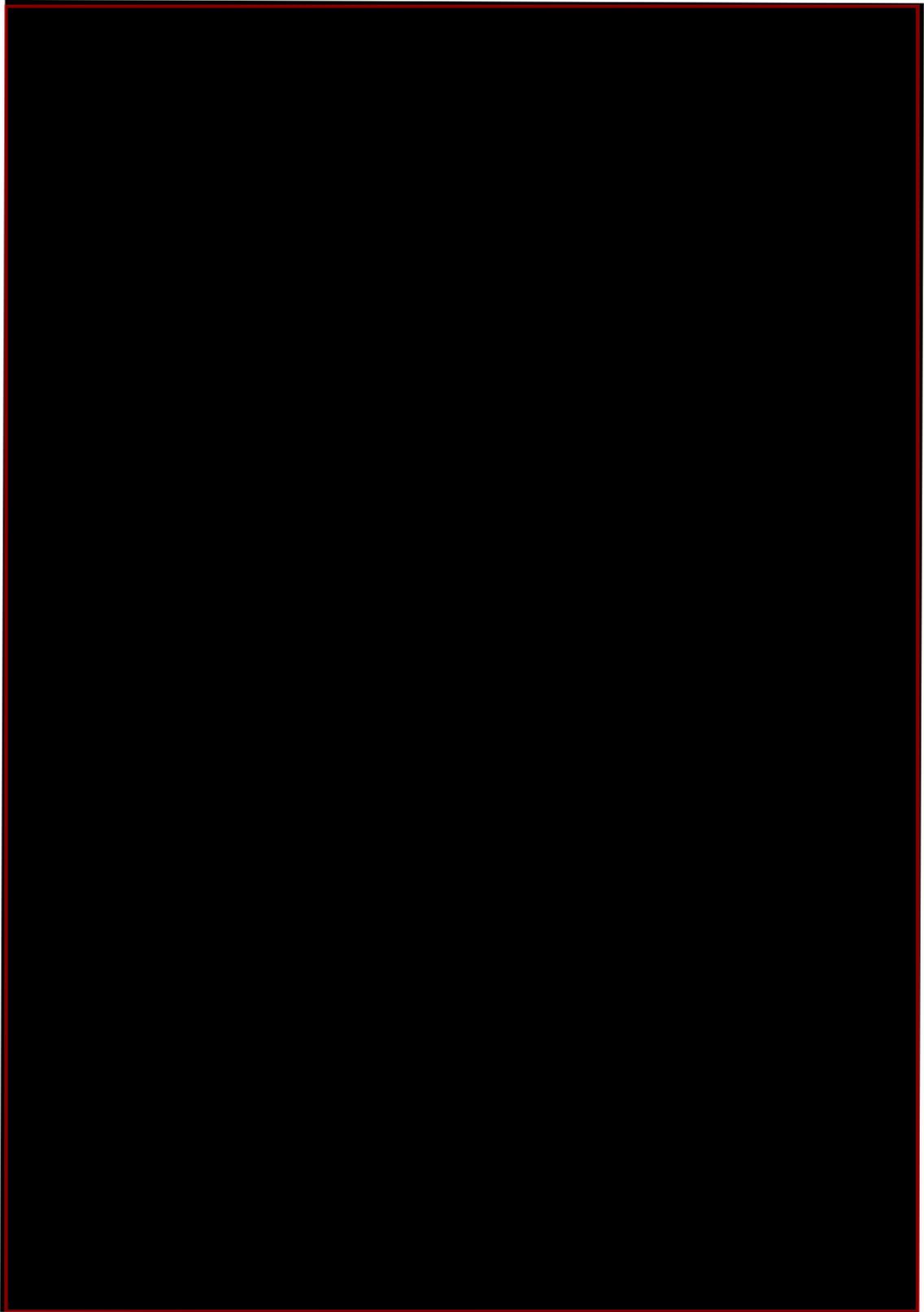


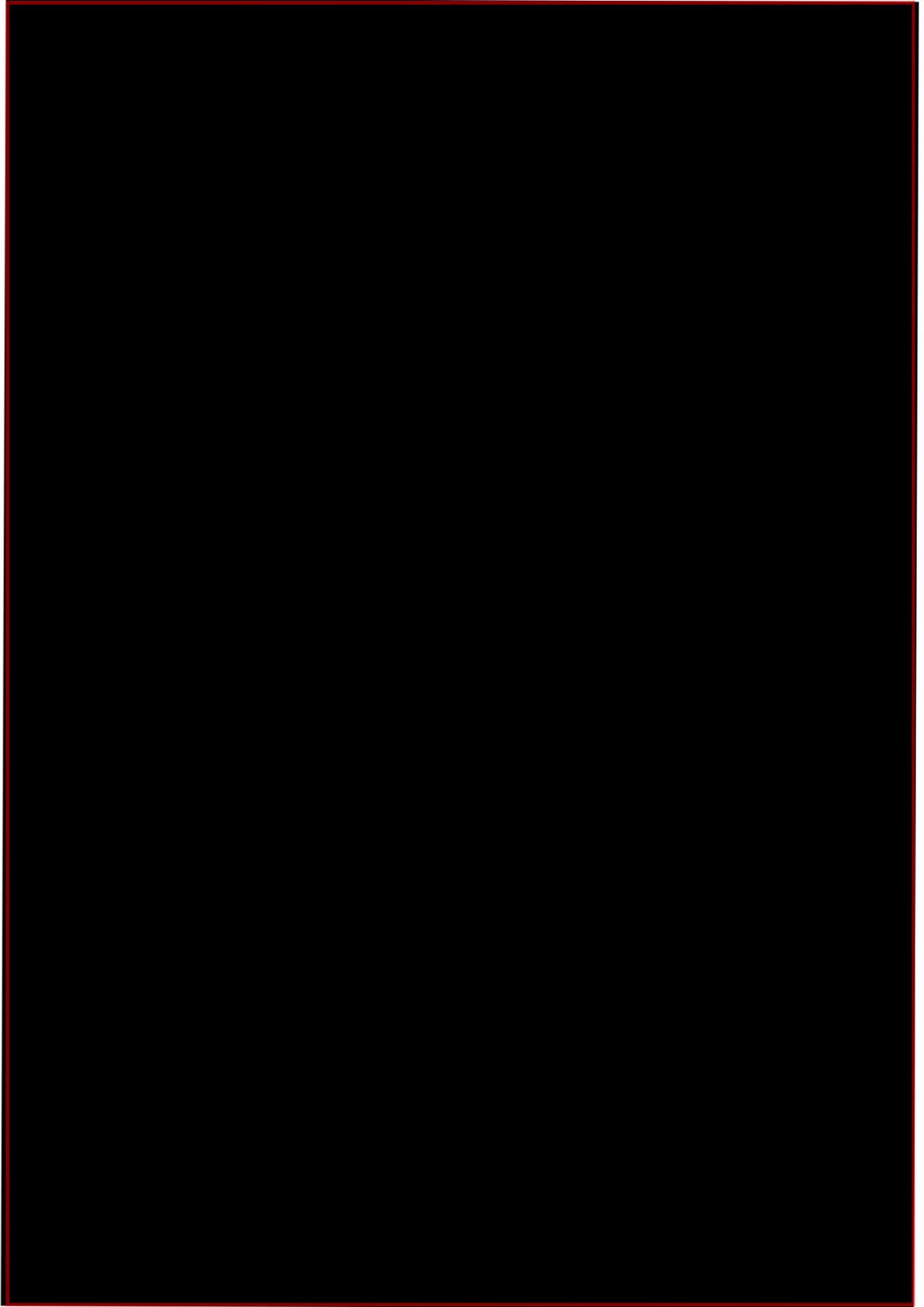


Adiana System on 7/22/2004.

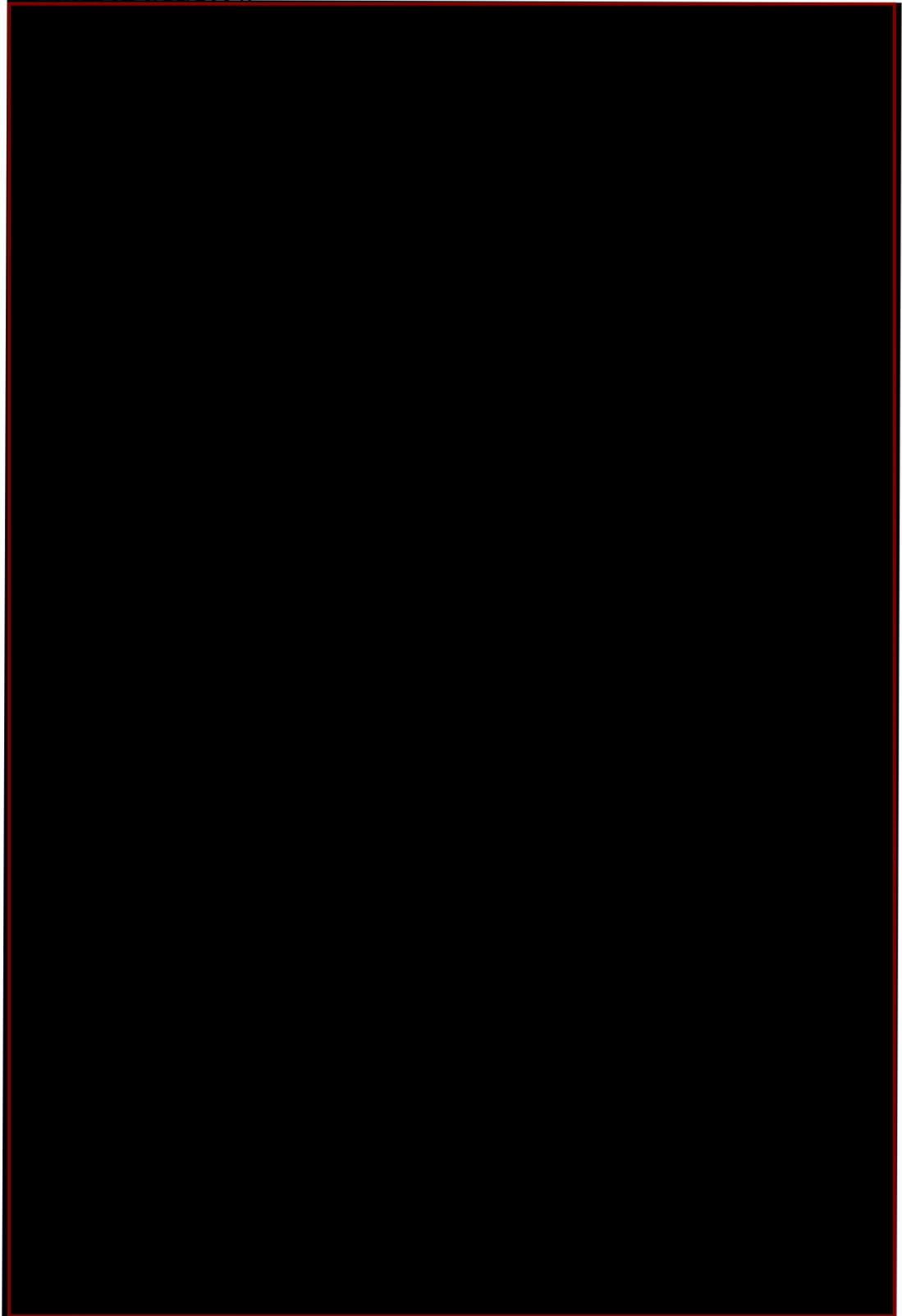


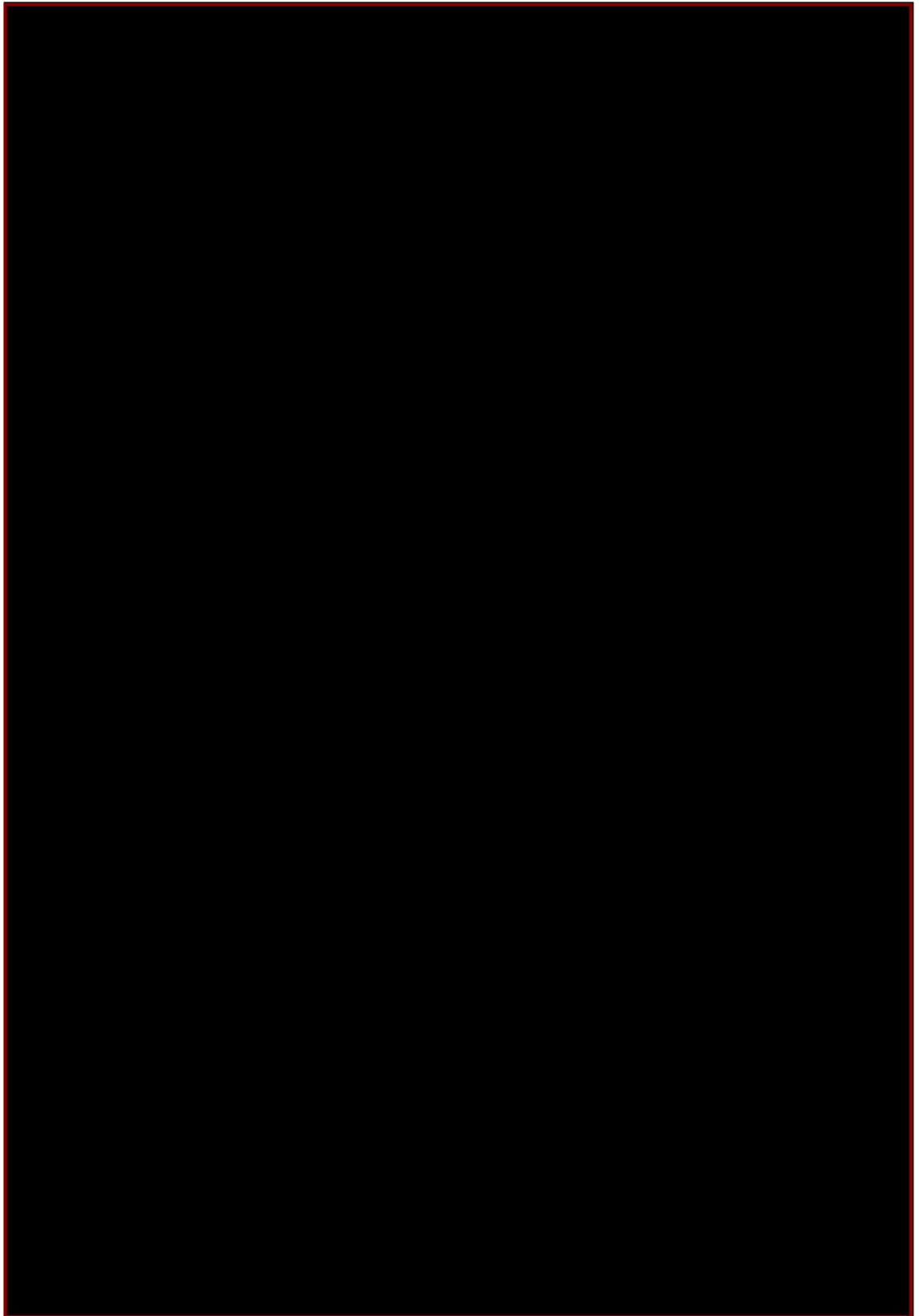


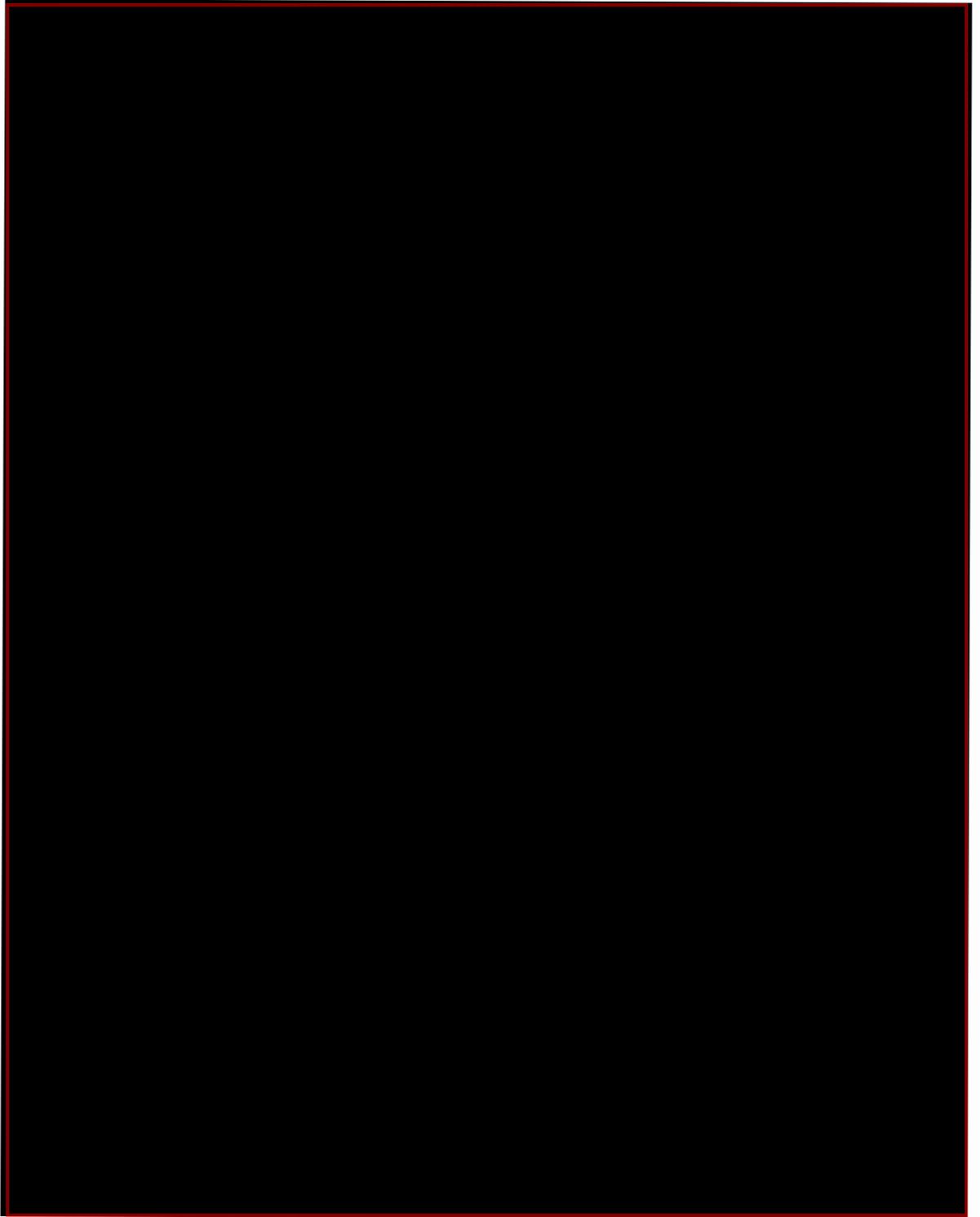




System on 6/11/2004.







One additional significant adverse event is described for a patient who experienced a minor complication resulting from the treatment procedure.

**Case Discussion:**



**9.3.3 Analysis and Discussion of Serious Adverse Events and Other Significant Adverse Events**

Procedure Related Event

The one report of a procedure related SAE involved an incident of hyponatremia/hypervolemia following the occurrence of a fluid deficit of 3000cc glycine during the treatment procedure (see narrative for patient [REDACTED] in Section 9.3.2 above). The patient was treated conservatively with Lasix and discharged later the same day, with no medical sequelae resulting from this event. This was the only fluid overload incident reported in the 645 patients treated in this study.

Fluid overload is a reported complication of hysteroscopy. Rates vary dependent upon the associated procedure which affects the surface area exposed and the rate of fluid absorption. Other determinants include the height of the bag of hysteroscopy fluid which affects the hydrostatic pressure, and the length of the procedure. In cases of myomectomy resection, the estimated rate of absorption is 10cc/minute however with sterilization procedures there is no issue of open vascularity and the rate is presumed to be similar to a diagnostic hysteroscopy which is lower.



The type of fluid absorbed systemically has an impact on the outcome. Glycine is the recommended distention fluid for the Adiana System procedure. Glycine is hypotonic, electrolyte free, nonconductive, nonhemolytic, and transparent. At a fluid loss or deficit of 1500cc the patient may suffer symptomatic hyponatremia complaining of headache, nausea, emesis and confusion. Ammonia is a metabolite of glycine and can contribute to CNS symptoms associated with excessive absorption. Although sorbitol and mannitol are fluid distention options, they also carry the risk of hyponatremia. Sorbitol metabolizes to fructose and glucose and can cause hyperglycemia.

If fluid overload is suspected and serum sodium is significantly decreased to 125mmol/L the patient should be monitored and treated despite symptomatology until electrolyte balance is documented. Treatment includes diuresis and fluid replacement. Hypertonic saline should be avoided in general.<sup>25, 26, 27</sup>

Because this type of potential complication is known, it is possible to minimize the risk of occurrence in the treated population through training for safety with targeted messages to the physician and clearly described limits for fluid and procedure time management. The EASE clinical protocol (P0071- section 9.5.3) required termination of the procedure when fluid deficit exceeded 800cc as a precautionary measure. Following this serious adverse event, the investigator was reminded of the protocol requirements and there were no such additional occurrences of fluid overload in the clinical trial.

#### Device Related Events

Two serious adverse events reported in the trial were determined to be related to the Adiana device. Both involved ectopic pregnancies in patients who were relying on the Adiana System for pregnancy prevention (see narratives for patients [REDACTED] and [REDACTED] in Section 9.3.2 above). One woman was treated conservatively with Methotrexate and subsequent salpingectomy at the time of her laparoscopic tubal sterilization. The second woman underwent laparoscopic treatment and bilateral tubal sterilization. Both patients continue to be followed for safety endpoints and neither have had any further medical sequelae resulting from the ectopic pregnancies.

Approximately 2 per 100 pregnancies in the general population in the US occur outside of the uterus and are diagnosed as ectopic.<sup>28</sup> Although the incidence of ectopic pregnancy has increased over the last 25 years from 4.5 per 1000 pregnancies

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<sup>25</sup> Estes CM., Maye JP. Severe intra-operative hyponatremia in a patient scheduled for elective hysteroscopy: a case report. AANA Journal. 2003. 71;3: 203-05.

<sup>26</sup> Kriplani A, Nath J, Takkar D, et al. Biochemical hemodynamic and hematologic changes during transcervical resection of the endometrium using 1.5% glycine as the irrigating solution. Euro J Obs Gyn Repro Bio. 1998. 80;99-104.

<sup>27</sup> Baxter healthcare Corporation. Product information. January 2005.

<sup>28</sup> MMWR 1995;44(03):46-8)

to 19.7 per 1000 in 1992, the case fatality rates have decreased.<sup>29</sup> Between 1979 and 1986, 13% of maternal deaths were attributed to ectopic pregnancy.<sup>30</sup> By 1992 this number decreased to 9%<sup>31</sup> and by 1999 to 6%.<sup>32</sup> Specific accounting for the rise in rate is difficult given improved diagnostic tools (more widely available highly sensitive rapid quantitative pregnancy tests and high resolution transvaginal ultrasound (TVUS)), and an increase in several population based risk factors such as sexually transmitted infections and the increased use and availability of Assisted Reproductive Technology (ART) which carries the increased risk of ectopic pregnancy.

Tubal sterilization in the United States is common. An estimated 700,000 women choose tubal sterilization each year. Although pregnancy following sterilization is uncommon compared with the non-contracepting population, there is an increased risk that the pregnancy, if it occurs, is ectopic. Based on analysis of data from the U.S. Collaborative Review of Sterilization (CREST) published in 1997 using cumulative life table probabilities and proportional hazards analysis, the 10 year cumulative probability of ectopic pregnancy for all methods of tubal sterilization (including unipolar, bipolar, Hulka Clip, Falope Ring and partial salpingectomy) was 7.3 per 1000 procedures. Rates varied significantly with age and method. Fifteen to 65 percent of post sterilization failures were ectopic, dependent upon the procedure.<sup>33</sup> Bipolar tubal coagulation is the most commonly used tubal sterilization method in the United States and may carry the highest associated risk of failure and ectopic pregnancy due to recanalization or uteroperitoneal fistula formation. The CREST study had a 42% loss to follow-up rate at 8-14 years. Of those women contacted and willing to participate, 47/143 pregnancies identified were ectopic (only one was ovarian), equivalent to an ectopic pregnancy rate of 32.9%.

In comparison, in the 625 women in the EASE clinical trial who had Adiana devices placed (unilateral, n=14; bilateral, n=611) two of the fourteen total pregnancies (relying and non-relying patients) reported as of March 1, 2007 were ectopic pregnancies (see Section 9.4.1 for summary of pregnancy events). Thus, the observed ectopic rate in the EASE trial is 14.3%. Table 9-2 summarizes the types of pregnancies that occurred in the EASE trial by year.

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<sup>29</sup> Ectopic Pregnancy- United States, 1990-1992. JAMA. 1995;273:533

<sup>30</sup> MMWR 1992;41:591-594

<sup>31</sup> JAMA, 1995 op. cit.

<sup>32</sup> MMWR 2003; 52 No SS2;1

<sup>33</sup> Peterson HB. et al. The risk of ectopic pregnancy after sterilization. N Engl J Med 1997;336:762-7

**Table 9-2: Summary of Types of Pregnancies in the EASE Trial**

	Relying Ectopic Pregnancies	Relying Intrauterine Pregnancies	Non-relying Intrauterine Pregnancies	Total Pregnancies
Year 1	1	5	5	11
Year 2	1	2	0	3
Year 3	0	0	0	0
Total	2	7	5	14

The DSMB reviewed the ectopic rate observed in the EASE trial and found it to be within the range expected for a post-sterilization population when considered against the CREST study outcomes as a valid control. Because there have been no pregnancies in the Essure pivotal trials it has not been used as a control. There are, however, reports of ectopic pregnancy in Essure users in the Maude Database.

The Adiana device and all other approved sterilization methods are protective against ectopic pregnancy because they are highly effective in preventing pregnancy. Targeting both sterilization users and their health care providers with a message that these women, along with all women who have undergone any form of tubal manipulation, should be evaluated immediately for an ectopic if pregnancy does occur has been successful as evidenced by the declining ectopic related mortality rates in the US. In the Adiana EASE trial all women who became pregnant were seen within 6 weeks of conception, with one exception at 8 weeks. The two women who experienced ectopic pregnancies were diagnosed at 5 and 6 weeks following their last menstrual period.

Events Unknown if Related to Device or Procedure

Two events occurred in patients within close proximity to the Adiana Procedure and were therefore classified as “unknown if related” by the DSMB. One case consisted of persistent pelvic pain evaluated by laparoscopy three months post procedure. The etiology of the pelvic pain was ultimately considered due to irritable bowel syndrome. The second case involved patient hospitalization four days post-procedure for chest pressure and nausea, which ultimately resulted in a diagnosis of GERD. These appeared to be isolated events, with no obvious trends indicating an adverse impact on patient safety following the treatment procedure.

Events Occurring Secondary to Menorrhagia or Dysmenorrhea

Ten patients reported SAE’s that occurred secondary to menorrhagia or dysmenorrhea or to treatment of the complaint. One of these events was determined to be “possibly device related” by the DSMB, and the remaining nine were not device or procedure related.



The event that was considered to be possibly device related involved a case of persistent dysmenorrhea that was evaluated and treated with polypectomy at 17 months post procedure. The investigator considered this event unrelated to the Adiana device. The DSMB agreed that the event was likely unrelated and that the polyp had probably been present at the time of the Adiana Procedure but not identified; however, without definitive evidence they felt the event should be classified as "possible device related" (see narrative for patient [REDACTED] in Section 9.3.2. above). This was an isolated event.

The remaining nine non-device related serious adverse events that occurred secondary to menorrhagia/dysmenorrhea, were critically reviewed, along with other adverse event reports for these patients, to rule out any patterns of relationship of the complaint to the Adiana Procedure or device use (including treatment itself as a qualifier, or a complication of the treatment as a qualifier). We specifically looked at time proximity of the treatment event and the nature of the complaint leading to the event.

One event involved a patient who was treated by her private gynecologist for menorrhagia/dysmenorrhea with [REDACTED] endometrial ablation (see narrative for patient [REDACTED] in Section 9.3.2 above). The patient had a history of dysmenorrhea and oral contraceptive use prior to her sterilization. Based on a review of the literature (see below) this history increased her risk for post sterilization menstrual cycle change and hysterectomy. Her endometrial ablation procedure was uncomplicated; however, the patient subsequently was hospitalized for Group B Streptococcal septicemia. She defervesced and was discharged on oral antibiotics. She has not been retreated since that time for infection according to the Adiana study investigator. At 22 months post-procedure, the patient underwent total vaginal hysterectomy and culdoplasty. Pathology confirmed residual proliferative phase endometrium.

Serious invasive Group B Streptococcal disease (*Streptococcus agalactiae*) in non-pregnant adults occurs predominantly in those with significant underlying conditions such as the elderly with diabetes, neurologic impairment or cirrhosis. Skin and soft tissue, osteoarticular infections, pneumonia or urosepsis are common presentations. Disease is often nosocomial and recurrent disease occurs in 4.3% of survivors.<sup>34</sup> Skin and soft tissue infections are the most frequently reported clinical syndromes associated with invasive Group B Streptococci such as decubitus ulcers or chest wall cellulitis following surgery.

Although the infection can be treated with early recognition using aggressive antibiotic therapy the carrier state is not eradicated and prophylactic antibiotic

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<sup>34</sup> Farley, MM. group B Streptococcal Disease in Nonpregnant Adults. *Emerging Infections*.2001 (15 August) 556-561.

treatment is warranted if the patient undergoes surgical procedures following treatment.

A review of the literature describes a small number of cases of severe infection following operative hysteroscopy including pyometra, fatal toxic shock syndrome, and tubo-ovarian abscess. More recently the literature describes rare complications specific to endometrial ablation including pelvic abscess, tubo-ovarian abscess and other complications secondary to thermal injury to bowel or uterine perforations. Bacteremia following hysteroscopic surgery without prophylactic antibiotic use is significant however organisms identified appear to be normal vaginal flora and therefore the finding has not prompted an established standard of use of prophylaxis.<sup>35, 36</sup>

In this case it is likely that the patient suffered normal tissue trauma with endometrial ablation and as a carrier of GBS may have been at greater risk of an infection following the procedure. Recommendations for prophylaxis were not found in the literature. Given the nature of the Adiana device (inert silicone Matrix) it is not likely that the device would act as a nidus. This is further evidenced by the successful early treatment and lack of recurrence of the infection.<sup>37</sup>

Of the remaining eight serious adverse events related to menorrhagia/dysmenorrhea, three patients were using hormonal contraception, and all but one had prior complaints of menorrhagia, dysmenorrhea, and/or fibroids prior to sterilization.

The relationship of female sterilization and long-term health effects of tubal sterilization on menstrual pattern disturbance (post-tubal ligation syndrome) have been well studied and appear to be negligible. Early studies of menstrual disturbances after sterilization failed to account for confounding variables, such as pre-sterilization use of hormonal contraceptives that can mask underlying menstrual dysfunction.<sup>38, 39</sup>  
<sup>40</sup> Most recent studies that controlled for these factors have found little or no

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<sup>35</sup> Roth TR . Tuboovarian Abscess: A Postoperative Complication of Endometrial Ablation. *Obs Gyn* 2004. 104(5) 198-199

<sup>36</sup> Kirwan SD. Pelvic Abscess following microwave endometrial ablation. *BJOG*. 2005. 112:118-119

<sup>37</sup> APollack-personal communication with D. Patton, J Anderson. October 2006.

<sup>38</sup> Alder E, Cook A, Gray J, Tyrer G, Warner P, Bancroft J, et al. Their effects of sterilization: a comparison of sterilized women with wives of vasectomized men. *Contraception* 1981;23:45-54.

<sup>39</sup> Gentile GP, Kaufman SC, Helbig DW. Is there any evidence for a post-tubal sterilization syndrome? *Fertil Steril* 1998;69:179-86.

<sup>40</sup> Poma PA. Tubal sterilization and later hospitalizations. *J Reprod Med* 1980;25:272-8.

difference in menstrual patterns between women before and after sterilization.<sup>41, 42, 43, 44, 45, 46, 47, 48</sup>

Despite this, and although there is no known biologic mechanism to support a causal relationship between tubal sterilization and hysterectomy, the reported association between sterilization and hysterectomy tends to be strong.<sup>49, 50, 51, 52, 53, 54</sup> Women who undergo tubal sterilization appear to be 4 to 5 times more likely to undergo hysterectomy than those whose partners underwent vasectomy.<sup>55</sup> Increased risk was associated with a pre-sterilization history of menstrual or other benign gynecologic disorders.<sup>56</sup>

In the EASE clinical trial, 48.2% of the intent to treat subjects used hormonal contraception prior to sterilization, thus putting them at risk of recognizing menstrual changes post sterilization perceived as a change in the menstrual cycle.

It is also well described in the literature that menorrhagia (as defined as blood loss of greater than 80mL per cycle) is seldom either measured or a predictor of treatment; however, 30% of all women report having menorrhagia, and it accounts for 60-70% of all hysterectomies and endometrial ablation procedures.<sup>57, 58</sup>

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<sup>41</sup> Gentile GP, op.cit.

<sup>42</sup> Bhiwandiwalla PP, Mumford SD, Feldblum PJ. Menstrual pattern changes following laparoscopic sterilization with different occlusion techniques: a review of 10,004 cases. *Am J Obstet Gynecol* 1983;145:684-94

<sup>43</sup> DeStefano F, Perlman JA, Peterson HB, Diamond EL. Long-term risk of menstrual disturbances after tubal sterilization. *Am J Obstet Gynecol* 1985;152:835-41.

<sup>44</sup> Foulkes J, Chamberlain G. Effects of sterilization on menstruation. *South Med J* 1985;78:544-7.

<sup>45</sup> Rivera R, Gaitan JR, Ruiz R, Hurley DP, Arenas M, Flores C, et al. Menstrual patterns and progesterone circulating levels following different procedures of tubal occlusion. *Contraception* 1989;40:157-69.

<sup>46</sup> Rulin MC, Davidson AR, Philliber SG, Graves WL, Cushman LF. Long-term effect of tubal sterilization on menstrual indices and pelvic pain. *Obstet Gynecol* 1993;82:118-21.

<sup>47</sup> Sahwi S, Topozada M, Kamel M, Anway MY, Ismail AA. Changes in menstrual blood loss after four methods of female tubal sterilization. *Contraception* 1989;40:387-98.

<sup>48</sup> Thranov I, Herz JB, Kjer JJ, Andresen A, Micic S, Nielsen J, et al. Hormonal and menstrual changes after laparoscopic sterilization by Falope-rings or Filschie-clips. *Fertil Steril* 1992;57:751-5.

<sup>49</sup> Rulin MC, Davidson AR, Philliber SG, Graves WL, Cushman LF. Long-term effect of tubal sterilization on menstrual indices and pelvic pain. *Obstet Gynecol* 1993;82:118-21.

<sup>50</sup> Hillis SD, Marchbanks PA, Tylor LR, Peterson HB. Higher hysterectomy risk for sterilized than nonsterilized women: findings from the U.S. Collaborative Review of Sterilization Working Group. *Obstet Gynecol* 1998;91:241-6.

<sup>51</sup> Cohen MM. Long-term risk of hysterectomy after tubal sterilization. *Am J Epidemiol* 1987;125:410-9.

<sup>52</sup> Goldhaber MK, Armstrong MA, Golditch IM, Sheehe PR, Petitti DB, Friedman GD. Long-term risk of hysterectomy among 80,007 sterilized and comparison women at Kaiser Permanente, 1971-1987. *Am J Epidemiol* 1993;138:508-21.

<sup>53</sup> Kendrick JS, Rubin GL, Lee NC, Schulz KF, Peterson HB, Nolan TF. Hysterectomy performed within 1 year after tubal sterilization. *Fertil Steril* 1985;44:606-10.

<sup>54</sup> Stergachis A, Shy KK, Grothaus LC, Wagner EH, Hecht JA, Anderson G, et al. Tubal sterilization and the long-term risk of hysterectomy. *JAMA* 1990;264:2893-8.

<sup>55</sup> Hillis SD. op.cit

<sup>56</sup> Ibid.

<sup>57</sup> Pitkin, J. Dysfunctional Uterine Bleeding. *BMJ* 2007;334:1110-1111

Of the ten total events, one occurred within the first year following the procedure; four within the second year; two within the third year, and three within the fourth year. Thus, no clear pattern of time proximity relating duration of device use and occurrence was identified.

Taking the literature and the EASE study population into account, the Data Safety Review Board did not identify any unusual pattern of menorrhagia/dysmenorrhea related adverse events that might indicate a direct relationship to the Adiana Procedure or device.

Other Device Unrelated Events of Note

There were two cases of new onset Multiple Sclerosis (MS) reported during the follow-up period (see narratives for patients [REDACTED] and [REDACTED] in Section 9.3.2 above).

People with a family history of Multiple Sclerosis (MS) and those who live in a geographical area with a higher incidence rate for MS have a higher risk of the disease. No other specific etiologic agent has been associated with the disease which is autoimmune in nature. MS is more common in women and in Caucasians. The average age of onset is between 18 and 35, but the disorder may develop at any age. MS is the most common neurological cause of debilitation in young people and affects about 500,000 people in the United States. Worldwide, the incidence is approximately 0.1%. Northern Europe and the northern United States have the highest prevalence, with more than 30 cases per 100,000 people.

Our study records do not reflect where these two study participants grew up, or their family histories. Their procedures were done in Florida and Texas. Because the event is rare in the study population, comparison of a study rate to the general population would not be statistically valid.

Other Significant Adverse Events

One additional, minor adverse event is reported here as it occurred during a treatment procedure (see narrative for patient [REDACTED] in Section 9.3.2 above). In this case, the physician did not remove the introducer after the Adiana catheter was inserted. During the procedure the introducer was advanced into the hysteroscope such that the tip of the introducer was past the valve. When the Adiana catheter was removed, the physician closed the pivot valve, and the introducer was "sheared off". The tip of the introducer was within the fluid of the endometrial cavity and was subsequently expelled and retrieved by the patient. *(Note; the introducer is an accessory supplied with the Delivery Catheter which protects the catheter from damage during*

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<sup>58</sup> Warner PE, Critchley HO, Lumbsden MA, et al. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. Am J Obstet Gynecol. 2004; 190(5): 1224-9

*hysteroscope insertion*). The patient has had no health events reported that could be related to this incident. She was successfully treated with bilateral placement and is currently relying on the Adiana System for pregnancy prevention. The physician was instructed to be sure to remove the introducer following insertion of the catheter into the hysteroscope. No other occurrences of this type of event were reported during the trial.

#### 9.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

##### 9.4.1 Summary of Pregnancy Events and Outcomes

As of March 1, 2007, there have been a total of 14 pregnancies reported in the EASE trial. These include pregnancies that have occurred in patients who were not relying on the Adiana System for pregnancy prevention as well as pregnancies that have been reported in relying patients during both the first and second year of reliance. All events that have occurred in relying patients have previously been reported to FDA. Table 9-3 summarizes events in relying patients. Detailed case reports for each patient can be found in Appendix 13.3.4.

##### Pregnancy Events in Non-Relying Patients during Waiting Period

Three patients were reported as pregnant due to apparent alternative contraceptive failure during the Waiting Period, prior to reliance on the Adiana device. These patients had NOT yet begun the Wearing Period and were NOT relying on the Adiana System for pregnancy prevention (Patient ID: [REDACTED])

##### Pregnancy Events in Non-Relying Patients during Safety Endpoint Follow-up

Two patients became pregnant following a failed placement procedure due to a failure of alternative contraceptive methods, during the *safety endpoint follow up phase*. These patients were NOT relying on the Adiana Device for pregnancy prevention (Patient ID: [REDACTED])

##### Pregnancy Events in Relying Patients during First Year of Reliance

There were a total of six pregnancy events reported during the first year of the Wearing Period in patients relying on the Adiana System for pregnancy prevention.

Three of the pregnancies were a result of physician error (Patient ID: [REDACTED] and [REDACTED]). These events occurred due to physician misinterpretation of HSG results or faulty HSG technique.

The remaining three pregnancies occurred due to method failure. Two of these cases were normal intrauterine pregnancies (Patient ID: [REDACTED]) The third case was an isthmic ectopic pregnancy that was treated conservatively with Methotrexate and subsequent salpingectomy at the time of laparoscopic tubal sterilization (Patient ID: [REDACTED])

Pregnancy Events in Relying Patients due to Method Failure during Second Year of Reliance

There have been three reports of pregnancy during the second year of the Wearing Period that occurred due to method failure. Two of these cases were normal intrauterine pregnancies (Patient ID: [REDACTED]). The third was an ectopic ampullary pregnancy which was successfully resolved by bilateral salpingectomy (Patient ID: [REDACTED]).

**Table 9-3: Summary of Pregnancies in Relying Patients**

<u>Patient ID</u>	<u>Date of Pregnancy</u>	<u>Age</u>	<u># Days of Wearing</u>	<u>Pregnancy Outcome</u>
[REDACTED]	7/10/2004	27	289	Missed abortion
[REDACTED]	3/1/2005	32	208	Normal Term pregnancy [REDACTED]
[REDACTED]	9/9/2005	24	90	Normal Term pregnancy [REDACTED]
[REDACTED]	9/15/2005	29	24	Termination/BTL
[REDACTED]	1/9/2006	34	220	Isthmic pregnancy resolved with Methotrexate
[REDACTED]	4/1/2006	32	375	L ampullary pregnancy resolved with salpingectomy
[REDACTED]	4/30/2006	22	317	Spontaneous abortion
[REDACTED]	6/18/2006	25	576	Spontaneous abortion
[REDACTED]	6/22/2006	33	546	Normal Term pregnancy [REDACTED]

A review of the pregnancies in relying patients was conducted and no clinical trend was observed that would independently account for the failures. Therefore, a review of the Delivery Catheter versions and associated shelf ages was conducted to determine whether the catheter itself could be correlated to the pregnancy outcomes.

Overall, results from the use of 19 Delivery Catheters were included in the analysis. This number was based on the fact that two catheters were used for each of the nine patients who became pregnant and one additional catheter was used to re-treat a patient on one side. Based on this review, no connection between the Delivery Catheter version and the pregnancy outcome could be established; see Table 11.2.18.1.

Separate from the device version, the shelf age of the 19 Delivery Catheters was evaluated. The mean shelf age was 3.6 months, with a range of 1-8 months. In 15 cases, the shelf age of the missing matrices was between 0-4 months, and in 4 cases it was between 5-8 months. No product used in these cases was greater than eight months old. Thus, no correlation between pregnancy prevention failure and either Delivery Catheter version or extended shelf age of the product could be established. It therefore does not appear that any of the failures are device-related.

### **Pregnancy Outcomes**

Of the total 14 pregnancies, one woman was lost to follow-up following ultrasound documentation of an intrauterine gestation [REDACTED] and her pregnancy outcome is unknown. Of the remaining 13 pregnancies, six resulted in uncomplicated intrauterine pregnancies with normal deliveries. Two additional patients elected to terminate their pregnancies. Two pregnancies were ectopic (tubal pregnancies), which were discussed in detail in Section 9.3.3. The remaining three pregnancies resulted in empty sac/missed abortions or spontaneous first trimester abortions.

Spontaneous abortion can be subdivided into threatened abortion, inevitable abortion, incomplete abortion, missed abortion, septic abortion, complete abortion, and recurrent spontaneous abortion. Rates in the general population are age dependent and based on NSFG data<sup>59</sup> range from 14-28% of recognized pregnancies. Most literature refers to a 20% spontaneous abortion rate in the general population.<sup>60</sup>

The Adiana EASE Clinical Trial had too few pregnancies to determine spontaneous abortion as an extraordinary outcome. Upon review of the observed rate of spontaneous abortion outcomes to pregnancies the DSMB considered the observed rate to be within the expectation of the event in the general population.

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<sup>59</sup> Schieve: *Obstet Gynecol*, Volume 101(5, Part 1). May 2003.959-967

<sup>60</sup> Speroff L, Glass RH, Kase NG. *Clinical gynecologic endocrinology and infertility*. Baltimore, Maryland: Lippincott Williams and Wilkins, 1999.

### 9.5 Safety Conclusions

Adverse events were reported for the 645 patients in the Intent-to-Treat population. The total device exposure for this population is equivalent to over 1300 patient years.

The majority of adverse events reported on the day of the procedure were anticipated and minor in nature, and consisted of cramping – not related to menses – (25%), spotting (24%), post-procedural bleeding (10%), pelvic pain (9%), back pain (6%), nausea (6%), and headache (4%). Of these events, 73.4% were reported as having some degree of device or procedure relatedness. However, none of the events required significant intervention other than medication (27.8% were treated with medication), and, with the exception of back pain, all resolved within a mean duration of three days; the mean duration for back pain was nine days. These rates 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 within the fluid of the endometrial cavity of the patient and was 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, and one ectopic pregnancy with methotrexate), and the remaining two required surgical intervention (an ectopic pregnancy salpingectomy and the endometrial polyp resection).

Hyponatremia and ectopic pregnancy events are known complications of hysteroscopic sterilization procedures; thus, these events were readily identified when they occurred, as well as properly managed and resolved. The DSMB concluded that these events were not unexpected, had a low incidence rate, and did not represent an unknown or unreasonable risk to the patient. The DSMB also reviewed the ectopic pregnancy rate observed in the EASE trial and found it to be within the range expected for a post-sterilization

population; this conclusion was reached, in part, through consideration of the CREST study outcomes.

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 the dysmenorrhea/metrorrhagia 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.

In the EASE clinical trial, 48.2% of the intent-to-treat subjects used hormonal contraception prior to sterilization, thus putting them at risk of recognizing menstrual changes post sterilization, perceived as a change in the menstrual cycle. It is also well described in the literature that menorrhagia (as defined as blood loss of greater than 80 mL per cycle) is seldom either measured or a predictor of treatment; however, 30% of all women report having menorrhagia, and it accounts for 60-70% of all hysterectomies and endometrial ablation procedures.<sup>63</sup>, <sup>64</sup>, <sup>65</sup>, <sup>66</sup> Taking the literature and the EASE study population into account, the DSMB did not identify any unusual pattern of menorrhagia/dysmenorrhea related adverse events that might indicate a direct relationship to the Adiana Procedure or device.

Additionally, of the ten patients who have undergone hysterectomies for medical reasons, eight had explant tubal tissue obtained and evaluated. Results from the histological evaluation of these long-term implant specimens indicated 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 matrices. There have been no reported allergic or

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<sup>63</sup> Gentile GP, Kaufman SC, Helbig DW. Is there any evidence for a post-tubal sterilization syndrome? *Fertil Steril* 1998;69:179-86.

<sup>64</sup> Rulin MC, Davidson AR, Philliber SG, Graves WL, Cushman LF. Long-term effect of tubal sterilization on menstrual indices and pelvic pain. *Obstet Gynecol* 1993;82:118-21.

<sup>65</sup> Pitkin, J. Dysfunctional Uterine Bleeding. *BMJ* 2007;334:1110-1111

<sup>66</sup> Warner PE, Critchley HO, Lumbsden MA, et al. *Am J Obstet Gynecol*. 2004; 190(5): 1224-9

adverse reactions to the implants, no signs of infection related to the implants, and no need for implant removals.

In conclusion, the results of this study demonstrate that the Adiana Procedure is safe, as evidenced by the lack of any serious adverse events related to the device during the treatment procedure and only one anticipated, serious adverse event related to the hysteroscopic procedure. Additionally, adverse events reported during and immediately following the procedure are comparable to those reported in the published literature, thus indicating that the Adiana Procedure is tolerated as well as other hysteroscopic procedures. Finally, safety in the long-term wearing of the device, with more than 16,000 patient-months of exposure, is demonstrated by the low incidence of device-related events and the absence of allergic or adverse reactions to the implant, infection related to the implants, or need for any implant removals.

**V. D. 7. HYSTERECTOMY POPULATION –  
HISTOLOGY RESULTS**

#### 9.4.2 Summary of Hysterectomy Events

There have been a total of ten hysterectomies reported in patients treated in the EASE trial as of March 1, 2007. Of these, seven cases were considered serious adverse events based on criteria established in the EASE Trial protocol (overnight hospitalization). The remaining three hysterectomies are considered adverse events (uncomplicated out-patient procedures). See Table 9-4 below for a summary of events by patient.

##### Indication

Seven cases out of ten had menorrhagia as the primary indication; two cases out of ten had complaints of dysmenorrhea or pelvic pain as the primary indication; one case out of ten had a pre-cancerous lesion of the cervix as the primary indication. In one case medical treatment of Multiple Sclerosis was considered the cause of menorrhagia. (See Appendix 13.3.5 for individual case reports).

##### Timing and Age

Four of the ten hysterectomy cases occurred prior to 24 months post-device placement. Of these cases, two had a primary complaint of menorrhagia, one of dysmenorrhea and one of a precancerous cervical lesion. All four patients had a prior history of dysmenorrhea and two were 30 years old or less.

The remaining six hysterectomy cases occurred between 30 and 48 months post-device placement. All six had a primary complaint of menorrhagia and were in women over 30 years old.

##### Explant Tissue Examination

Of the ten patients who have undergone hysterectomies, eight were consented for further examination of explant tubal tissue and tissue was successfully obtained. The explanted samples were prepared for histological analysis and slides were reviewed by [REDACTED]

Results from the histological evaluation of all specimens indicated 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. A detailed report of the hysterectomy explant histology evaluation can be found in Appendix 13.6.

**Table 9-4: Summary of Hysterectomies**

<u>Patient ID</u>	<u>Age at Event</u>	<u>Year of Follow-up in which event occurred</u>	<u>Type of Procedure</u>	<u>Explant tissue collected</u>
	40	5	Out-patient	Yes
	35	4	Hospitalization	Yes
	41	3	Out-patient	Yes
	46	4	Hospitalization	Yes
	42	4	Hospitalization	Yes
	36	3	Hospitalization	No
	31	2	Out-patient	No
	26	2	Hospitalization	Yes
	27	2	Hospitalization	Yes
	31	2	Hospitalization	Yes

Discussion

The EASE Trial hysterectomy rate of 1.6% in the patient population that received either unilateral or bilateral implants (n=625) appears to be within reasonable expectation compared to findings in studies reported in the literature. Follow-up is inadequate to provide statistical analysis at this time; however, the DSMB reviewed all study cases and the current literature described below to support this conclusion.

Goldhaber (Goldhaber, Armstrong et al. 1993)<sup>61</sup> first reported on an elevated risk of post sterilization hysterectomy in a retrospective analysis of historical discharge summaries of 40,000 sterilized parous women compared to age and parity matched controls. Sterilized women were significantly more likely than the comparison group (relative risk (RR) = 1.35, 95% CI 1.65-2.13) to undergo hysterectomy and relative risk was highest for women sterilized at a younger age (RR = 2.45 at age 20-24). Risk was not related to degree of tissue damage or method of occlusion. The authors concluded that although a latent biologic effect was possible, the risk might be related to the relative willingness of sterilized women to have their uteri removed. Hillis (Hillis, Marchbanks et al. 1998)<sup>62</sup> reported higher hysterectomy rates for sterilized vs. non-sterilized women in the CREST cohort. When compared to women whose husbands had vasectomy the five year cumulative probability of hysterectomy was 8% in sterilized women and 2% in the control group. The increased risk was observed across all methods of tubal occlusion. Hillis (Hillis, Marchbanks et al.

<sup>61</sup> Goldhaber, M. K., M. A. Armstrong, et al. (1993). "Long-Term Risk of Hysterectomy among 80,007 Sterilized and Comparison Women at Kaiser Permanente, 1971-1987." American Journal of Epidemiology 138(7): 508-521.

<sup>62</sup> Hillis, S. D., P. A. Marchbanks, et al. (1998). "Higher hysterectomy risk for sterilized than nonsterilized women: findings from the U.S. Collaborative Review of Sterilization. The U.S. Collaborative Review of Sterilization Working Group." Obstetrics and gynecology. 91(2): 241-6.



1997)<sup>63</sup> also reported that in the same cohort the cumulative probability of undergoing hysterectomy 14 years after sterilization was 17%; the highest rates were seen in women with menstrual disorders prior to sterilization.

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<sup>63</sup> Hillis, S. D., P. A. Marchbanks, et al. (1997). "Tubal sterilization and long-term risk of hysterectomy: findings from the United States collaborative review of sterilization. The U.S. Collaborative Review of Sterilization Working Group." Obstetrics and gynecology. 89(4): 609-14.

**SECTION BREAK**

## Hysterectomy Histology Report EASE Clinical Trial

### Overview

Cytec has been conducting a clinical evaluation of the Aadiana Transcervical sterilization system under a protocol entitled:

### ***A Multi-Center, Prospective Evaluation of the Aadiana System for Transcervical Sterilization Using Electrothermal Energy in Women Aged 18-45 - The EASE Trial***

Objectives of this trial are:

- 1) To demonstrate that the Aadiana System is effective in preventing pregnancy over a 12-month wearing period
- 2) To describe the device placement rates, safety of device placement and wearing, and patient satisfaction and comfort with device placement and wearing

During this trial, adverse events have been collected from this population. Patients reporting symptoms that may lead to a hysterectomy are offered the opportunity to participate in a sub study in which the explanted uterus is analyzed and the Aadiana Matrix is removed and histologically analyzed.

To date, out of ten hysterectomies reported, eight hysterectomy samples have been retrieved, and tissue histology analyzed.

### Occurrences

There have been a total of ten hysterectomies reported in patients treated in the EASE trial as of March 1, 2007. Of these, seven cases were considered serious adverse events based on criteria established in the EASE Trial protocol (overnight hospitalization). The remaining three hysterectomies are considered adverse events (uncomplicated out-patient procedures).

### Indications

Seven cases out of ten had menorrhagia as the primary indication; two cases out of ten had complaints of dysmenorrhea or pelvic pain as the primary indication; one case out of ten had a pre-cancerous lesion of the cervix as the primary indication. In one case medical treatment of Multiple Sclerosis was considered the cause of menorrhagia. (Appendix 13.3.3 in R0071, EASE Report, includes individual case reports).

### Timing and Age

Four of the ten hysterectomy cases occurred prior to 24 months post-device placement. Of these cases, two had a primary complaint of menorrhagia, one of dysmenorrhea and one of a precancerous cervical lesion. All four patients had a prior history of dysmenorrhea and all two were 30 years old or less.

The remaining six hysterectomy cases occurred between 30 and 48 months post-device placement. All six had a primary complaint of menorrhagia and were in women over 30 years old.

#### Pregnancy Outcomes

There were no pregnancies in this subset of patients and implant time ranged from 17 to 48 months.

#### Findings

##### Explant Tissue Examination

Of the ten patients who have undergone hysterectomies, eight were consented for further examination of explant tubal tissue and tissue was successfully obtained. The explanted samples were prepared for histological analysis and slides were reviewed by [REDACTED]

##### Sample Retrieval & Preparation

A total of 15 implants were recovered from 8 patients. Only one implant was recovered from bilaterally treated patient [REDACTED]. One of the patient's tubes was diagnosed patent by HSG and the patient subsequently received a tubal ligation. Transvaginal ultrasound prior to tubal ligation identified an implant in this tube, but no implant was recovered at time of hysterectomy. Since only a small section of the UTJ is removed following the hysterectomy, it is speculated that the matrix may have been inadvertently missed during sample retrieval, or perhaps was disturbed by the prior tubal ligation. The remaining 7 patients were diagnosed bilaterally occluded by HSG.

Each specimen had slides prepared by serial sectioning for histology staining with Haematoxylin and Eosin, special stains (Masson's Trichrome stain for collagen), and numerous immunohistochemical stains for identification of specific cell types in the inflammatory and wound healing response.

##### Evaluation Method

The method of scoring tissue ingrowth into the implant in the Adiana procedure is based upon the mechanism of action. To permanently occlude the fallopian tube, it is desired that ingrowth into the porous implant be space filling and have long-term biocompatibility. It is believed that long-term stability will be achieved through a benign host integration of the implant. Several characteristics are required for complete integration of the implant. It is necessary that there be an adequate blood vessel support to maintain healthy tissues and that the implant not trigger a chronic foreign body inflammatory response which could lead to encapsulation or walling off.

The presence of blood vessels is the hallmark of healthy tissue (Anderson 1993). Biomaterial implants alone do not generally stimulate a sufficient microvascular supply for full function (Kidd, Nagle et al. 2002). The lesion stimulates angiogenesis by the release of angiogenic factors from macrophages recruited to the wound site (Crowther, Brown et al. 2001). This angiogenesis is important in granulation tissue formation for wound repair (Howdieshell, Callaway et al. 2001). Thus, the lesion directs the ingrowth toward healthy tissue by the formation of an adequate blood supply rather than the formation of scar tissue and/or fibrotic capsule around the implant.

While an acute inflammatory response to the lesion is expected, the desire for long-term acceptance of the implant suggests the absence of a chronic inflammatory response would be beneficial. A chronic inflammatory response might lead to walling off of the implant, decreased blood supply and eventual necrosis of the tissue ingrowth.

██████████ employed five parameters to evaluate biocompatibility, inflammatory response and wound healing response. These five parameters include acute inflammation, chronic inflammation, tissue ingrowth, foreign body reaction, and fibrous capsule formation. Acute inflammation was identified by the presence of polymorphonuclear leukocytes. Chronic inflammation was identified by the presence of monocytes and lymphocytes. Tissue ingrowth was identified by evaluating the extent of fibroblast proliferation as well as angiogenesis into the pores of the implant. Foreign body reaction was identified by the presence of macrophages and foreign body giant cells on the surface of the implant and fibrous capsule formation was identified by the presence of fibroblasts and fibrosis surrounding the implant. The responses were scored with the following scoring system: 0, none; +1, minimal; +2, mild; +3 moderate; +4 extensive.

### Results

Individual scores for each specimen are provided in the table below. No specimen showed the presence of acute inflammation or chronic inflammation. This indicates the overall biocompatibility of the implant. Tissue ingrowth was identified in all cases as being +4, extensive, with total occlusion of the fallopian tubes. Significant and extensive fibroblast ingrowth into the porous structure was identified with angiogenesis or new blood capillary formation. In all specimens, tissue sections showing the complete occlusion of the fallopian tube with tissue ingrowth into the porous luminal implant was identified. A normal foreign body reaction consisting of macrophages and foreign body giant cells was identified on the surfaces of the pores of the implant as well as the external surface. This layer of macrophages and foreign body giant cells was minimal, 1 to 2 cells in thickness, and was considered to be normal. None of the specimen showed fibrous capsule formation, which is consistent with a biocompatible, porous implant.

Patient No.	Left / Right Tube	Specimen	Acute Inflammation	Chronic Inflammation	Tissue Ingrowth	Foreign Body Reaction	Fibrous Capsule
[REDACTED]	left	AR-1603	0	0	+4	+3	0
	right	AR-1602	0	0	+4	+4	0
	left	AR-1604	0	0	+4	+3	0
	right	AR-1605	0	0	+4	+3	0
	right	AR-1607	0	0	+4	+3	0
	left	AR-1608	0	0	+4	+4	0
	right	AR-1609	0	0	+4	+4	0
	left	AR-1610	0	0	+4	+4	0
	right	AR-1611	0	0	+4	+4	0
	left	AR-1612	0	0	+4	+4	0
	right	AR-1613	0	0	+4	+4	0
	left	AR-1614	0	0	+4	+4	0
	right	AR-1615	0	0	+4	+4	0
	left	AR-1616	0	0	+4	+4	0
	right	AR-1617	0	0	+4	+4	0

Discussion

Overall, the histological evaluation of all specimens indicated 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.

(Attachments; Two reports, [REDACTED], Dated October 16, 2006 & May 17, 2007)

**SECTION BREAK**

## ADIANA EXPLANT EVALUATION

### HISTOLOGY EVALUATION



Histology slides from 8 specimens were received for evaluation of the biocompatibility, inflammatory response, and wound healing of porous silicone rubber implants in fallopian tubes. Each specimen had a significant number of slides prepared by serial sectioning for histology staining with Haematoxylin and Eosin, special stains (Masson's Trichrome stain for collagen), and numerous immunohistochemical stains for identification of specific cell types in the inflammatory and wound healing responses. The Haematoxylin and Eosin stained slides were utilized for this histological evaluation.

Five parameters were evaluated to determine biocompatibility, inflammatory response, and wound healing response. These five parameters are acute inflammation, chronic inflammation, tissue ingrowth, foreign body reaction, and fibrous capsule formation. Acute inflammation was identified by the presence of polymorphonuclear leukocytes. Chronic inflammation was identified by the presence of monocytes and lymphocytes. Tissue ingrowth was identified by evaluating the extent of fibroblast proliferation as well as angiogenesis into the porosity/pores of the porous silicone rubber implant, foreign body reaction was identified by the presence of macrophages and foreign body giant cells on the surfaces of the silicone rubber implant, including the porous surfaces, and fibrous capsule formation was identified by the presence of fibroblasts and fibrosis surrounding the implant. The responses were scored with the following scoring system: 0, none; +1, minimal; +2, mild; +3, moderate; +4, extensive.

The individual scores for each specimen are provided in the attached table. No specimen showed the presence of acute inflammation or chronic inflammation. This indicates the overall

biocompatibility of the porous silicone rubber implant. Tissue ingrowth was identified in all cases as being +4, extensive, with total occlusion of the fallopian tubes. Significant and extensive fibroblast ingrowth into the porous structure was identified with angiogenesis or new blood capillary formation. In all specimens, tissue sections showing the complete occlusion of the fallopian tube with tissue ingrowth into the porous luminal implant was identified. A normal foreign body reaction consisting of macrophages and foreign body giant cells was identified on the surfaces of the pores of the implant as well as the external surface. This layer of macrophages and foreign body giant cells was minimal, 1 to 2 cells in thickness, and was considered to be normal. None of the 8 specimens showed fibrous capsule formation on the outer surface. The 8 specimens showed no fibrous capsule formation, which is consistent with a biocompatible, porous implant.

Overall, the histological evaluation of these 8 specimens indicated the biocompatibility of the porous silicone rubber implant, the capability to provide total occlusion of the fallopian tube by tissue ingrowth into the porous structure of the silicone rubber implant, and the presence of a normal foreign body reaction on these surfaces indicating a normal biocompatible implant response.



October 16, 2006

ADIANA EXPLANT EVALUATION

HISTOLOGY EVALUATION



<u>Specimen</u>	<u>Acute Inflammation</u>	<u>Chronic Inflammation</u>	<u>Tissue Ingrowth</u>	<u>Foreign Body Reaction</u>	<u>Fibrous Capsule</u>
AR-1602 B	0	0	+4	+4	0
AR-1603 B	0	0	+4	+3	0
AR-1603 C	0	0	+4	+3	0
AR-1604 B	0	0	+4	+3	0
AR-1604 C	0	0	+4	+3	0
AR-1605 B	0	0	+4	+3	0
AR-1605 C	0	0	+4	+3	0
AR-1607 A	0	0	+4	+3	0

**SECTION BREAK**

## ADIANA EXPLANT EVALUATION

### HISTOLOGY EVALUATION

[REDACTED]

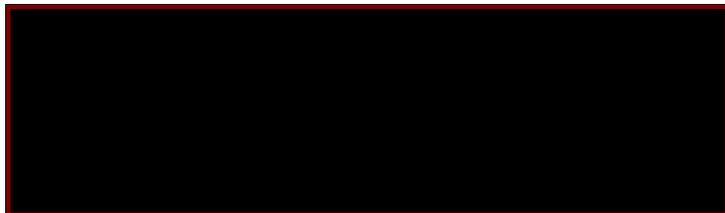
Histology slides from 10 specimens were received for evaluation of the biocompatibility, inflammatory response, and wound healing of porous silicone rubber implants in fallopian tubes. Each specimen had a significant number of slides prepared by serial sectioning for histology staining with Haematoxylin and Eosin, special stains (Masson's Trichrome stain for collagen), and numerous immunohistochemical stains for identification of specific cell types in the inflammatory and wound healing responses. The Haematoxylin and Eosin stained slides were utilized for this histological evaluation.

Five parameters were evaluated to determine biocompatibility, inflammatory response, and wound healing response. These five parameters are acute inflammation, chronic inflammation, tissue ingrowth, foreign body reaction, and fibrous capsule formation. Acute inflammation was identified by the presence of polymorphonuclear leukocytes. Chronic inflammation was identified by the presence of monocytes and lymphocytes. Tissue ingrowth was identified by evaluating the extent of fibroblast proliferation as well as angiogenesis into the porosity/pores of the porous silicone rubber implant, foreign body reaction was identified by the presence of macrophages and foreign body giant cells on the surfaces of the silicone rubber implant, including the porous surfaces, and fibrous capsule formation was identified by the presence of fibroblasts and fibrosis surrounding the implant. The responses were scored with the following scoring system: 0, none; +1, minimal; +2, mild; +3, moderate; +4, extensive.

The individual scores for each specimen are provided in the attached table. No specimen showed the presence of acute inflammation or chronic inflammation. This indicates the overall

biocompatibility of the porous silicone rubber implant. Tissue ingrowth was identified in all cases as being +4, extensive, with total occlusion of the fallopian tubes. Significant and extensive fibroblast ingrowth into the porous structure was identified with angiogenesis or new blood capillary formation. In all specimens, tissue sections showing the complete occlusion of the fallopian tube with tissue ingrowth into the porous luminal implant was identified. A normal foreign body reaction consisting of macrophages and foreign body giant cells was identified on the surfaces of the pores of the implant as well as the external surface. This layer of macrophages and foreign body giant cells was minimal, 1 to 2 cells in thickness, and was considered to be normal. None of the 10 specimens showed fibrous capsule formation on the outer surface. The 10 specimens showed no fibrous capsule formation, which is consistent with a biocompatible, porous implant.

Overall, the histological evaluation of these 10 specimens indicated the biocompatibility of the porous silicone rubber implant, the capability to provide total occlusion of the fallopian tube by tissue ingrowth into the porous structure of the silicone rubber implant, and the presence of a normal foreign body reaction on these surfaces indicating a normal biocompatible implant response.



May 17, 2007

ADIANA EXPLANT EVALUATION

HISTOLOGY EVALUATION



<u>Specimen</u>	<u>Acute Inflammation</u>	<u>Chronic Inflammation</u>	<u>Tissue Ingrowth</u>	<u>Foreign Body Reaction</u>	<u>Fibrous Capsule</u>
AR-1608	0	0	+4	+4	0
AR-1609	0	0	+4	+4	0
AR-1610	0	0	+4	+4	0
AR-1611	0	0	+4	+4	0
AR-1612	0	0	+4	+4	0
AR-1613	0	0	+4	+4	0
AR-1614	0	0	+4	+4	0
AR-1615	0	0	+4	+4	0
AR-1616	0	0	+4	+4	0
AR-1617	0	0	+4	+4	0

SCORE: 0, None; +1, Minimal; +2, Mild; +3, Moderate; +4, Extensive

**SECTION BREAK**

Pages 697-700 have been removed.