

Evaluation of the Gynesonics System for Transcervical Treatment of Symptomatic Uterine Fibroids with Radiofrequency Ablation under Integrated Intrauterine Sonography Guidance

Sonography Guided Transcervical Ablation of Uterine Fibroids (SONATA)

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Person(s) designated by the sponsor to verify the progress of a clinical investigation, i.e. verify that it is conducted, recorded and communicated according to the clinical investigation plan, the written procedures, the ISO 14155 standard and the applicable requirement(s), are identified for each site as applicable on the Investigational Site Listing, available upon request.

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1 REVISION HISTORY

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2 RELATED DOCUMENTS

Statistical Analysis Plan	CL 04502-004
Investigational Site Listing	CL 04502-003

Investigator Brochure:

Sonata Operators' Manual	LS 03818
Sonata Clinical Evaluation Summary	DMR 02768-001
Sonata System Summary of Product Safety Testing	LS 04566

3 ACRONYMS, INITIALS, and DEFINITIONS

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
ADE	Adverse Device Effect
AUB	Abnormal Uterine Bleeding
AUB-C	Abnormal Uterine Bleeding in the presence of Coagulopathy
AUB-L	Abnormal Uterine Bleeding in the presence of Leiomyomata
AUB-M	Abnormal Uterine Bleeding in the presence of Malignancy, Hyperplasia
CA	Competent Authority
CBC	Complete Blood Count
CRF	Case Report Form
Clinically Relevant Fibroids	Fibroids that are ≥ 1 cm and are classified as FIGO type 1 through type 4 fibroids as well as type 2-5 (transmural) fibroids
DVT	Deep Vein Thrombosis
EC	Ethics Committee
EDC	Electronic Data Capture
EQ-5D	Standardized instrument covering five quality of life dimensions for use as a health outcome measure
FIGO	International Federation of Gynecology and Obstetrics
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GnRH-a	Gonadotropin-Releasing Hormone Agonist
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HMB	Heavy Menstrual Bleeding
HTN	Hypertension
HPV	Human Papillomavirus
HRQL	Health Related Quality of Life, a subscale of the UFS-QOL
IDE	Investigational Device Exemption
IFU	Instructions for Use
Intramural fibroid	A fibroid that is completely surrounded by myometrium
IRB	Investigation Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
IUUS	Intrauterine Ultrasound
LCL	Lower Confidence Limit
LNG-IUS	Levonorgestrel Intrauterine System (Mirena®)
LOS	Length of Stay
MRgFUS	Magnetic Resonance-guided Focused Ultrasound
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
NSF	Nephrogenic Systemic Fibrosis
OTE	Overall Treatment Effect
PBAC	Pictorial Blood Loss Assessment Chart

PE	Pulmonary Embolism
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PID	Pelvic Inflammatory Disease
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SERM	Selective Estrogen Receptor Modulator
SIS	Saline-Infused Sonohysterography
SPRM	Selective Progesterone Receptor Modulator
SSS	Symptom Severity Score, a subscale of the UFS-QOL
Submucous fibroid	A fibroid that lies beneath and makes contact with the overlying endometrium to the extent that there is distortion of the endometrial cavity. These are subdivided into three categories: type 0, type 1, and type 2.
Subserous fibroid	A fibroid that makes contact with the uterine serosa (visceral peritoneum) to the extent that it distorts the external contour of the uterus. These are subdivided into three categories: type 5, type 6, and type 7.
Type 0 fibroid	An intracavitary pedunculated fibroid
Type 1 fibroid	A submucous fibroid that is < 50% intramural
Type 2 fibroid	A submucous fibroid that is ≥ 50% intramural
Type 3 fibroid	A fibroid that contacts the endometrium but is otherwise intramural
Type 4 fibroid	A fibroid that is entirely surrounded by myometrium
Type 5 fibroid	A subserous fibroid that is ≥ 50% intramural
Type 6 fibroid	A subserous fibroid that is < 50% intramural
Type 7 fibroid	A pedunculated subserous fibroid
Type 2-5 fibroid	A fibroid that is submucous and subserous, each with less than half their diameter in the endometrial and peritoneal cavities, respectively
TVUS	Transvaginal Ultrasound
UADE	Unanticipated Adverse Device Effect
UAE	Uterine Artery Embolization
UFS-QOL	Uterine Fibroid Symptom and Quality of Life Questionnaire
VAS	Visual Analog Scale
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

4 **STUDY ABSTRACT**

A. STUDY TITLE

Evaluation of the Gynesonics System for Transcervical Treatment of Symptomatic Uterine Fibroids with Radiofrequency Ablation under Integrated Intrauterine Sonography Guidance

B. SHORT TITLE

Sonography-Guided Transcervical Ablation of Uterine Fibroids (SONATA)

C. PROTOCOL NUMBER

CL 04502

D. STUDY OBJECTIVE

To establish the safety and effectiveness of the Sonata System in the treatment of symptomatic uterine fibroids.

E. STUDY DESIGN

Prospective, longitudinal, multicenter, single-arm cohort study with the subject serving as her own control

F. STUDY DEVICE

Sonata® System

G. NUMBER OF SUBJECTS

147 treated subjects; at least 50% will be enrolled and treated within the United States

H. NUMBER OF SITES

Up to 27 investigational sites in the United States, Europe, and Mexico will participate in this study. At least half of the sites will be in the United States.

I. FOLLOW-UP

Subjects will be followed at 10 days, 30 days, 3 months, 6 months, 12 months, 24 months, and 36 months. The 24 and 36 month follow-up timepoints are included to gather longer-term data postmarket and will not be required to support a marketing application.

J. STUDY DURATION

Overall study duration (first subject enrolled through last subject exit) will be comprised of approximately 22 months of subject enrollment and 36 months of follow-up for a total duration of up to 58 months.

Study duration for an individual subject, once she provides her informed consent, will be up to 3 months for screening (including baseline measurements) and treatment, and 36 months for follow up for a total duration of approximately 38-39 months.

K. ENDPOINTS

Endpoints are reached at 12 months. Selected measurements will also be obtained at 10 days, 30 days, 3 months, 6 months, 24 months, and 36 months.

1) CO-PRIMARY ENDPOINTS

- (a) Reduction in menstrual blood loss (MBL) as assessed by pictorial blood loss assessment chart (PBAC)
- (b) Rate of surgical reintervention for heavy menstrual bleeding (HMB) due to treatment failure

2) SECONDARY ENDPOINTS

The following secondary endpoints will also be evaluated

- (a) Safety - adverse device effects
- (b) Reduction in total and perfused fibroid volume as measured by contrast-enhanced MRI
- (c) Change in the symptom severity score and health-related quality of life subscales of the Uterine Fibroid Symptom and Quality-of-Life (UFS-QOL) Questionnaire
- (d) Overall subject treatment outcome using the Overall Treatment Effect Scale (OTE)
- (e) Time to return to normal activity (days)
- (f) Subject Satisfaction
- (g) Change in general health outcome as measured with the EuroQOL EQ-5D questionnaire
- (h) Subject pain and tolerance of procedure
- (i) Mean institutional length of stay (LOS)
- (j) Occurrence of pregnancy and pregnancy outcome
- (k) Change in work productivity and activity impairment due to uterine fibroid symptoms as measured with the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)

L. Selection Criteria

The criteria listed below shall be used to determine if a patient is eligible for entry into the study. A patient must meet ALL of the study inclusion criteria and NONE of the study exclusion criteria in order to be considered eligible for participation.

Inclusion Criteria

- 1) Are premenopausal
- 2) Are ≥ 25 and ≤ 50 years of age at time of enrollment
- 3) Have experienced heavy menstrual bleeding associated with fibroids (AUB-L) for at least the previous three months as reported by the subject
- 4) Have ≥ 1 and ≤ 10 fibroids of FIGO types 1, 2, 3, 4, and/or type 2-5, with diameter ≥ 1.0 cm and ≤ 5.0 cm as determined by credentialed transvaginal sonography or magnetic resonance imaging (MRI). Fibroids of type 5, 6, and 7 do not count toward the clinically relevant total, irrespective of size.
- 5) Have at least one type 1, type 2, type 3, or type 2-5 fibroid.
- 6) Pictorial blood loss assessment chart (PBAC) score ≥ 150 and ≤ 500 during a single baseline cycle
- 7) Consistent menstrual cycles of between 22 to 35 days in duration that meet the following requirements for at least 4 of the last 6 menstrual cycles prior to enrollment as reported by the subject:
 - (1) Variations in cycle length of no more than ± 4 days, and
 - (2) Bleeding duration of 3-10 days, in which the bleeding requires use of more than a pantiliner
- 8) Subject is not at material risk for pregnancy (not sexually active; has been sterilized; does not have a male partner or is in a monogamous relationship with a sterilized male partner; reliably uses barrier contraception, or oral or vaginal hormonal contraception. Subject is willing to maintain use or non-use of non-injectable hormonal contraception uniformly from 6 months pre-study through the 12-month follow-up period.¹ If a subject is on oral/vaginal hormonal contraception solely for bleeding control, or if a subject does not wish to commit to 12 months of consistent hormonal contraceptive use, subject must discontinue use as per the washout period specified in Appendix H.
- 9) Speaks and reads a language for which validated questionnaires are available
- 10) Willing and able to read, understand, and sign the informed consent form, to participate in the study and to adhere to all study follow-up requirements

¹ If changes in medical insurance would require a change in birth control preparation, then the study sponsor will provide the oral contraceptives taken at study enrollment free of charge until the one-year follow-up visit is completed.

Exclusion Criteria

- 1) Pregnancy, as determined by urine or serum hCG obtained within 24 hours prior to treatment with Sonata
- 2) Urgent need for surgery to treat fibroid symptoms
- 3) Desire for current or future childbearing
- 4) Presence of a tubal implant for sterilization
- 5) Postmenopausal by history
- 6) Presence of type 0 fibroids, unless < 1 cm in diameter and are unlikely to contribute to bleeding in the judgment of the investigator.
- 7) Presence of a single polyp ≥ 1.5 cm, or multiple polyps of any size, within the uterine cavity, or excision of polyps within three months of completing any screening procedures
- 8) Any fibroid of FIGO type 1, type 2, type 3, type 4, or type 2-5 with diameter > 5.0 cm as determined by transvaginal sonography or magnetic resonance imaging (MRI)
- 9) Bulk symptoms (pelvic pressure, frequent urination) that significantly interfere with normal daily activities in the presence of one or more fibroids of FIGO type 5, type 6, or type 7
- 10) Exclusive presence of fibroids that, despite meeting other eligibility criteria, are insufficient to explain the severity of symptoms in the judgment of the Investigator
- 11) Presence of clinically relevant fibroids that cannot be treated for technical reasons (e.g. cervical fibroid)
- 12) Presence of an extrauterine pelvic mass that has not been diagnosed as benign
- 13) IUD/IUS in situ within the washout period specified in Appendix H prior to undergoing any screening procedures
- 14) Not used
- 15) Previous procedure for fibroids or heavy menstrual bleeding other than myomectomy. Examples of excluded procedures: endometrial ablation,

- uterine artery/fibroid embolization, uterine artery occlusion, MR guided focused ultrasound, radiofrequency ablation.
- 16) Myomectomy by any route within 12 months prior to undergoing any screening procedures, or myomectomy > 12 months with less than 6 months of symptom relief
 - 17) Any abnormality of the endometrial cavity that, in the judgment of the Investigator, obstructs access of the Sonata Handpiece to the endometrial cavity or fibroids (e.g., significant intrauterine synechiae)
 - 18) Contraindication to MRI, including MR-incompatible implants, allergy to contrast media or claustrophobia, and weight that is above the limitation of the site-specific MRI scanner credentialed for the study
 - 19) Total uterine volume \geq 1000 cc as determined by transvaginal sonography
 - 20) Clinically significant adenomyosis based on sonography; presence confirmed by MRI (defined as more than 10% of the junctional zone measuring more than 10 mm in thickness as measured by MRI)
 - 21) Confirmed or suspected diagnosis of clinically relevant endometriosis
 - 22) One or more clinically relevant fibroids that are significantly calcified. If suspicion of calcification, refer to MRI. (Significant calcification is defined as

- being associated with a majority of the fibroid not showing enhancement on volume via contrast-enhanced MRI)
- 23) Previous pelvic irradiation
 - 24) Not used
 - 25) Renal insufficiency [serum creatinine \geq 1.5 mg/dL (132.6 μ mol/L)]
 - 26) Evidence of disorders of hemostasis (AUB-C) as assessed through structured interview and confirmed by hematologic evaluation consistent with a coagulopathy (see Appendix D)
 - 27) Abnormal cervical cytology that is unevaluated or untreated in adherence with national guidelines
 - 28) Endometrial hyperplasia (AUB-M), including simple hyperplasia without atypia, as determined by an endometrial biopsy within 12 months prior to enrollment
 - 29) Confirmed abdominal / pelvic malignancy within the previous five years
 - 30) Active pelvic infection (e.g., active salpingitis or other pelvic inflammatory disease) or current positive testing for pelvic gonorrhea or chlamydia; entry into the study would require a test of cure after treatment
 - 31) Use of a GnRH agonist, depomedroxyprogesterone acetate or other hormonally-relevant medication within the washout period as specified in Appendix H prior to undergoing any screening procedures
 - 32) Use of an antifibrinolytic agent while undergoing any screening procedures.
 - 33) Current use of anticoagulant therapy (warfarin derivatives or heparin)
 - 34) Chronic pelvic pain (disruptive for at least six months) or baseline pelvic or menstrual pain $>$ 6 as captured using the Numeric Rating Scale (NRS-11) as shown in Appendix J.2
 - 35) Chronic uncontrolled moderate and severe hypertension. (Chronic mild hypertension may be enrolled after obtaining medical clearance from a physician not participating in the study.)
 - 36) A hypoplastic or otherwise short uterus (distance from the top of the endometrial cavity to the external cervical os $<$ 4.5 cm, as determined by transvaginal sonography or prior uterine sounding)
 - 37) Major medical or psychiatric illness or other factors that, in the judgment of the Investigator may affect general health or subject's ability to adhere to the follow-up schedule or provide valid subject self-assessment data
 - 38) Any other reason for which, in the opinion of the Investigator, the individual study subject is not appropriate or suitable for participation in the clinical trial

² McCaffery, M., & Beebe, A. (1993). Pain: Clinical Manual for Nursing Practice. Baltimore: V.V. Mosby Company.

5 INTRODUCTION

Uterine fibroids or myomata are the most common benign tumors in women. The prevalence of fibroids is approximately 20-25% in adult women, and the incidence increases with premenopausal age. The lifetime risk of developing fibroids is as high as 70% in white women and greater than 80% in women of African ancestry³. Most fibroids are asymptomatic. However, depending on the size and location of the tumors, fibroids can be symptomatic and may involve one or more of the following: heavy menstrual bleeding (HMB), dyspareunia, dysmenorrhea, anemia, pelvic/abdominal pressure, urinary retention, constipation, subfertility, pregnancy loss and preterm labor. Because they are prevalent and often symptomatic, fibroids impact the quality of life of millions of women and are associated with an increased utilization of health care resources involving treatments that are often invasive and expensive⁴.

Surgical options for treatment of myomata include hysterectomy and myomectomy, each of which can be performed via a number of approaches, such as laparotomy, laparoscopy, and hysteroscopy. Hysterectomy is the most common treatment for fibroids in the United States and, as with other surgical procedures, is associated with morbidity and mortality.

Pharmacotherapy with agents such as GnRH agonists is impractical as a long-term treatment due to their costs, side effects, and risks. Fibroids return to baseline size within weeks to months once such medications have been discontinued.⁵ However, GnRH agonists can be a useful adjunct to surgical procedures.

Uterine artery embolization (UAE) is an interventional radiology procedure that treats fibroids by blocking their blood supply. This involves catheterization of one or both femoral arteries and selective embolization of the uterine arteries. Despite its minimally invasive nature, UAE has been associated with post-procedure morbidity and complications, including post-embolization syndrome, rare uterine necrosis and, particularly in women 40 years of age and over, premature ovarian failure⁶.

A technique called magnetic resonance-guided focused ultrasound (MRgFUS) uses a therapeutic ultrasound source guided by real-time MR imaging. This approach has been shown to provide symptomatic relief from myomas. However, the degree of fibroid volume reduction may be much less than that seen after UAE. Adoption has been limited due to the length of time required for treatment, suboptimal reimbursement and the need for costly equipment in combination with an MRI system⁷.

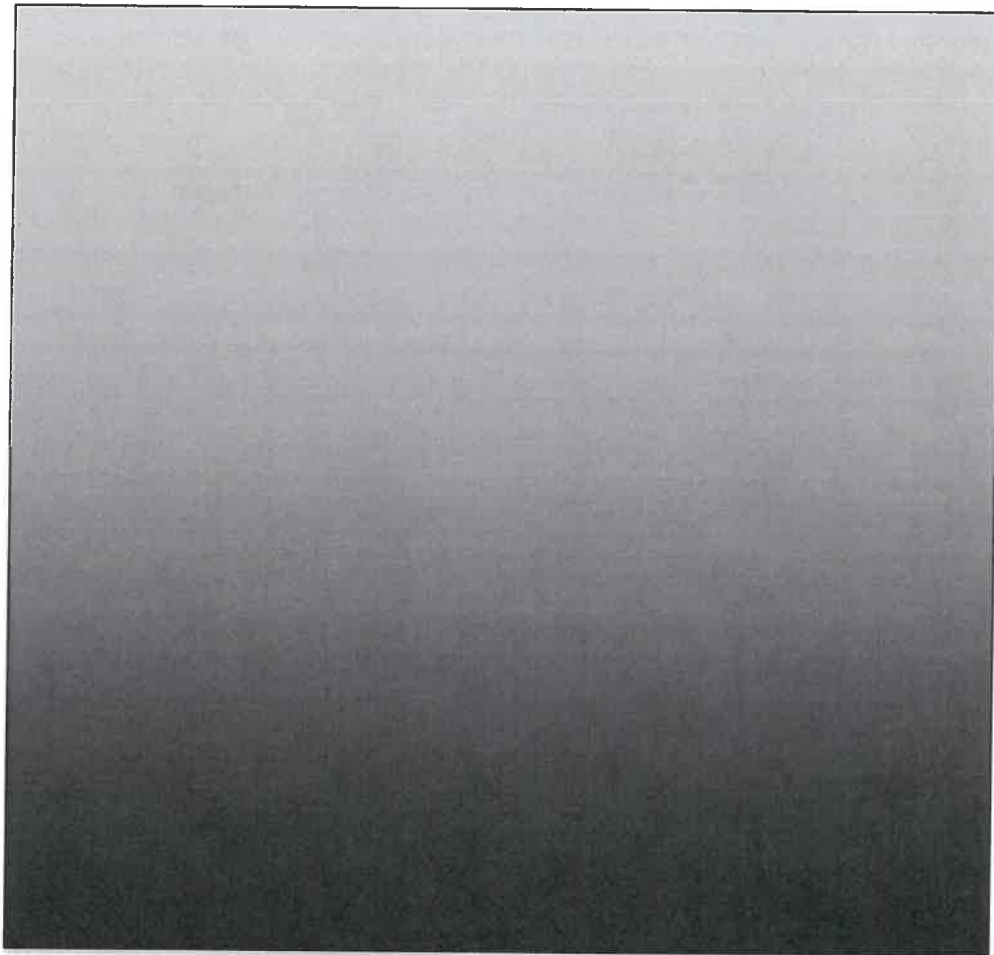
Gyonesonics has developed a device for performing minimally invasive transcervical fibroid visualization and ablation, the Sonata System. The Sonata System combines

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- ³ Baird D, Dunson D, Hill M, Cousins D, Schectman J. "High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence." *Am J Obstet Gynecol* 2003; 188: 100-7.
- ⁴ Lefebvre G, Vilos G, Allaire C, Jeffrey J, Arneja J, Birch C, Fortier M, Wagner MS; Clinical Practice Gynaecology Committee, Society for Obstetricians and Gynaecologists of Canada. "The management of uterine leiomyomas." *J Obstet Gynaecol Can.* 2003 May;25(5):396-418; quiz 419-22.
- ⁵ Broekmans FJ. GnRH agonists and uterine leiomyomas. *Hum Reprod.* Nov 1996;11 Suppl 3:3-25.
- ⁶ Volkens NA, Hehenkamp WJ, Birnie E, deVries C, Holt C, Ankum WM, Reekers JA. "Uterine artery embolization in the treatment of symptomatic uterine fibroid tumors (EMMY trial): periprocedural results and complications." *J Vasc Interv Radiol.* 2006; 17:471-480.
- ⁷ Stewart EA, Ravinovici J, Tempany CM, Inbar Y, Regan L, Gostout B, Hesley G, Kim HS, Hengswt S, Gedroyc WM. "Clinical outcomes of focused ultrasound surgery for the treatment of uterin fibroids." *Fertil Steril.* 2006 Jan; 85(1): 22-9.

intrauterine ultrasound (IUUS) with radiofrequency (RF) ablation in a single handpiece. Sonata is suitable in an inpatient or outpatient setting, and is intended to provide focal treatment of symptomatic fibroids responsible for heavy menstrual bleeding (HMB).

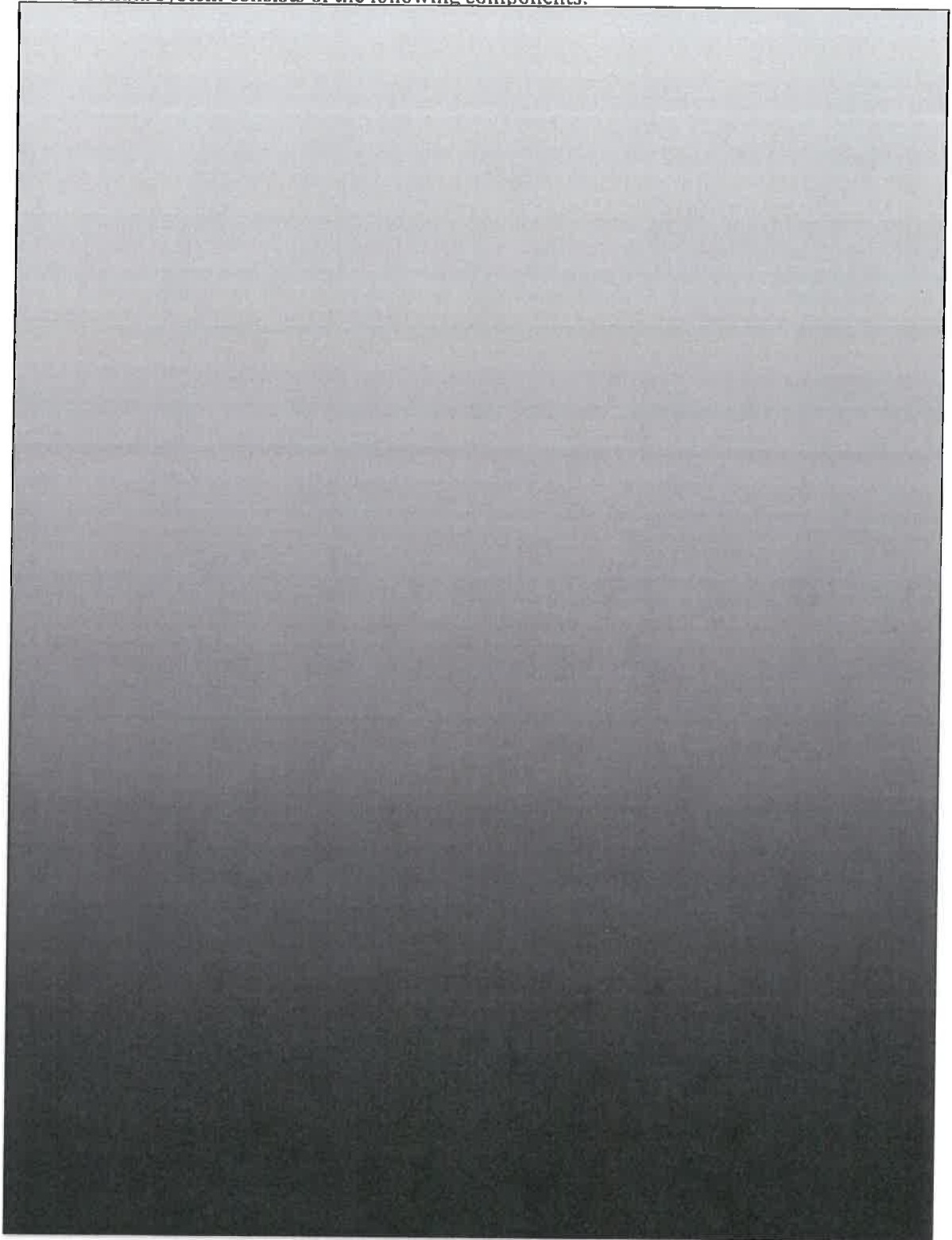
6 STUDY DEVICE AND PROCEDURES

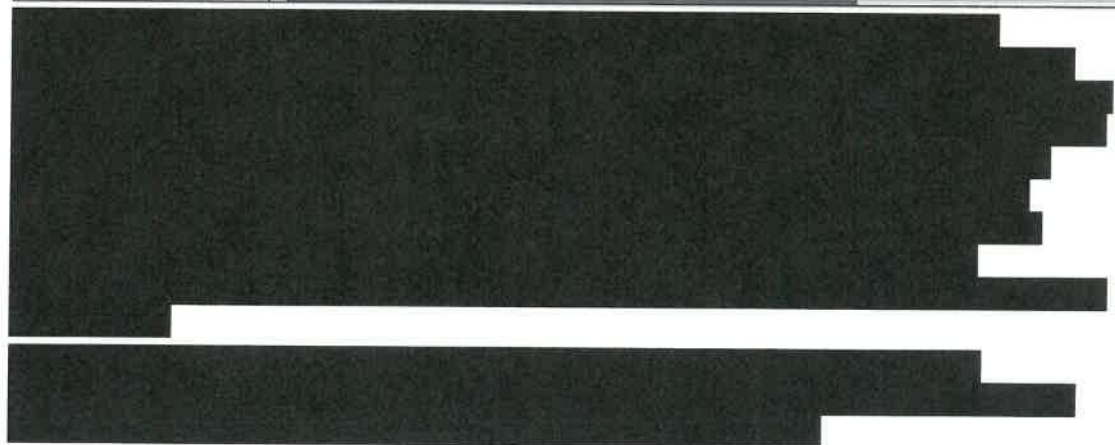
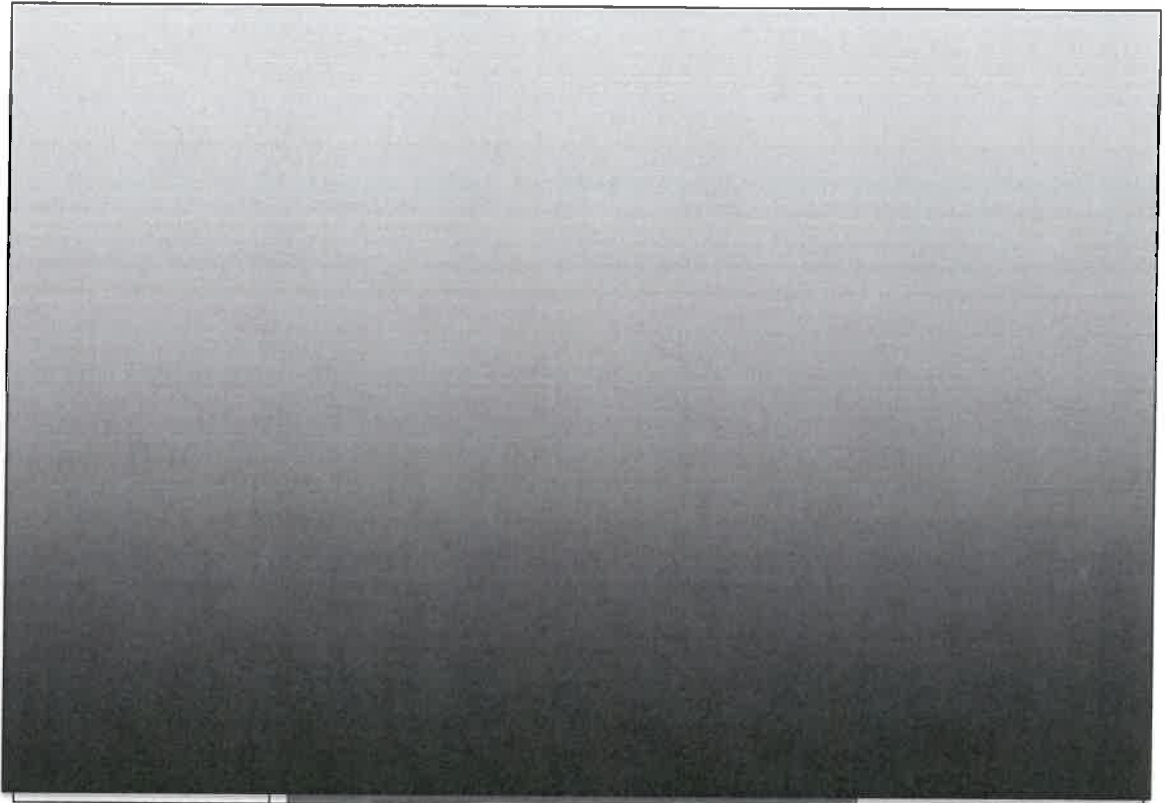
The Sonata™ System is intended for the transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding, under intrauterine ultrasound guidance.

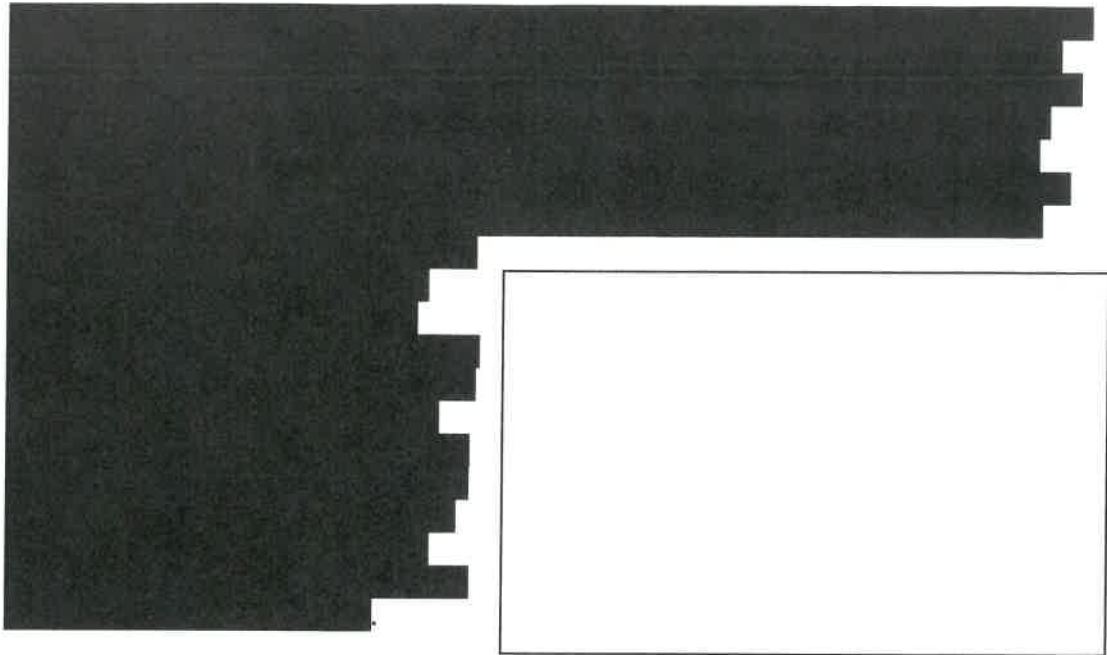


6.1 Sonata System

The Sonata System consists of the following components:







6.2 Treatment Procedure

[Redacted text block containing multiple lines of blacked-out content under the heading '6.2 Treatment Procedure']

7 STUDY OBJECTIVE

The objective of this study is to establish the safety and effectiveness of the Sonata System in the treatment of symptomatic uterine fibroids.

8 STUDY DESIGN AND SAMPLE SIZE

The study is designed as a prospective, longitudinal, multicenter, single-arm cohort study with the subject serving as her own control. A baseline assessment of Menstrual Blood Loss (MBL), fibroid volume, fibroid-associated symptoms/quality-of-life (UFS-QOL), general quality of life (EQ-5D), and work productivity and activity impairment (WPAI:SHP) will be collected, which will allow a subject to serve as her own control.

The single-arm design is consistent with regulatory precedent for pivotal studies of devices intended for the treatment of uterine fibroids. Likewise, the co-primary endpoints of reduction in menstrual blood loss and reintervention are consistent with regulatory precedent for fibroid studies. Use of the pictorial blood loss assessment chart is consistent with regulatory precedent for other pivotal studies involving menstrual blood loss as a primary endpoint, such as studies of thermal endometrial ablation devices. The validity of the patient inclusion / exclusion criteria is supported by inclusion of patients with heavy menstrual bleeding (HMB) and fibroid types likely responsible for HMB, and exclusion of other causes such as adenomyosis or as indicated by presence of irregular bleeding.

The sample size for this study is at least 125 treated subjects to achieve 90% power with α level equal to 0.05 and an assumed success rate of 60%. To allow for 15% loss to follow-up, up to 147 women will be enrolled and treated. The statistical rationale for this sample size may be found in the Statistical Analysis Plan.

Overall study duration (first subject enrolled through last subject exit) will be comprised of approximately 22 months of subject enrollment and 36 months of follow-up post-treatment for a total study duration of up to 58 months.

Study duration for an individual subject, once she provides her informed consent, will be up to 3 months for screening (including baseline measurements) and treatment, and 36 months for follow-up for a total duration of approximately 38-39 months.

9 ENDPOINTS

Endpoints are reached at 12 months. Selected measurements will also be obtained at 10 days, 30 days, 6 months, 24 months, and 36 months.

9.1 CO-PRIMARY ENDPOINTS & SUCCESS CRITERIA

Table 1 provides a list of the test method, subject success criteria, and study success criteria for the co-primary endpoints. The co-primary endpoints are reached at 12 months.

Table 1 Co-Primary Endpoints & Success Criteria

Co-Primary Endpoint	Test Method	Subject Success Criteria ^{Note 1}	Study Success Criteria ^{Note 2}
Reduction in Menstrual Blood Loss (MBL) at 12 months	Pictorial blood loss assessment chart (PBAC), Appendix F. This is a validated measure of MBL ⁹ . Scoring instructions are included in Appendix G.	≥ 50% reduction in PBAC score, and a final PBAC score < 250	LCL of the percentage of subject success ≥ 45%
Rate of surgical re-intervention for HMB due to treatment failure at 12 months	Surgical re-intervention for HMB due to treatment failure	No surgical re-intervention for HMB due to treatment failure at 12 months	LCL of the percentage of subject success ≥ 75%

Table Notes

- 1) Subject success is calculated separately for the two co-primary endpoints, such that it is possible for a subject to be considered a success for one co-primary endpoint and not for the other.
- 2) Study success is achieved if both of the study success criteria are met.

⁹ Janssen C, Scholten P, Heintz P. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet & Gynec.* 1995;85:977-982.

9.2 SECONDARY ENDPOINTS

Table 2 provides a list of the secondary endpoints in the study and the method of measurement for each. The secondary endpoints are reached at 12 months.

Table 2 Secondary Endpoints

Secondary Endpoint	Test Method
Safety - Adverse Device Effects	Procedure safety will be assessed by recording all adverse device effects that occur during or subsequent to treatment on the day of the procedure. Longer-term safety will be assessed by recording at each follow-up visit any untoward medical occurrence since baseline. Each adverse device effect will be assessed for severity.
Reduction in total and perfused fibroid volumes	Change in total and perfused volume of clinically relevant fibroids will be determined by comparing contrast-enhanced MRI at baseline and at 12 months. All MRI's will be forwarded to a central reader (core lab).
Change in the symptom severity and quality of life subscales of the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) Questionnaire	The Symptom Severity Score (SSS) and Health-Related Quality of Life Score (HRQL) are calculated from a subset of the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, a validated and fibroid-specific assessment tool. ¹⁰ The questionnaire and the SSS component have been used in several studies of subjects with fibroids. A copy of the UFS-QOL questionnaire is included as Appendix B.
Time to return to normal daily activity (days)	Subjects will be given a Treatment Recovery Questionnaire at discharge and asked to complete questions daily regarding return to normal activities for the first two weeks post-procedure. A copy of the questionnaire is included as Appendix C.
Overall subject treatment outcome using the Overall Treatment Effect Scale (OTE)	Subject-perceived overall treatment effect (OTE) will be assessed using the OTE Scale. ¹¹ Subjects will be asked to indicate whether their uterine fibroid symptoms have improved, remained the same, or worsened. If the subject indicates that her symptoms have improved, she will be asked to rate the degree of improvement on a 7-point scale from "almost the same, hardly better at all" (1) to "a very great deal better" (7). If the subject indicates that her symptoms worsened, she will be asked to rate the degree of worsening on a 7-point scale from "almost the same, hardly worse at all" (-1) to "A very great deal worse" (-7). OTE is assessed as part of the Subject Satisfaction Questionnaire included as Appendix I.

¹⁰ Spies JB, Coyne K, Guaou G, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, A new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol.* Feb 2002;99(2):290-300.

¹¹ Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10(4):407-415.

Secondary Endpoint	Test Method
Subject Satisfaction	Subjects will be asked to rate their level of satisfaction with the treatment and whether they would recommend the procedure to a friend with the same health problems. The Subject Satisfaction Questionnaire is included as Appendix I.
Change in general health outcome	EuroQOL EQ-5D. The EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. A copy of the US version of the questionnaire is included as Appendix A. ¹²
Subject pain and tolerance of procedure	Prior to discharge, subjects will be asked to rate their tolerance of the procedure and rate their experience of pain using a pain VAS.
Mean length of stay (LOS)	Length of stay (in hours) will be assessed by recording the duration from the start of the procedure to discharge. If recovery time is not longer than expected and study center scheduling prevents same-day discharge, LOS will be calculated based on the time at which discharge would otherwise have occurred as documented by the Investigator in the CRF.
Occurrence of Pregnancy and Pregnancy Outcome	Subjects will be asked at each study visit about the possible occurrence of pregnancy. If a pregnancy has occurred, information regarding pregnancy outcome will be recorded from subject self-report and from medical records if available at the study site.
Work Productivity and Activity Impairment	WPAI:SHP. The WPAI is a standardized instrument for use in assessing productivity and activity impairment for use in health economics outcomes research. ¹³ The WPAI:SHP is a version of the WPAI as adapted to address a specific health problem. The questionnaire is adjusted from its validated 7-day time frame to a 28-day time frame to capture the impact of uterine fibroids over a full menstrual cycle. A copy of the US English version of the questionnaire is included as Appendix K

¹² Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics*. Jan 2000;17(1):13-35.

¹³ Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4(5):353-65.

10 **SUBJECTS**

10.1 Selection Criteria

Please refer to Section 4L on page 11.

10.2 Subject Identification

Each subject will be assigned a unique subject identification number at the time of signing the informed consent. This subject identification number will be used during screening and retained throughout the study if the subject is enrolled. Investigational sites will keep a confidential log that notes the subject's name and corresponding subject identification number. All case report forms will be tracked, evaluated, and stored using only the subject ID number and initials. No personal identifying information will be included on the case report forms.

"Protected Health Information" will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy rule.

The informed consent form will notify subjects that study monitors, auditors, and representatives of government agencies will have access to personal identifying information to ensure that data reported on the case report forms corresponds to the person who signed the consent form and the information contained in the source documentation.

10.3 Informed Consent Process

- A. The Investigator will obtain written informed consent from the subject using the IRB/EC-approved consent form prior to initiation of any study-specific assessments or procedures that are not part of routine care. The consent form shall be provided in a language understandable to the subject. Consent of the subject is documented by the dated signatures of the subject, witnesses if applicable, the person conducting the consent discussion, and the Investigator if required by the governing IRB.
- B. In some cases, local regulations require one or two impartial witnesses. In these cases, after the written informed consent form and any other written information to be provided to subjects is provided and explained in the subject's own language, and after the subject has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject, and that informed consent was freely given by the subject.

- C. Potential subjects will be given adequate time to review the consent form, ask questions, and consider their options before being asked to sign the form. Informed consent shall be obtained under circumstances that are intended to prevent coercion or undue influence. The information that is given to the subject shall be in language understandable to the subject. The subject will not be led to believe that they are waiving their rights as a subject or the liability of the sponsor or Investigator.
- D. Subjects will be informed that the sponsor and regulatory authorities will have access to personally identifying information for the purposes of monitoring data against source documentation. However, all data stored and presented by the sponsor will be in anonymous form.
- E. One original, signed and dated informed consent will be retained in the subject's study records and a copy (or second original) provided to the subject. A third copy of the consent form, or a progress note documenting the consenting process and date will be added to the patient medical chart in accordance with investigational site policy.
- F. Any modification to the study sample informed consent form made by the Investigational Site must be approved by the sponsor and the IRB/EC before use. Each Investigational Site will provide the sponsor with a copy of the IRB/EC-approved consent forms.
- G. Informed consent completion will be monitored regularly by the sponsor or sponsor representatives.

10.4 Moment of Enrollment

Subjects will be considered "enrolled" in the study once the approved consent form is signed and compliance with all inclusion and exclusion criteria has been verified and documented. At that point, the subject will enter the treatment phase of the study.

10.5 Subject Adherence

- A. The Investigator should instruct the subject regarding the importance of complying with the data collection and follow-up visit requirements. Poor subject adherence may result in the sponsor discontinuing the subject from the study.
- B. Subjects will be asked at each follow-up visit if they have adhered to study instructions regarding continuous use of the same means for birth control.

10.6 Subject Discontinuation or Withdrawal

- A. Subjects may be involuntarily removed from the study for failure to adhere to the protocol, failure to attend follow-up visits, or due to safety reasons. In such cases, the Investigator shall arrange for an exit visit and complete a study exit case report form for the subject.
- B. Subjects may voluntarily withdraw from the study at any time without reason. The Investigator shall make an effort to obtain an exit visit but cannot insist on the visit if the subject does not wish to come in. The Investigator shall complete a study exit case report form with as much information as is available at the time of withdrawal.
- C. In cases of early termination, as many of the month 12 study procedures should be performed as possible at the time of withdrawal. All information relative to the withdrawal must be fully documented in the subject chart.
- D. If the subject requires removal from the study due to medical reasons (i.e. adverse event) or reasons related to the procedure, the site staff should contact the Gynesonics Medical Director. Adverse device effects that are ongoing at the time of withdrawal will be reported and followed up to 6 weeks following the study treatment or until the adverse device effect resolves or is considered stable, whichever comes last, unless the subject has withdrawn consent for any such follow-up. In such cases, the final follow-up can be either a telephone contact or an office visit.
- E. A subject will be withdrawn from the study if, subsequent to enrollment, she is diagnosed with any condition that could affect menstrual bleeding volume, or if she becomes pregnant at any time following Sonata treatment. In the case of pregnancy, the Investigator and study coordinator should make every attempt to obtain basic pregnancy outcome information and complete the applicable case report form.
- F. A subject may be withdrawn after enrollment and before receiving the study treatment if, at the Investigator's discretion, she has developed a general health condition that would increase risks from study treatment

10.7 Subject Cost and Compensation

Subjects will not need to pay for any of the protocol-driven visits, procedures, or materials during the course of this study.



10.8 Research-Related Injury

If the subject is injured as a result of her participation in this study, the subject will be treated appropriately until resolution or stabilization of the injury. If it is determined that the Sonata treatment is responsible for physical injury to the subject, the sponsor will cover the cost of treatment for the injury, provided that the Sonata treatment was performed according to accepted medical practice and in accordance with the study protocol, the Instructions for Use, and other instructions provided by the sponsor, and to the extent that such costs are not covered by the subject's health insurance policy. The sponsor will not cover non-medical expenses and will not pay any compensation other than that which national laws may require.

10.9 Contact for Follow-up and Loss to Follow-up

Follow-up visits should be scheduled when the subject is present for the preceding visit. The Investigational Site may utilize postal mail, e-mail, and/or phone calls to send visit reminders.

Subjects who miss a study visit should be contacted immediately by the Investigational Site to determine the reason for the missed visit and to reschedule the visit as soon as possible to meet the study visit window. If the subject cannot be located after 5 attempts through a variety of communication modes (phone, email, letter), then the subject will be considered lost to follow-up. The Investigational Sites should collect multiple contact information (home phone, cell phone, work phone, email, home address, etc.) from the subject in order to minimize loss to follow-up. All attempts to contact the subjects will be documented and retained in the subject study record.

11 STUDY INVESTIGATORS

11.1 Investigational Sites

Up to 27 investigational sites may participate in this study in the United States, Europe, and Mexico.

11.2 Investigator Selection

- A. To qualify for participation in this study, investigators will have performed open and minimally invasive gynecologic procedures involving ultrasound, hysteroscopic surgery and electrosurgery, and have extensive experience to safely manage both anticipated and unanticipated operative and investigational occurrences.
- B. Selection criteria will include
 - 1) Experience with hysteroscopic and/or laparoscopic surgery and electrosurgery
 - 2) General proficiency with ultrasound

- 3) Access to a fibroid / HMB patient population that is sufficient to meet enrollment goals
 - 4) Study coordinator/research coordinator with sufficient time to dedicate to study
 - 5) Adequate facilities to reprocess the Sonata IUUS Probe according to the Instructions for Use
 - 6) Access to MRI
 - 7) Willingness to comply with all study requirements imposed by the protocol, Investigator Agreement, IRB / EC or equivalent review board, and local Ministry of Health regulations as applicable
 - 8) Not participating in a competing study
 - 9) Not on the FDA debarment list or otherwise restricted or disqualified as a clinical investigator by the FDA
- C. Selected investigators will include a mix of academic and community or private physicians who meet the required qualifications above.

11.3 Investigator Training

Investigators will undergo a hands-on training program prior to performing their first Sonata treatment. The record of complete training will be signed by the trainer and the Investigator prior to performance of any treatment. Initial treatments will be supervised by the Gynesonics case support team.

11.4 Investigator Discontinuation

Prior to participation in the study, all investigators must sign the Investigator Agreement, which outlines the Investigator's obligations in the study. The sponsor may elect to discontinue, or suspend, the Investigator's participation in the study due to poor study compliance, lack of compliance with applicable regulations or IRB/EC requirements, or insufficient recruitment of study subjects.

12 STUDY FLOW AND VISIT SCHEDULE

The study will be conducted in three phases as discussed below and depicted in Figure 1.

Consent

1. Screening and baseline phase
2. Treatment phase
3. Follow-up phase

Each of these phases is discussed separately below, following Table 3 Schedule of Screening Assessments and Table 4 Schedule of Study Assessments.

Overall study duration (first subject enrolled through last subject exit) will be comprised of approximately 22 months of subject enrollment and 36 months of follow-up post-treatment for a total duration of up to 58 months.

Study duration for an individual subject, once consented, will be up to 3 months for screening (including baseline measurements) and 36 months for follow up for a total duration of approximately 38-39 months.

Figure 1 Study Flow

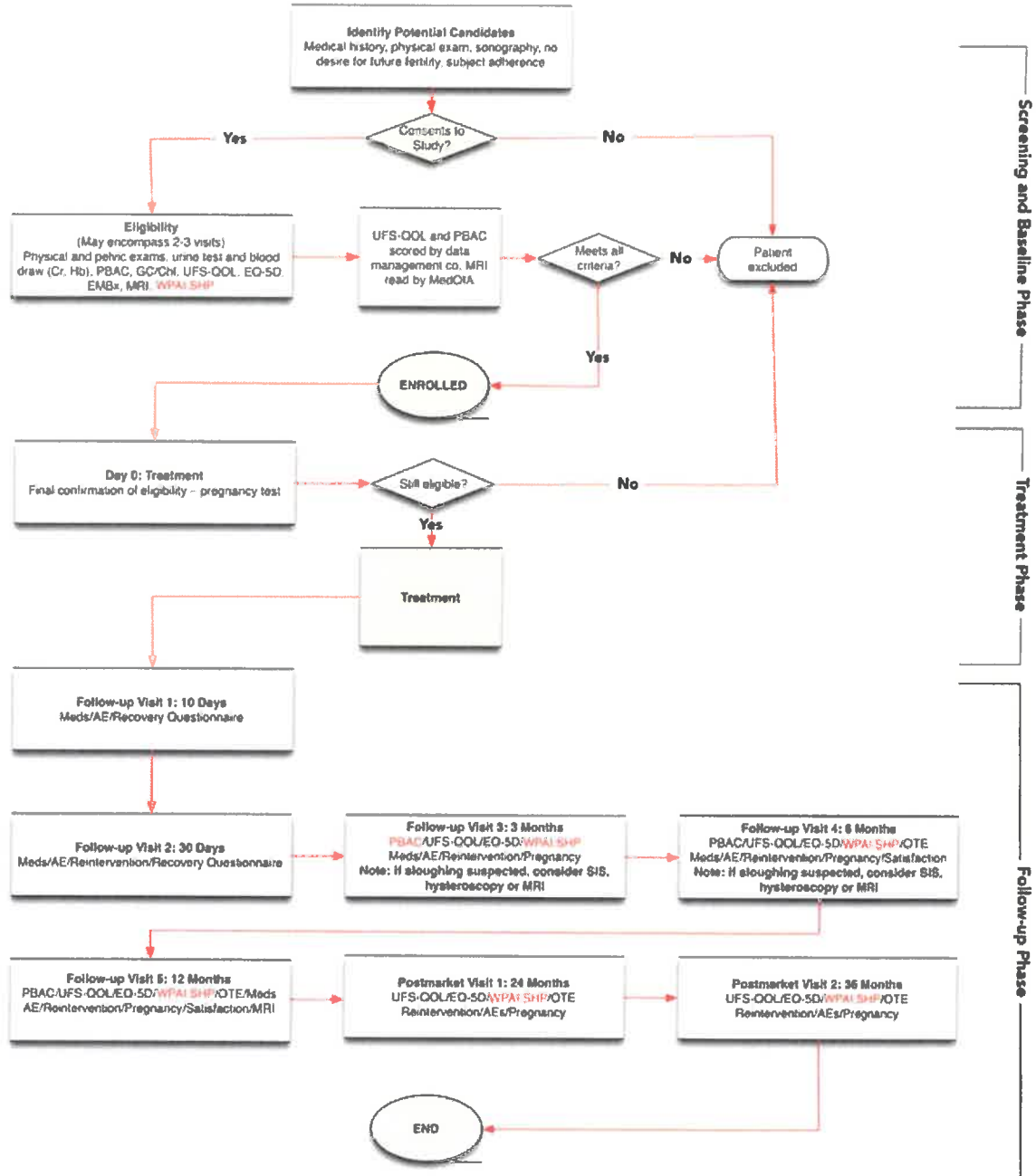


Table 3 Schedule of Screening Assessments

ASSESSMENT	Timing of Assessment Prior to Enrollment				Immediately prior to Treatment
	Any time	Within 3 years	Within 12 Months	Within 3 Months	
Demographics	X				
Medical / Surgical History				X	
Pelvic / Menstrual History (at least last 3 months, but 6 months is preferable)				X	
Pelvic / Menstrual Pain - Numeric Rating Scale (NRS-11)				X	
Menstrual Diary (Pictorial blood loss assessment chart or "PBAC")				X	
Vital signs (temperature, pulse, blood pressure, height, weight)				X	
Pelvic Exam				X	
Cervical cancer screening (per subject history with adherence to national guidelines)		X			
Endometrial biopsy			X		
TVUS (SIS or hysteroscopy is optional for further assessment of the endometrial cavity)				X	
Hemoglobin level				X	
Serum creatinine			X		
Hemostasis assessment			X		
Urine or serum hCG				X	X
Cervical GC and chlamydia testing				X	
ce-MRI (screen MRI). MRI's will be forwarded to a central reader.				X	
UFS-QOL, EQ-5D, and WPAI:SHP Questionnaires				X	
Birth control assessment			Ongoing		
Concomitant medications			Ongoing		
Adverse events			Ongoing		
Final eligibility assessment					X

Table 4 Schedule of Study Assessments

Assessment	Baseline [Screening assessment]	Day 0 Treatment	FU Visit 1 10 day	FU Visit 2 30 day	FU Visit 3 3 mo	FU Visit 4 6 mo	FU Visit 5 12 mo	FU Visit 6 2 year	FU Visit 7 3 year
PBAC	[Screening assessment]				X	X	X		
UFS-QOL, EQ-5D, and WPAI:SHIP Questionnaires	[Screening assessment]				X	X	X	X	X
Vital signs as per screening		X							
Urine/serum hCG, (<i><24 hours pre-procedure</i>)		X							
Venous thromboembolism risk classification		X							
Birth control adherence		X	X	X	X	X	X		
Sonata Treatment & Procedure Assessments <i>Procedure & discharge times, pain VAS & tolerance, anesthesia and concomitant medications</i>		X							
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X		
ce-MRI	[Screening assessment]						X		
Return to normal daily activity**				X					
Post-procedure follow up <i>Update to medical history and symptoms</i>			X	X	X	X	X		
Pregnancy /pregnancy outcome				X	X	X	X	X	X
OTE and Subject satisfaction						X	X	X	X
Surgical Reintervention*						X	X	X	X

* if subject undergoes hysterectomy, operative and pathology reports shall be forwarded to study sponsor

**Subjects who are not back to normal activity will be followed weekly by phone until normal activity has resumed or is not expected to change

12.1 Screening / Baseline Phase

A. Candidate Identification

All patients at the Investigational Sites with a complaint of HMB will be asked about their interest in study participation. For those patients who express an interest to participate, the inclusion/exclusion criteria will be reviewed against existing medical history and the results of any standard clinical work-up to assess preliminary eligibility. Additionally, subjects may be recruited from site catchment area.

If the patient is not excluded on the basis of existing medical history and standard clinical work-up, the patient will be asked to provide informed consent to participate in the study. Before being asked to sign the informed consent form, patients will be given adequate time to consider the potential risks and benefits of study participation, as well as the study's follow-up schedule of 36 months and study requirements to complete various questionnaires and undergo various evaluations. If the patient understands the risks and benefits, and still wishes to participate, she will be asked to sign the informed consent form.

B. Final Screening/Baseline Assessments

Screening assessments include the following as shown in Table 3

- Demographics
- Medical / surgical history, including pregnancy history (prior pregnancies, live birth, c-section) and previous fibroid treatment (surgery, UAE, MRgFUS, GnRH-a, SPRM)
- Interview regarding hemostasis and menstrual history
- Vital signs (including temperature, pulse, blood pressure, height, weight), pelvic exam, and cervical cancer evaluation
- Endometrial biopsy
- Transvaginal ultrasound (TVUS)
- Saline-infused sonohysterography (SIS) or hysteroscopy is optional for further assessment of the endometrial cavity if needed to assess suspicion of intracavitary mass or significant intrauterine synechiae.
- Blood test (hemoglobin, serum creatinine)
- Cervical gonorrhea (GC) and chlamydia testing
- Urine or serum hCG
- UFS-QOL Questionnaire - to be completed with consideration to symptoms experienced during the last three menstrual cycles.
- EQ-5D Questionnaire - to be completed with consideration to symptoms experienced during the first full day of bleeding during the menstrual cycle in which the subject completes the Menstrual diary (PBAC).

- WPAI :SHP Questionnaire – to be completed with consideration to symptoms experienced during the last 28 days (most recent menstrual cycle)
 - Concomitant medications
 - ce-MRI. All MRI's will be forwarded to a central reader (core lab).
 - Menstrual diary (PBAC); Completion instructions will note that only the sanitary products provided should be used during the study while completing the PBAC.
- C. Each site will maintain a screening log noting the reasons for screening failures, including reasons for refusal to consent.
- D. At the time a subject initiates the screening process, she will be given a "Screening Kit" with tote bag, which will be comprised of the following:
- Menstrual diary (PBAC) and instructions
 - EQ-5D Questionnaire
 - A supply of sanitary products in sufficient quantity to cover use for one menstrual cycle while completing the PBAC.
- E. Subjects will be required to use catamenial products (sanitary pads and/or tampons) provided by the study sponsor for the screening and all subsequent study PBAC assessments.
- F. Subjects will be asked at each visit that requires completion of the PBAC whether they have used any non-study provided catamenial products during the time of the assessment. If the proper catamenial products were not used, the subject will be asked to complete a replacement PBAC during her next cycle.

12.2 Treatment Phase

- A. Once the subject has signed the study informed consent form, has completed the screening/baseline assessments, and has met all inclusion and exclusion criteria, the subject can be scheduled to undergo Sonata treatment. The treatment shall be performed in accordance with the physician Instructions for Use. Treatment phase activities will generally occur in a single visit.
- B. Prior to the treatment, the subject will be given a "Subject Post-Treatment Kit", that will be comprised of the following
- Subject Discharge Instructions (Appendix L)
 - Subject Treatment Recovery Questionnaire, with instructions on how to complete and when to return to Investigational Site
 - Study follow-up schedule
 - Investigational site contact information

C. Pre-treatment Work-up

The following assessments will be performed at the time of preadmission testing such that results are available prior to treatment, to update status and to confirm that the subject remains a suitable candidate for the investigational treatment.

- 1) Vital signs (including temperature, pulse, blood pressure, height, weight)
- 2) Urine or serum hCG
- 3) Venous thromboembolism risk classification (Table 5 below) per ACOG Practice Bulletin 84 (Appendix E)
- 4) Birth control adherence
- 5) Concomitant medications

D. Thromboembolism prophylaxis

ACOG Practice Bulletin 84 “Prevention of Deep Vein Thrombosis and Pulmonary Embolism” defines suitable prophylaxis according to the patient risk classification. Risk classification is dependent in part on duration of the surgical procedure. Since it is not known at the beginning of the Sonata treatment whether or not the procedure will last more than 30 minutes, all subjects will be treated, at a minimum, with prophylaxis according to the Moderate Risk category as shown in Table 5. Subjects classified as High Risk must be treated with the corresponding prophylaxis. See Appendix F for complete guidelines.

Table 5 Risk Classification for Venous Thromboembolism (ACOG Page 84)

Level of Risk	Definition	Successful Prevention Strategies
Low	Surgery lasting less than 30 minutes in patients younger than 40 years with no additional risk factors	No specific prophylaxis; early and “aggressive” mobilization
Moderate	Surgery lasting less than 30 minutes in patients with additional risk factors; surgery lasting less than 30 minutes in patients aged 40–60 years with no additional risk factors; major surgery in patients younger than 40 years with no additional risk factors	Low-dose unfractionated heparin (5,000 units every 12 hours), low molecular weight heparin (2,500 units dalteparin or 40 mg enoxaparin daily), graduated compression stockings, or intermittent pneumatic compression device
High	Surgery lasting less than 30 minutes in patients older than 60 years or with additional risk factors; major surgery in patients older than 40 years or with additional risk factors	Low-dose unfractionated heparin (5,000 units every 8 hours), low molecular weight heparin (5,000 units dalteparin or 40 mg enoxaparin daily), or intermittent pneumatic compression device
Highest	Major surgery in patients older than 60 years plus prior venous thromboembolism, cancer, or molecular hypercoagulable state	Low-dose unfractionated heparin (5,000 units every 8 hours), low molecular weight heparin (5,000 units dalteparin or 40 mg enoxaparin daily), or intermittent pneumatic compression device/graduated compression stockings + low-dose unfractionated heparin or low molecular weight heparin Consider continuing prophylaxis for 2–4 weeks after discharge.

Modified from Geerts WH, Pineo GF, Helt JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(suppl):338S–400S.

E. Sonata Treatment

- 1) The treatment shall be performed in accordance with the physician Instructions for Use. Highlights are provided below.
 - (a) The intent is for all clinically relevant fibroids to be ablated during a single treatment session.
 - (b) Coincidental removal of an intrauterine polyp up to a maximum diameter of 1.5 cm and type 0 fibroids < 1.0 cm is allowed.
 - (c) A small number of sponsor representatives (generally one to three individuals) may be present during the procedure to provide equipment support if needed as well as for proctoring and general observation.
- 2) **Treatment and Recovery Assessments**
The following data will be collected on the day of the treatment prior to discharge:
 - (a) Treatment location (e.g. ambulatory care center, operating room, etc.)
 - (b) Treatment time, defined as time the Sonata device is inserted transvaginally to the time it is removed after the last ablation
 - (c) Room time, defined as time subject enters room to time subject exits room
 - (d) Actual discharge time
 - (e) Time that subject would have been eligible for discharge based on treatment recovery status (eg, "discharge in AM" order written) if scheduling, site policy, or non-procedure related health issues extend hospitalization
 - (f) Anesthesia and procedure-related medications
 - (g) Record of fibroids treated/untreated ("Treatment Assessment")
 - (h) Video of intrauterine ultrasound captured during treatment
 - (i) Subject assessment of pain and tolerance to treatment and recovery
 - (j) Pain medication use during recovery
 - (k) Narcotic use during recovery
 - (l) Concomitant meds
- 3) **Discharge Instructions**
Subjects will be given complete discharge instructions and will be cautioned that nothing should be placed in the vagina for 2 weeks following the Sonata treatment

12.3 Follow-up Phase

- A. Follow-up visits will occur in accordance with Table 6 below. The day of the Sonata treatment represents Day 0. Study visits that do not occur within the below time windows will be considered protocol deviations.

Table 6 Follow-up (FU) Visit Windows

Visit	Allowed Visit Date Range
FU Visit 1 - 10 days	± 4 days
FU Visit 2 - 30 days	± 1 week
FU Visit 3 - 3 months	± 2 weeks
FU Visit 4 - 6 months	± 4 weeks
FU Visit 5 - 12 months	± 2 months
FU Visit 6 - 2 years	± 2 months
FU Visit 7 - 3 years	± 2 months

- B. The measurements and evaluations that will occur at each follow-up visit are provided below.

- 1) Follow-up Visit 1: 10 Days (± 4 days)
(Phone Call or visit at Investigator's discretion)

(a) Adverse Events

The primary purpose of Follow-up Visit #1 is to assess safety. Subjects will be asked if they have experienced any untoward medical occurrences since the Sonata treatment. If so, these events will be recorded on the Adverse Event case report form, in accordance with the procedures outlined later in this protocol.

(b) Post-treatment follow up

Subjects will be asked whether there is any change to their medical status. Subjects will be asked specifically if they have experienced any signs or symptoms of fibroid shedding: cramping, bleeding, passage of any tissue per vaginam.

(c) Concomitant Medications

Subjects will be asked about concomitant medications, noting in particular concomitant medications taken for the treatment of HMB.

(d) Adherence with/Continuance of Birth Control Method

Subjects will be asked if they are adhering to their chosen method of birth control, and if there have been any changes in their birth control method, including changes to medication type and preparation.

2) Follow-up Visit #2: 30 Days (\pm 1 week)

(a) Adverse Events

Subjects will be asked if they have experienced any untoward medical occurrences since the Sonata treatment. If so, these events will be recorded on the Adverse Event case report form, in accordance with the procedures outlined later in this protocol.

(b) Return to Normal Daily Activity

Subjects will be asked to submit their completed Treatment Recovery Questionnaire (Appendix C). Subjects who are not back to normal activity will be followed up by phone visits weekly until the subject has resumed normal activity or the reason for not resuming normal activity is not expected to change.

(c) Surgical Reintervention

Subjects will be asked if they have undergone any surgical procedure to treat their heavy menstrual bleeding. If so, the procedure performed and the date of the reintervention will be recorded.

(d) Concomitant Medications

Subjects will be asked about concomitant medications, noting in particular concomitant medications taken for the treatment of HMB.

(e) Pregnancy/Pregnancy Outcomes

Subjects will be asked if they have become pregnant since the last follow-up visit. If so, the subject will be released from all protocol specified follow-up assessments and visits, however the subject will be followed and pregnancy outcomes (including any complications) will be recorded as described in Section 10.6 of this protocol.

(f) Post-treatment follow up

Subjects will be asked whether there is any change to their medical status. Subjects will be asked specifically if they have experienced any signs or symptoms of fibroid shedding: cramping, bleeding, passage of any tissue per vaginam.

(g) Adherence with/Continuance of Birth Control Method

Subjects will be asked if they are adhering to their chosen method of birth control, and if there have been any changes in their birth control method, including changes to medication type and preparation.

Note: During follow-up visit #2, the subject will be given study materials in anticipation of follow-up visit #3, which will be comprised of the following:

- a copy of the EQ-5D Questionnaire (Appendix A). The EQ-5D should be completed during the subject's 3rd menstrual cycle post-treatment, preferably on the first full day of bleeding. It should be completed based solely on symptoms from that cycle.
- Menstrual diary (PBAC) with completion instructions noting that only the sanitary products provided should be used during the study while completing the PBAC.
- A supply of sanitary products in sufficient quantity to cover use for one menstrual cycle for the completion of the PBAC.

3) Follow-up Visit #3: 3 Months (\pm 2 weeks)

(a) UFS-QOL, EQ-5D, and WPAI:SHP Questionnaires

Subjects will be asked to return their completed EQ-5D questionnaire and will be asked to complete the UFS-QOL and WPAI:SHP questionnaires.

(b) Menstrual Diary

Subjects will be asked to return their completed menstrual diary (PBAC) for the menstrual cycle preceding the visit.

(c) Adverse Events

Subjects will be asked if they have experienced any untoward medical occurrences since the Sonata treatment. If so, these events will be recorded on the Adverse Event case report form, in accordance with the procedures outlined later in this protocol.

(d) Surgical Reintervention

Subjects will be asked if they have undergone any surgical procedure to treat their heavy menstrual bleeding. If so, the procedure performed and the date of the reintervention will be recorded.

(e) Pregnancy/Pregnancy Outcomes

Subjects will be asked if they have become pregnant since the last follow-up visit. If so, the subject will be released from all protocol specified follow-up assessments and visits, however the subject will be followed and pregnancy outcomes (including any complications) will be recorded as described in Section 10.6 of this protocol.

- (f) Amenorrhea
If the subject becomes amenorrheic, a pregnancy test (urine or serum hCG) will be performed and, if negative, a serum FSH level determination will also be obtained
- (g) Concomitant Medications
Subjects will also be asked about concomitant medications, noting concomitant medications taken for the treatment of excessive uterine bleeding.
- (h) Post-treatment follow up
Subjects will be asked whether there is any change to their medical status. Subjects will be asked specifically if they have experienced any signs of fibroid shedding: cramping, bleeding, passage of any tissue per vaginam.
- (i) Adherence with/Continuance of Birth Control Method
Subjects will be asked if they are adhering to their chosen method of birth control, and if there have been any changes in their birth control method, including changes to medication type and preparation.

Note: During follow-up visit #3, the subject will be given study materials in anticipation of follow-up visit #4, which will be comprised of the following:

- A copy of the EQ-5D Questionnaire (Appendix A). The EQ-5D should be completed during the subject's 6th menstrual cycle post-treatment, preferably on the first full day of bleeding. It should be completed based solely on symptoms from that cycle. If the subject has become amenorrheic, the EQ-5D may be completed at any time during the follow-up visit window.
- Menstrual diary (PBAC) with completion instructions noting that only the sanitary products provided should be used during the study while completing the PBAC.
- A supply of sanitary products in sufficient quantity to cover use for one menstrual cycle for the completion of the PBAC.

- 4) Follow-up Visits #4-5: 6 Months (\pm 4 weeks) and 12 Months (\pm 2 Months)
- (a) MRI (12 months only)
 - (b) UFS-QOL, EQ-5D, and WPAI:SHP Questionnaires
Subjects will be asked to return their completed EQ-5D questionnaire and will be asked to complete the UFS-QOL and WPAI:SHP questionnaires.
 - (c) Menstrual Diary
Subjects will be asked to return their completed menstrual diary (PBAC) for the menstrual cycle preceding the visit.
 - (d) Adverse Events
Subjects will be asked if they have experienced any untoward medical occurrences since the Sonata treatment. If so, these events will be recorded on the Adverse Event case report form, in accordance with the procedures outlined later in this protocol.
 - (e) Surgical Reintervention
Subjects will be asked if they have undergone any surgical procedure to treat their heavy menstrual bleeding. If so, the procedure performed and the date of the reintervention will be recorded.
 - (f) Pregnancy/Pregnancy Outcomes
Subjects will be asked if they have become pregnant since the last follow-up visit. If so, the subject will be released from all protocol specified follow-up assessments and visits, however the subject will be followed and pregnancy outcomes (including any complications) will be recorded as described in Section 10.6 of this protocol.
 - (g) Post-treatment follow-up
Subjects will be asked whether there is any change to their medical status. Subjects will be asked specifically if they have experienced any signs of fibroid shedding: cramping, bleeding, passage of any tissue per vaginam.
 - (h) Amenorrhea
If the subject becomes amenorrheic, a pregnancy test (urine or serum hCG) will be performed and, if negative, a serum FSH level determination will also be obtained.
 - (i) Concomitant Medications
Subjects will also be asked about concomitant medications, noting concomitant medications taken for the treatment of excessive uterine bleeding.

(j) Subject Satisfaction

Subjects will be asked to rate their satisfaction with the treatment, with responses based on a 6-point Likert scale ranging from “very satisfied” to “very dissatisfied”. They will also be asked if they would recommend the treatment to a friend with the same health problems using a 4-point scale from “definitely yes” to “definitely not”.

(k) Overall Treatment Effect (OTE)

Subjects will be asked to indicate whether their uterine fibroid symptoms have improved, remained the same, or worsened. If the subject indicates that her symptoms have improved, she will be asked to rate the degree of improvement on a 7-point scale from “almost the same, hardly better at all” (1) to “a very great deal better” (7). If the subject indicates that her symptoms worsened, she will be asked to rate the degree of worsening on a 7-point scale from “almost the same, hardly worse at all” (-1) to “A very great deal worse” (-7).

(l) Adherence with/Continuance of Birth Control Method

Subjects will be asked if they are adhering to their chosen method of birth control, and if there have been any changes in their birth control method, including changes to medication type and preparation.

Note: During follow-up visit #4, the subject will be given study materials in anticipation of follow-up visit #5, which will be comprised of the following:

- A copy of the EQ-5D Questionnaire (Appendix A). The EQ-5D should be completed during the subject’s 12th menstrual cycle post-treatment, preferably on the first full day of bleeding. It should be completed based solely on symptoms from that cycle. If the subject has become amenorrheic, the EQ-5D may be completed at any time during the follow-up visit window.
- Menstrual diary (PBAC) with completion instructions noting that only the sanitary products provided should be used during the study while completing the PBAC.
- A supply of sanitary products in sufficient quantity to cover use for one menstrual cycle for the completion of the PBAC.

- 5) Follow-up Visit 6 and 7: 2 and 3 years
(Phone Call or mail at Investigator's discretion)
- (a) UFS-QOL, EQ-5D, and WPAI:SHP Questionnaires
Subjects will be asked to return their completed EQ-5D questionnaire and will be asked to complete the UFS-QOL and WPAI:SHP questionnaires.
- (b) Pregnancy/Pregnancy Outcomes
Subjects will be asked if they have become pregnant since the last follow-up visit. If so, the subject will be released from any remaining protocol specified follow-up assessments and visits, however the subject will be followed and pregnancy outcomes (including any complications) will be recorded as described in Section 10.6 of this protocol.
- (c) Adverse Events
Subjects will be asked if they have experienced any untoward medical occurrences related to the abdomen and/or pelvis since the Sonata treatment. If so, these events will be recorded on the Adverse Event case report form, in accordance with the procedures outlined later in this protocol.
- (d) Surgical Reintervention
Subjects will be asked if they have undergone any surgical procedure to treat their heavy menstrual bleeding. If so, the procedure performed and the date of the reintervention will be recorded.
- (e) Subject Satisfaction
Subjects will be asked to rate their satisfaction with the treatment, with responses based on a 6-point Likert scale ranging from "very satisfied" to "very dissatisfied". They will also be asked if they would recommend the treatment to a friend with the same health problems using a 4-point scale from "definitely yes" to "definitely not".
- (f) Overall Treatment Effect (OTE)
Subjects will be asked to indicate whether their uterine fibroid symptoms have improved, remained the same, or worsened. If the subject indicates that her symptoms have improved, she will be asked to rate the degree of improvement on a 7-point scale from "almost the same, hardly better at all" (1) to "a very great deal better" (7). If the subject indicates that her symptoms worsened, she will be asked to rate the degree of worsening on a 7-point scale from "almost the same, hardly worse at all" (-1) to "A very great deal worse" (-7).

13 RISK/BENEFIT ANALYSIS

The following are the potential risks and benefits of study participation, and the steps taken to minimize anticipated risks.

13.1 Potential Risks

Ultrasound and radiofrequency electrosurgery are both well-established technologies. To qualify for participation in this study, investigators will have performed open and minimally invasive gynecologic procedures involving ultrasound, laparoscopic and/or hysteroscopic surgery and electrosurgery, and have extensive experience to safely manage both anticipated and unanticipated operative and investigational occurrences.

Intrauterine sonography-guided RF ablation does not require the level of uterine distention required for hysteroscopic surgery. The volume of fluid instillation is small, pressure within the endometrial cavity would not be greater than mean arterial pressure, and no large venous sinuses are exposed that would promote fluid intravasation. Therefore, the risks of fluid overload (hyponatremia) and pulmonary/cerebral edema associated with hysteroscopic myomectomy do not apply to the Sonata procedure.

Risks associated with the use of the Sonata System are expected to be similar to other complications associated with hysteroscopic fibroid resection and endometrial ablation, and include the following rare, but serious events:

- Bradycardia or other cardiovascular response to the procedure
- Thermal damage to adjacent organs or tissue
- Air/gas embolism
- Deep venous thrombosis/pulmonary embolism
- Myocardial infarction
- Hemorrhage
- Pelvic infection, including pelvic inflammatory disease (PID), endometritis, or tuboovarian abscess, fibroid or pelvic abscess
- Sepsis
- Bowel or bladder perforation
- Unintended/inadvertent ablation of undiagnosed endometrial carcinoma/uterine sarcoma, leading to delayed diagnosis and a potentially higher cancer stage at the time of diagnosis

Passage of an ablated myoma per vaginam may occur. Lower severity outcomes are associated with smaller fibroids. Passage of a larger fibroid is more likely to require medical or surgical intervention. The incidence is significantly less common than that observed for UAE. Risks associated with surgical intervention are considered equivalent to those associated with standard therapy.

Retention of a device fragment may occur.

Safety of treatment with the Sonata System with respect to future pregnancies has not been studied. For this reason, patients are not able to participate in this study if they may want to become pregnant in the future.

The following more common but less serious side effects and complications can occur:

- Nausea and/or vomiting
- Abdominopelvic pain or cramping
- Vaginal bleeding or discharge, including increased volume due to shedding of treated fibroid tissue
- Cervical/vaginal laceration or tear
- Minor infection, including urinary tract infection, vaginal infection, or IV site infection
- Uterine perforation
- Cervical stenosis
- Hematometrium
- Fever
- Thermal burn at the site of the dispersive electrodes
- Allergic reaction to device materials

There are also standard risks associated with the screening assessments, the chosen anesthesia method, magnetic resonance imaging, and with exposure to gadolinium-based contrast agents used in conjunction with the MRI.

A more detailed discussion of risks is provided in the Investigator's Brochure.

13.2 Previously Reported Adverse Events

The Sonata device has been evaluated in more than 100 subjects in peri- and pre hysterectomy settings, and in 50 subjects under a symptom effectiveness study with eligibility and follow-up similar to this protocol.

There has been one report of death due to myocardial infarction (as listed on death certificate) several days following treatment with an early version of the Sonata System. This event was determined by the Investigator to be not device-related or procedure-related. It was determined by the company's Medical Advisory Board to be **not** device-related, but potentially a delayed procedure-related pulmonary embolus. No autopsy was performed, so cause of death cannot be confirmed.

Among the 50 subjects treated under similar clinical study, there have been two serious adverse events. One report of overnight hospitalization stay without complications for abdominal pain and self-reported fever; the patient was afebrile at initial presentation and during admission. This was determined by the Investigator to be 'probably related' to the Sonata treatment. One report of overnight stay for bradycardia (mild) that was felt by the Investigator to have been related to the general anesthesia used during the procedure.

Non-serious adverse events reported include dysmenorrhea (16%), bleeding (12%), pelvic pain and cramping (12%), urinary tract infection (2%), and passage of a treated myoma per vaginam (2%).

13.3 Risk Minimization

The Sonata System has been designed to include ultrasound visualization and guidance to assist the physician in proper device placement. Therefore, unlike other “blind” transcervical procedures such as endometrial biopsy, D&C, etc., treatment with the Sonata System is done with real-time visualization, which is expected to decrease the risk of perforation.

The risk of thermal injury has been minimized through the inclusion of a custom designed Gynesonics graphic user interface that has a needle guide and a treatment specific algorithm including an “Ablation Zone” and a “Thermal Safety Border” depicted on the ultrasound screen. These guides enable the physician to ensure that the border of the serosa is located outside of the treatment area surrounding the RF needle electrodes. The ablation guides have been validated through bench testing, procedure temperature monitoring, computer modeling and histopathological analysis of extirpated uteri from hysterectomy subjects who were treated with the Sonata System just prior to their hysterectomy. In addition, the risk of thermal injury is very limited with the Sonata System because the power levels of the applied radiofrequency outputs are relatively low and the device is insulated to prevent current diversion.

The risk of thermal burns at the site of the dispersive electrodes is minimized through use of two custom dispersive electrodes with large leading edges, large surface areas, and low impedance. In addition, impedance of the dispersive electrodes is monitored during treatment.

The risk of infection will be minimized through use of sterile technique during the procedure. The Sonata RFA Handpiece is supplied sterile and is disposable. Validated processing instructions are provided for cleaning and sterilization of the reusable intrauterine ultrasound probe prior to use.

The risk of venous thrombosis and pulmonary embolism will be minimized through the use of DVT / PE risk classification and use of appropriate prophylaxis according to ACOG Guidelines.

The risk of unintended/inadvertent ablation of undiagnosed endometrial carcinoma is minimized by inclusion of an endometrial biopsy during screening. Appropriate medication and resuscitation equipment will be available to respond to potential complications.

13.4 Potential Benefits

The main potential benefit to study participation is successful treatment for symptomatic fibroids with a minimally invasive uterine-sparing procedure. As with all clinical studies with regular and long-term follow-up, there are also the potential benefits associated with more frequent health monitoring. Subjects will also be provided with catamenial products free of charge in quantities sufficient to complete the PBAC for the baseline, six- and twelve-month follow-up.

13.5 Risk/Benefit Analysis

The above listed risks and benefits are similar to those for several currently marketed device therapies for subjects with uterine fibroids, particularly other electrosurgical devices deployed hysteroscopically, laser treatment, and MR-guided high-focused ultrasound treatment. There do not appear to be any new risks with the Sonata System that would lead to an unfavorable risk/benefit ratio. Also, compared to more invasive treatment options, such as hysterectomy, laparoscopic myomectomy, laparoscopic RF ablation, and uterine artery embolization, the anticipated risk/benefit ratio for the Sonata System appears to be favorable.

14 **ADVERSE EVENTS AND DEVICE DEFICIENCIES**

14.1 Definitions¹⁴

A. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1: This includes events related to the procedures involved.

NOTE 2: For users or other persons this is restricted to events related to the investigational medical device.

NOTE 3: An elective surgical reintervention for HMB or change in a measured endpoint is not considered an adverse event.

NOTE 4: An overnight stay for observation does not constitute hospitalization for the purposes of this protocol as long as there are no reported adverse events associated with the stay.

B. Adverse Device Effect (ADE)

Adverse Event related to the use of a medical device. This includes:

- 1) Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the medical device.
- 2) Any event that is a result of a use error or intentional misuse.

C. Anticipated

An effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis.

D. Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labeling.

E. Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan.

¹⁴ Reference ANSI/AAMI/ISO 14155:2011

- F. Serious Adverse Event (SAE)
Adverse Event that
- 1) Led to death
 - 2) Led to a serious deterioration in the health of the subject that either:
 - (a) resulted in a life-threatening illness or injury, or
 - (b) resulted in a permanent impairment of a body structure or a body function, or
 - (c) required in-patient hospitalization, or prolongation of existing hospitalization, of more than 24 hours, or
 - (d) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
 - 3) Led to fetal distress, fetal death or congenital abnormality or birth defect

NOTE 1: A planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered to be a serious adverse event.

NOTE 2: If recovery time from treatment with the Sonata System is not longer than expected and site scheduling prevents same-day discharge, overnight stay is not considered prolonged hospitalization for purposes of classification as a serious adverse event.

- G. Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
- H. Unanticipated Adverse Device Effect (UADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis as presented in the Investigators Brochure.
- I. Relatedness
The determination of the level of relatedness of the adverse event to the study device or procedure will be made according to the definitions below. Adverse events considered to be “possibly”, “probably”, or “definitely”

related to the use of the study device will be classified as an ADE or an SADE for purposes of statistical analysis.

- 1) **Definitely Related**
The adverse event was directly and clearly related to the Sonata device or procedure
- 2) **Probably Related**
The adverse event may have been related to the Sonata device or procedure. Alternative causes are possible but are less likely
- 3) **Possibly Related**
The adverse event may have been related to the Sonata device or procedure, but an alternative cause is equally likely
- 4) **Unlikely to be Related**
The adverse event may have been related to the Sonata device or procedure, but an alternative cause is more likely
- 5) **Definitely Not Related**
The adverse event was not related to the Sonata device or procedure
- 6) **“Device-related” events are Adverse Device Effects directly related to use of the Sonata System, for example a skin burn at the site of the dispersive electrode or thermal damage to adjacent structures. (Reference 14.1B)**
- 7) **“Procedure-related” events are those attributable to use of another medical device or medication during treatment with Sonata, for example reactions to anesthesia. Also included are events that would be expected with any transcervical or intrauterine procedure, such as cramping and vaginal discharge.**

J. **Severity**

Investigators will also be asked to assess the severity of all adverse events. The following definitions will be used. These definitions are for descriptive purposes only and are independent of the judgment of whether an event is classified as an AE or an SAE.

- 1) **Mild:**
Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not typically require a medical evaluation or any medication other than that which is commonly available over the counter; signs or symptoms are transient.
- 2) **Moderate:**
Interferes with the subject’s usual activity and may require medical evaluation and symptomatic treatment.
- 3) **Severe:**
Symptom(s) causing severe discomfort and significant impact of the

subject's usual activity and requires both medical evaluation and symptomatic treatment.

14.2 Principal Investigator responsibility - Safety reporting

- A. Carefully monitor all subjects during the study (subsequent to consent) for possible adverse events, and fully investigate any observed AE. All AEs will be followed, with laboratory tests if appropriate, until resolution or until the Investigator judges the outcome to be chronic or stable,
- B. Record every adverse event and observed device deficiency, together with an assessment, using the appropriate case report form. The case report form for adverse events will include an assessment of severity, seriousness, relatedness to the investigational device and/or procedure, and whether it was anticipated in the investigational plan,
- C. Report to Gynesonics, within 24 hours of learning of an event, all serious adverse events and any device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports using the specific medical diagnosis, or using signs, symptoms or abnormal laboratory values if no medical diagnosis can be identified. The PI shall supply Gynesonics upon request with any additional information related to the safety reporting of a particular event,

A follow-up written report of all serious adverse events (SA(D)Es) shall be *emailed or faxed* to Gynesonics within 48 hours and shall include the following information:

- 1) Nature of adverse event
 - 2) Severity of adverse event
 - 3) Date of onset of adverse event
 - 4) Date of resolution of adverse event, if applicable
 - 5) Statement as to why it is considered unanticipated, if applicable
 - 6) Statement as to why it is considered serious, if applicable
 - 7) Statement as to the degree to which it is considered device related, and why
 - 8) Results of any diagnostic tests that were performed
 - 9) Description of any treatment administered
 - 10) Statement of subject's current clinical status
 - 11) Investigator's signature and date
- D. Report to the IRB / EC all serious adverse events and any device deficiencies that could have led to a serious adverse device effect as soon as possible, but in no event later than 10 working days after the investigator first learns of the occurrence.

14.3 Sponsor responsibility - Safety evaluation and reporting

Gynesonics is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall

- A. Review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device and to the procedure; these assessments will be reviewed by the independent Medical Advisory Board. In case of disagreements between the sponsor and the principal investigator(s) in which the principal investigator's opinion is more serious and/or more related, both opinions will be included in adverse event reports,
- B. Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; these assessments will be reviewed by the independent Medical Advisory Board. In case of disagreements between the sponsor and the principal investigator(s) in which the principal investigator's opinion is more serious and/or more related, both opinions will be included in adverse event reports,
- C. Ensure that Medical Advisory Board review of serious adverse events, unanticipated adverse device effects, and device deficiencies that could have led to a serious adverse device effect occurs within 5 working days of receipt of the report,
- D. Ensure that Medical Advisory Board review of other adverse events and device deficiencies occurs on a quarterly basis,
- E. Report or ensure reporting by the PI to the IRB / EC of all serious adverse events and device deficiencies that could have led to a serious adverse device effect as soon as possible, but in no event later than 10 working days after the investigator first learns of the occurrence,
- F. Inform all principal investigators in writing of all serious adverse events at all investigation sites that have been reported to Gynesonics, and ensure that they are reported to their IRB / EC. The time frame for this reporting shall be established based on the perceived risk as defined in the risk analysis report,
- G. Report any unanticipated adverse device effects to the FDA, other applicable ministry of health, and all participating investigators within 10 working days after Gynesonics first receives notice of the effect,
- H. Ensure that all SADEs are reported to other affected national ministries of health in accordance with national regulation,

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- I. In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required. Any protocol modifications deemed necessary by this review will be reported to the IRB/EC and to the applicable Ministry of Health,
 - J. If it is determined that the continuation of the investigational study presents an unreasonable risk to subjects, the study or portions of the study that present that risk will be modified to eliminate the risk or terminated. The terminated study will not be resumed without approval of the IRB/EC and any other applicable governing regulatory agencies. See also §16.5 regarding early study discontinuation.

15 DOCUMENTATION

Accurate, complete, and timely documentation is essential to the successful conduct of this study. The Investigator will maintain medical and study records for every subject participating in the study. The Investigator will also maintain original source documentation from which study-related data are derived. Investigators are responsible for creating and maintaining the following documentation

15.1 Required Records

- 1) Case histories
- 2) Clinic progress notes recording the subject's medical history and medications
- 3) Hospital medical charts with operative reports and condition of subject upon discharge
- 4) Informed consents
- 5) Subject diaries and questionnaires
- 6) Source document worksheets
- 7) Case report forms
- 8) Adverse event reports to sponsor
- 9) Adverse reports to IRB/EC
- 10) Image files, including TVUS, IUUS, MRI
- 11) Investigational device logs
- 12) Monitoring logs
- 13) IRB/EC approval for protocol
- 14) IRB/EC approval for informed consent
- 15) IRB/EC approval for subject materials
- 16) Annual report to sponsor and IRB/EC
- 17) Final report to sponsor and IRB/EC
- 18) Records of deviations, violations, and amendments

15.2 Required Documents

In addition, the following documents shall be maintained

- 1) Protocol (including all revisions)
- 2) Investigators Brochure
- 3) Investigator Agreement
- 4) All correspondence related to the study

15.3 Record Retention

- A. Investigators shall maintain all study related documentation for a period that is the longer of
 - 1) Three years' following completion of the study
 - OR**
 - 2) Study document retention regulations established by regulatory agencies governing the investigational site.
- B. It is the responsibility of the Investigator to notify the sponsor prior to disposal of any records and to allow the sponsor to make other arrangements for on-going storage of study records.

16 **STUDY MANAGEMENT**

Study management will occur in accordance with ISO 14155, (Clinical investigation of medical devices for human subjects – Good clinical practices), the Declaration of Helsinki, the applicable national regulations and Institutional research policies and procedures. National regulations include U.S. FDA regulations pertaining to IDE (21 CFR 812), IRB (21 CFR 56), Informed Consent (21 CFR 50), and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy rule. Several key components of study management are discussed separately below.

16.1 Study Registration

The study will be registered with www.clinicaltrials.gov in accordance with section 801 of the U.S. Food and Drug Administration Amendments Act and the World Medical Association Declaration of Helsinki (2013, #35).

16.2 Study Amendments

- A. Study amendments are allowed only with prior written agreement by the sponsor.
- B. Substantive changes: If changes may affect the rights, safety and well-being of human subjects, or are related to the clinical investigation objectives or endpoints, the proposed amendment will be submitted to the IRB/EC. Changes may not be implemented until approval is obtained.
- C. Administrative changes: If changes are non-substantive, a simple notification of amendment will be submitted to the IRB / EC.

16.3 Monitoring Plan

- A. Gynesonics employees or representatives will monitor the study according to company standard operating procedures, ISO 14155, and U.S. FDA regulations. Study monitoring reports will be completed for each visit.
- B. Study-related data will be reviewed with the sponsor's clinical research personnel or designated representatives to ensure compliance with the clinical protocol, FDA and international regulations, and specific IRB / EC requirements. Data will be reviewed remotely and during on-site visits. Monitoring objectives include, but are not limited to:
 - 1) Assessment of compliance to the protocol, any amendment(s), applicable regulations, and IRB / EC requirements
 - 2) Review of completed case report forms in comparison to source documentation to ensure:
 - (a) that case report forms are accurate, complete, and up to date,
 - (b) that all source documentation is attributable, legible, contemporaneous, original, and accurate, and
 - (c) that clinical investigations records are stored and maintained appropriately
 - 3) Verification that open action items from a previous visit are closed
 - 4) Verification that informed consent has been obtained for all subjects prior to initiation of study-specific screening assessments
 - 5) Verification that any subject non-compliance with the requirements stated in the informed consent have been documented and discussed with the Principal Investigator or his/her authorized designee.
 - 6) Verification that only authorized individuals are participating in the clinical investigation
 - 7) Ensuring that adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay,
- C. Monitoring results will be reviewed with the principal investigator(s) or authorized designee. Any deviations identified will be discussed, documented, and reported to the sponsor.
- D. The first monitoring visit after initiation (or re-initiation) of a trial site will take place as early as possible after enrollment of the first subject. The frequency of further monitoring (onsite or remote) will depend on site recruitment rate, data quality, and subject follow-up visit schedules but will occur at least twice per year until completion of the site's last subject 12-

Month Visit. Monitoring of the 24- and 36-Month Visit data will be done remotely..

16.4 Data Management Plan

Data collected for the study will be entered into a web-based system through electronic Case Report Forms (eCRFs) by each investigational site. The Electronic Data Capture (EDC) system maintains a complete electronic audit trail enabling full compliance with 21 CFR Part 11 and GCP guidelines. The design and specification of eCRFs as well as edit checks will be in accordance with the study requirements. Prior to database lock, the following steps must be completed: data entry or transferring as required per protocol, source verification, query resolution, data review by clinical data managers and final sign-off by site principal investigators.

For statistical analysis, data stored in the central database will be exported to SAS files (SAS Institute Inc, Cary, NC, USA). The data extract from the final locked database will be used to generate the final clinical study report.

16.5 Study Discontinuation

A. Premature termination is only possible:

- 1) If no positive decision is obtained with regard to the research or if the judgment of the FDA or competent medical research ethics committee that has assessed the research is irrevocably revoked;
- 2) If a reasonable case can be made for terminating the research in the interest of the subjects' health;
- 3) If it transpires that continuation of research cannot serve any scientific purpose, and this is confirmed by the medical research ethics committee that has issued a positive decision on the research;
- 4) If the FDA or other Competent Authority (CA) has made an irrevocable objection;
- 5) If one of the two parties (sponsor or institution) has been declared insolvent, or if a petition has been filed for liquidation of one of the two parties;
- 6) If one of the two parties fails to comply with the obligations arising from the agreement and, provided compliance is not permanently impossible, this compliance has not taken place within thirty days after the defaulting party has received written request to comply, unless failure to comply is out of reasonable proportion to the premature termination of the research.

B. When terminating the study, the sponsor and Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

16.6 Study Audits

The sponsor and representatives of regulatory health authorities are permitted to inspect the study documents (protocol, case report forms, study-related medical records, study correspondence with EC and sponsor, etc.). In addition to ongoing monitoring of the study, GCP audits by the sponsor or its representatives are also permitted. All attempts will be made to preserve subject confidentiality.

17 Deviations

17.1 Definitions

- A. A study deviation is defined as any event or change where the Investigator or site personnel did not conduct the study in compliance with the protocol as agreed to by a signed contract.
- B. Major Deviation / Violation:
Any deviation that may affect subject's rights, safety and well-being, or the scientific integrity of the clinical investigation, for example:
 - 1) any deviation from subject inclusion and exclusion criteria;
 - 2) any deviation from subject informed consent procedures (e.g., failure to obtain informed consent or failure to obtain informed consent prior to study entry);
 - 3) failure to report a serious adverse event or unanticipated adverse device effect within applicable regulatory timeframes;
 - 4) device accountability issues (e.g., missing or lost investigational product); or
 - 5) device misuse / unauthorized device use.
- C. Minor deviation:
a deviation that does not affect subject's rights, safety and well-being, or as a singular event, will not impact the scientific integrity of the clinical investigation. Examples of deviations of this type include a follow up visit conducted outside the visit window or failure of the research subject to accurately complete a study-required questionnaire not associated with a primary endpoint.

17.2 Policy

The Investigator is not allowed to deviate from the protocol without prior written agreement by the sponsor and, except as noted below, prior review and documented approval/favorable opinion from the IRB/EC.

- A. Under emergency circumstances, deviation from the protocol to protect the rights, safety and well-being of a study subject may proceed without prior approval of the sponsor and the IRB/EC. Such deviations shall be documented and reported to the sponsor and to the IRB/EC as soon as possible.
- B. Minor deviations as defined above may be initiated based on sponsor approval alone, without notification to or approval of the IRB/EC.

17.3 Procedure

In the event of an occurrence of unapproved deviation:

- A. The Investigator, or person designated by the Investigator should document and explain any deviation from the approved protocol on the designated deviation case report form as soon as they become aware of the deviation.
 - 1) Deviations must be reported to the sponsor regardless of the extent to which a deviation was medically justifiable.
 - 2) Deviations must be reported to the sponsor regardless of whether a specific subject is involved, e.g. unauthorized use of a study device outside the study, unauthorized use of a study device by a physician who has not signed an Investigator Agreement, etc.
 - 3) The explanation should include the dates of and reason for each deviation, and include discussion of any corrective action made by the Principal Investigator(s) or designated site staff to prevent recurrence of the deviation.
- B. The sponsor shall continuously monitor occurrences of protocol deviations and review Investigator-initiated corrective actions for adequacy. The sponsor will classify each deviation as major or minor per the definitions above and will:
 - 1) review the investigator's assessment of all deviations and determine and document in writing whether the deviation may affect subject's rights, safety and well-being, or the scientific integrity of the clinical investigation; these assessments will be reviewed by the independent Medical Advisory Board,
 - 2) report or ensure reporting by the PI to the IRB / EC of all protocol violations adverse events and device deficiencies that could have led to a serious adverse device effect as soon as possible, but in no event later than 10 working days after the investigator first learns of the occurrence,

- C. The sponsor may initiate an audit of the clinical investigation at a clinical site as a result of serious or repeated protocol deviations.
- D. The sponsor will consider terminating or suspending the participation of a particular investigation site or investigator if monitoring or auditing identifies serious or repeated deviations on the part of the investigator.
- E. A list of site-specific study deviations will be included in the Annual Progress Report and as part of the Final Report upon completion of the study.

18 Device Accountability

Access to the investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation with Sponsor approval and according to the protocol. The Investigator or an authorized designee shall maintain adequate records documenting the receipt, use, return, and disposal of all investigational devices, which shall include,

- A. The date of receipt
- B. Identification of each investigational device (batch number, lot/serial number or unique code),
- C. The expiry date, if applicable,
- D. The date(s) of use,
- E. Identification of the subject on whom the device was used,
- F. The date of return of unused, expired or malfunctioning investigational devices.

When the enrollment is complete, the Investigator shall return to the study sponsor any unused devices and a copy of the completed device inventory.

19 **STATISTICAL CONSIDERATIONS**

19.1 Sample Size

A. Reduction in Menstrual Blood Loss (MBL) at 12 months

Ho: Population proportion of MBL success < 0.45

Ha: Population proportion of MBL success ≥ 0.45

In order to claim study success for MBL, the lower limit of the 95% confidence interval must be ≥ 0.45 .

Under the assumption that the MBL success rate is at least 0.60, a sample size of 125 subjects provides better than 90% power to demonstrate that the lower limit of the 95% confidence interval exceeds the pre-specified threshold.

B. Rate of surgical re-intervention for HMB

Ho: Population proportion of no surgical re-intervention success < 0.75

Ha: Population proportion of no surgical re-intervention success ≥ 0.75

In order to claim study success for surgical re-intervention, the lower limit of the 95% confidence interval must be ≥ 0.75 . Under the assumption that the no surgical re-intervention success rate is at least 0.9, a sample size of 75 provides better than 90% power to demonstrate that the lower limit of the 95% confidence interval exceeds the pre-specified threshold.

C. Allowance for expected dropout rate

To account for an assumed 15% subject dropout rate (subjects lost to follow-up at the 12-month visit), a sample size of 147 treated subjects will be enrolled and treated.

19.2 Investigative Centers

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site. At least half of the investigational sites and 50% of the subjects will be from the United States. The study is intended to be conducted in a manner such that a target of at least 7 subjects will be enrolled for any study site. Sites enrolling fewer than 7 subjects will be pooled for analysis.

The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. To verify that the success rate is similar among the analysis centers, an analysis will be performed to compare the results for each of the co-primary efficacy endpoints among analysis centers using a two-tailed test with α of 0.15. If the result is not statistically significant, the sites will be pooled for the analysis. If the result is statistically significant, a weighted average will be used for the analysis.

19.3 Efficacy Analyses

A. Primary Efficacy Analysis

Each subject will be determined to be a Success or Failure per the subject success criteria. Subject success is calculated separately for the two co-primary endpoints, such that it is possible for a subject to be considered a success for one co-primary endpoint and not for the other.

B. Secondary Efficacy Analysis

Secondary endpoints will be summarized using descriptive statistics.

19.4 Other

Additional details, including handling of dropouts or missing data, are described in the study Statistical Analysis Plan referenced in Section 2.

20 ADMINISTRATIVE REQUIREMENTS

20.1 Institutional Review Board/Ethics Committee Approval

Before commencement of the study, each investigator must provide Gynesonics Inc. with written documentation of IRB/EC approval of both the protocol and the informed consent form, which must comply with all requirements outlined by Gynesonics. The approval letter must specify the documents and document revision and/or date being approved. If an Investigator is also a member of the review committee, the Investigator must not participate in the committee decision; non-participation must be noted in the approval letter.

20.2 Competent Authority

Gynesonics Inc. is responsible for obtaining regulatory approval for the study from the relevant Competent Authority as per national requirements.

21 PERSONNEL RESPONSIBILITIES

21.1 Site Principal Investigator

- 1) Ensure that the rights, safety, and welfare of subjects are protected
- 2) Implement study in accordance with protocol
- 3) Possess thorough knowledge of the appropriate use of the study device as described in the protocol, instructions for use, and other information sources provided by the sponsor
- 4) Ensure sufficient study resources and staffing to enable proper conduct of study and timely completion of case report forms
- 5) Delegate significant study-related duties only to appropriately qualified and trained staff
- 6) Permit inspection of facilities and records by the study monitor and any governing regulatory agencies
- 7) Submit protocol and informed consent and other subject materials, and substantive amendments, to the IRB/EC and await approval.
- 8) Obtain informed consent of subjects
- 9) Complete case report forms; Ensure the accuracy, completeness, legibility, logic, contemporaneousness, and attribution of data reported to the sponsor
- 10) Record and explain deviations from protocol and report to monitor
- 11) Submit annual progress reports, final reports, and adverse effect reports to the EC and sponsor
- 12) Record the receipt, disposition, and return of study devices
- 13) Maintain medical histories of subjects
- 14) Retain records for the longer of 1) three years following study completion, or 2) local ministry of health regulations concerning required study document retention
- 15) Notify the sponsor prior to disposal of any records and to allow the sponsor to make other arrangements for on-going storage of study records

21.2 Sponsor

Prior to the commencement and for the duration of the clinical study, the sponsor shall

- 1) Select appropriately qualified Principal Investigators.
- 2) Ensure IRB/EC approval of protocol and informed consent, and that any future modification(s) required by the IRB/EC or regulatory authority are made and documented appropriately.
- 3) Obtain Investigator Agreement and curriculum vitae of all participating Investigators.
- 4) Ensure that a supply of investigational devices is available in a timely manner for the clinical investigation; ensure that investigational devices are not made available to the principal investigator until all requirements to start the clinical investigation are met. Ensure accountability of investigational devices throughout the clinical investigation
- 5) Ensure the members of the investigation site team and their designated authorizations(s) are identified in an log with details of responsibilities
- 6) Ensure documentation of training, for all the relevant parties involved in order to adequately conduct the study; includes training on use of the investigational devices, device accountability procedures, the Protocol and Investigators Brochure, CRFs and instructions for completion, the informed consent form and the consent process
- 7) Designate or appoint one or more monitors, or otherwise assume the responsibilities of the monitors
- 8) Investigate unanticipated, device related adverse effects
- 9) Document protocol deviations and violations
- 10) Maintain accurate and complete records relating to the investigation. These records include all correspondence including required reports, device accountability, monitoring reports and open action follow up, signed Investigator agreements including financial disclosure information, and records concerning complaints and adverse device effects whether anticipated or not
- 11) Provide the following reports in a timely manner to FDA, the IRB/EC, and/or the investigators.
 - (a) Unanticipated Adverse Device Effects
 - (b) Withdrawal of IRB or FDA Approval
 - (c) Current List of Investigators
 - (d) Recalls and Device Disposition
 - (e) Progress and Final Reports

21.3 Monitor

- A. Conduct the study initiation visit or meeting
- B. Conduct routine on-site monitoring visits to verify:
 - 1) Compliance to the protocol, any amendment(s), applicable regulations, and IRB / EC requirements
 - 2) Only authorized individuals are participating in the clinical study
 - 3) Investigational site resources remain adequate
 - 4) Signed and dated informed consent has been obtained for all subjects prior to initiation of study-specific screening assessments
 - 5) Source documents and other clinical study records are accurate, complete, up to date, and stored and maintained properly
 - 6) CRFs and queries are complete, recorded in a timely manner, and consistent with source documents
 - 7) Appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialed by the principal investigator or authorized designee; the monitor shall not make corrections, additions or deletions to the CRFs
 - 8) All adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay,
 - 9) All SAEs and deviations are reported to the IRB/EC, if required
 - 10) Storage and investigational device accountability are correct and the traceability process is being followed
 - 11) Required reports, notifications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated, and identify the clinical investigation
 - 12) Subject withdrawal has been documented and discussed with the principal investigator or authorized designee
 - 13) The principal investigator and investigational site team are informed and knowledgeable of all relevant document updates concerning the investigation, and
 - 14) Any corrective and preventive actions, as needed, have been implemented and are effective
- C. Prepare monitoring reports for submission to the sponsor. Provide a copy of the monitoring report or a summary of key findings to the principal investigator in writing. The report will include the date, investigational site information, name of the monitor and principal investigator, any other individuals contacted, a summary of what the monitor reviewed, observation(s) with regard to completion of previous action items,

significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

21.4 Central Reader (MRI Core Lab)

- A. Credential sites to assess ability to participate in the mandatory sequences
- B. Develop site-specific standardized protocols for MRI examinations at the clinical Sites to be used for both baseline and post-baseline studies
- C. Train and ensure competence of Clinical Site technologists
- D. Develop a protocol for HIPAA-compliant transfer of image data from Clinical Sites to Core Lab
- E. Assess, QC, and track all studies submitted
- F. Utilize standardized CAD (Computer-Assisted Diagnosis) technique for quantitative image analysis of baseline and post-baseline examinations
- G. Transfer all image and verified final reads with calculated volume measurements, changes from baseline and all follow-up reads
- H. Prepare final report for study MRI data

22 LIST OF APPENDICES

- Appendix A:** EuroQOL EQ-5D Questionnaire
- Appendix B:** Uterine Fibroid Symptom and Quality of Life (UFS-QOL) Questionnaire
- Appendix C:** Treatment Recovery Questionnaire
- Appendix D:** Assessment of Hemostasis
- Appendix E:** ACOG Practice Bulletin 84
- Appendix F:** Menstrual Diary [Pictorial Blood Loss Assessment Chart (PBAC)], and Completion Instructions
- Appendix G:** PBAC Scoring Instructions
- Appendix H:** Hormonal Washout Instructions
- Appendix I:** Overall Treatment Effect and Subject Satisfaction
- Appendix J:** Numeric Rating Scale (NRS-11)
- Appendix K:** Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)