# EvaluatiOn of Uterine Patency following Sonography-guided TranscErvical AblatioN of Fibroids (OPEN)

*The OPEN Study*

**Protocol Nº:** **CL 04897**
Revision: K
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|---|---|---|

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|---|---|---|

## Investigator's Statement and Signature

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study or protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to await Ethics Committee approval for the protocol and informed consent before initiating the study, to obtain informed consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare annual, final and adverse event reports as required by this protocol, and to maintain study documentation for the period of time required.

| Site Principal Investigator Name: | Site Principal Investigator Signature: | Date of Signature: |
|---|---|---|

## Clinical monitors for the sponsor

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

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**REVISION HISTORY**

| Revision | Date | Change |
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# 1 RELATED DOCUMENTS

| | |
|---|---|
| Sonata® System Operators' Manual | LS 03818-005 |

# 2 ACRONYMS

| | |
|---|---|
| AE | Adverse Event |
| ADE | Adverse Device Effect |
| CA | Competent Authority |
| CRF | Case Report Form |
| EC | Ethics Committee |
| EDC | Electronic Data Capture |
| ESH | European Society for Hysteroscopy |
| EQ-5D | EuroQuol 5 dimension (patient questionnaire) |
| 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 |
| IUUS | Intrauterine Ultrasound |
| LOS | Length of Stay |
| MRgFUS | Magnetic Resonance-guided Focused Ultrasound |
| MRI | Magnetic Resonance Imaging |
| OTE | Overall Treatment Effect |
| RF | Radiofrequency |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| TVUS | Transvaginal Ultrasound |
| UADE | Unanticipated Adverse Device Effect |
| UAE | Uterine Artery Embolization |

# 3 STUDY ABSTRACT

A. STUDY TITLE

EvaluatiOn of Uterine Patency following Sonography-guided TranscErvical AblatioN of Fibroids (OPEN)

B. SHORT TITLE

The OPEN Study

C. PROTOCOL NUMBER

CL 04897

D. STUDY OBJECTIVE

To document the presence or absence of intrauterine adhesions after treatment with the Sonata System when used in women with submucous and/or transmural fibroids in accordance with product labeling

E. STUDY DESIGN

Post-market prospective, multicenter, single-arm cohort study

F. STUDY PROCEDURES

Diagnostic hysteroscopy and ablation of uterine fibroids with the Sonata System per routine medical care, and postoperative second look hysteroscopy

G. NUMBER OF SUBJECTS

Up to 60 subjects

H. NUMBER OF SITES

Up to 12 sites Worldwide

I. FOLLOW-UP

Subjects will be followed at six weeks postoperatively

J. STUDY DURATION

Overall study duration is expected to be 10 months of enrollment and up to six weeks of follow-up for a total of 12 months.

Note: Patients may be dual-enrolled into the SAGE study (TranScervical Radiofrequency Ablation of Uterine Fibroids Global REgistry), protocol number CL 04878.

K. ENDPOINTS

1) Primary Endpoint

(a) Incidence of intrauterine synechiae at six weeks

Incidence of the formation of new intrauterine synechiae at six weeks will be assessed via diagnostic hysteroscopy, with any adhesions classified per the European Society of Hysteroscopy (ESH)[1] scoring system.

Diagnostic hysteroscopy will be captured on digital video and forwarded to two independent readers. In the event of a disagreement in ESH score between the readers, a third independent reader will perform a tiebreaker review.

L. ADDITIONAL ANALYSES

(a) Adverse Events

(b) Surgical Re-interventions

M. SELECTION CRITERIA

The Sonata System Operator's Manual shall be used to determine if a patient is suitable for treatment with the Sonata System. The criteria listed below shall be used to determine if a patient is eligible for entry into this study. A patient must meet ALL of the inclusion criteria and NONE of the exclusion criteria in order to be considered eligible for participation.

1) Inclusion criteria

(a) Have selected Sonata for treatment of fibroids in the presence of heavy menstrual bleeding

(b) Presence of at least one submucous myoma (type 1, type 2) or transmural fibroid (type 2-5)

(c) Are ≥ 18 years of age at the time of enrollment

(d) Willing and able to read, understand, and sign the informed consent form and to adhere to all study follow-up requirements

[1] Wamsteker K, De Block S. Diagnostic hysteroscopy: technique and documentation. In: Sutton C, Diamond M, eds. Endoscopic surgery for gynecologists. London: WB Saunders, 1998:511–24.

2) Exclusion criteria

(a) Preexisting adhesions within the endometrial cavity as indicated by an ESH score ≥ I as determined by the investigator

(b) One or more Type 0 fibroids and/or endometrial polyps of any size

(c) Any reason for which, in the opinion of the Investigator, the individual study patient is not appropriate or suitable for participation in this study

# 4 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 black women.[2] 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 expensive.[3]

There are several treatment options for uterine fibroids. The Sonata System combines intrauterine ultrasound (IUUS) with radiofrequency (RF) ablation in a single handpiece, enabling transcervical visualization and ablation of uterine fibroids without incisions. Sonata is intended to provide focal treatment of symptomatic fibroids responsible for heavy menstrual bleeding (HMB). 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.

One risk associated with some treatment options is adhesiogenesis. Obliteration of the endometrial cavity by adhesions can result in amenorrhea (Asherman syndrome), but lesser degrees of synechiae can impair fecundity and be associated with abnormal uterine bleeding and secondary dysmenorrhea. The pathophysiology involves mechanical disruption of the basalis layer of the endometrium (as after vigorous curettage), preventing endometrial regeneration;

[2] 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.

[3] 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.

local infection may also predispose to intrauterine adhesiogenesis. With hysteroscopic myomectomy, there is an overall 1.5% risk of adhesiogenesis 1-3 months after treatment for solitary myomata, but as high as 78% after resection of two or more apposing myomata.[4] However, hysteroscopic myomectomy involves resection of extensive areas of endometrium, often including the basalis layer, whereas focal myoma ablation may or may not involve the endometrium. While some studies have looked at patients up to three months status-post hysteroscopic myomectomy, adhesions were noted as early as 1-2 weeks postoperatively and the majority of studies suggest early second-look hysteroscopy (within 1-4 weeks) for early detection and lysis of intrauterine adhesions.[5][6][7][8] It should be noted that Sonata is designed to ablate targeted fibroid tissue and is not **endometrial** ablation. Unlike endometrial ablation, in which there is intentional obliteration/removal of the entire endometrium that can incite significant adhesions, the Sonata System delivers RF energy focally to ablate fibroids beneath the endometrium and does not destroy significant areas of endometrium.

Diagnosis of intrauterine adhesions is typically made via diagnostic hysteroscopy. There are different scoring systems for intrauterine adhesions. The 1989 classification from the European Society for Hysteroscopy (ESH) is commonly employed, is considered particularly useful.[9]

Published and anecdotal reports from the commercial use of the Sonata System have not suggested adhesiogenesis after use of the Sonata device. Of note, hysteroscopic myomectomy involves resection of extensive areas of endometrium, often including the basalis layer, which is felt to be a requirement for adhesion formation. Focal radiofrequency ablation of uterine fibroids (i.e., treatment with the Sonata System) can spare the endometrium and basalis layer; in all cases, the needle introducer that is inserted by the Sonata System is thin (2.4 mm in diameter) and is not believed to involve ablation of an area significant enough to incite adhesiogenesis. This study is being undertaken to evaluate the propensity for uterine synechiae after treatment with the Sonata System by performing a second-look hysteroscopy after treatment with Sonata and scoring any *de novo* adhesions, if present.

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[4] Yang JH, Chen MJ, Wu MY, Chao KH, et al. Office hysteroscopic early lysis of intrauterine adhesion after transcervical resection of multiple apposing submucous myomas. Fertil Steril. May 2008;89(5):1254-9.

[5] Li C, Wei ML, Lin XN, et al. [Effects of early intervention of second-look office hysteroscopy in the prevention of adhesion reformation for moderate-severe Asherman's syndrome]. *Zhonghua yi xue za zhi*. Dec 3 2014;93(45):3617-9.

[6] Lin B, Akiba Y, Iwata Y. One-step hysteroscopic removal of sinking submucous myoma in two infertile patients. *Fertil Steril.* Nov 2000;74(5):1035-8.

[7] Roy, K. K., et al. (2010). "Reproductive outcome following hysteroscopic myomectomy in patients with infertility and recurrent abortions." *Archives of Gynecology and Obstetrics* 282(5): 553-560.

[8] Yang, J. H., et al. (2013). "Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries." *Fertil Steril* 99(7): 2092-2096 e2093.

[9] Panagiotopoulou N, Nethra S, Karavolos S, Ahmad G, et al. Uterine-sparing minimally invasive interventions in women with uterine fibroids: a systematic review and indirect treatment comparison meta-analysis. *Acta Obstet Gynecol Scand*. Sep 2014;93(9):858-67.

# 5 PROCEDURES and DEFINITIONS

## A. DIAGNOSTIC HYSTEROSCOPY AND TREATMENT PROCEDURE

Diagnostic Hysteroscopy Procedure: Subjects who meet the Inclusion/Exclusion Criteria per medical history and clinical work-up will be consented. Consented subjects will undergo a diagnostic hysteroscopy as part of routine medical care. Adhesions will be scored using ESH if identified. Subjects with no adhesions identified or ESH <1 will continue to treatment with the Sonata System. Subjects that do not meet this criterion exit the study and may receive treatment for their fibroids with the Sonata System if desired.

Treatment Procedure: The Sonata System is a CE-marked device and is used within its intended purpose in this study. The following is a brief description of this treatment as outlined in the Sonata System Operators' Manual:

Two dispersive electrode pads are placed, one on each anterior thigh. After achieving cervical dilatation to 27 Fr (which may be accomplished mechanically, via osmotic dilators or pharmacologically), the integrated Treatment Device is inserted transcervically into the uterus. A small volume of hypotonic fluid is infused through the device for acoustic coupling. Leiomyomata are then visualized with the IUUS probe. After articulating the IUUS, the graphical overlay simulates various ablation widths, angles, and locations. Upon establishment of the desired size, angle, and location of the ablation, the gynecologist advances a trocar-tipped introducer into the fibroid under intrauterine sonographic visualization. The physician aligns the graphical overlay with the introducer tip and then rotates the Treatment Device about the introducer to assess the position of the Ablation Zone and Thermal Safety Border relative to the uterine serosa, as displayed on the graphical user interface, adjusting the size and/or position of the desired ablation if necessary. The needle electrode array is then deployed, again rotating to ascertain the position of the Thermal Safety Border relative to the serosa. Radiofrequency energy is provided to the fibroid. Upon completion of RF ablation, the needle electrodes are retracted along with the introducer and the device is withdrawn. Depending on the size of the targeted fibroid, ablation (time at temperature) ranges from 2-7 minutes per fibroid.

## B. SECOND LOOKHYSTEROSCOPY PROCEDURE (at the 6-Week Follow-up Visit)

Subjects who have been treated with the Sonata System will have a follow-up visit at 6 weeks (± 2 weeks) following treatment. The hysteroscopy performed during this visit is to assess presence or absence of newly formed adhesions.

C. DEFINITIONS

**Table 1 Definitions**

| | |
|---|---|
| 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. |
| 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 2-5 fibroid | A fibroid that is submucous and subserous, each with less than half their diameter in the endometrial and peritoneal cavities, respectively |

# 6 STUDY DESIGN AND SAMPLE SIZE

This is a study of a CE-marked product within its approved indications, in accordance with its instructions for use (the Sonata System). The study is designed as a post-market prospective, multicenter, single-arm cohort study.

The sample size for this study is up to 60 subjects. This is an exploratory study and is not intended to be statistically powered.

Note that patients may be dual-enrolled into the SAGE study (TranScervical Radiofrequency Ablation of Uterine Fibroids Global REgistry), protocol number CL 04878.

# 7 SUBJECTS

## 7.1 Selection Criteria

Please refer to Section 3M. The Sonata System Operator's Manual shall be used to determine if a patient is suitable for treatment with the Sonata System.

## 7.2 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. Study sites will maintain a means to link study subject ID number with the subject's name and contact information. All case report forms will be tracked, evaluated, and stored using only the subject ID number. No personal identifying information will be included on the case report forms other than relevant medical history, treatment and assessment dates.

"Protected Health Information" will be maintained in compliance with ISO14155, the EU Data Protection Directive and/or equivalent local regulation.

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.

7.3 Informed Consent Process

A. Written informed consent will be obtained from the patient in accordance with EC requirements prior to initiation of any study-specific assessments. The consent form shall be provided in a language understandable to the subject.

B. Informed consent completion will be monitored regularly by the sponsor or sponsor representatives.

7.4 Moment of Enrollment

A subject is considered "enrolled" in the study once the approved consent form is signed, all inclusion/exclusion criteria have been met, and a qualifying fibroid has been treated.

7.5 Subject Discontinuation or Withdrawal

A. Subjects may be involuntarily removed from the study due to safety reasons, at the discretion of the investigator.

B. Subjects may voluntarily withdraw from the study at any time without reason.

C. 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 notify the Medical or Clinical contact as identified on the cover page of the protocol. Adverse device effects that are on-going at the time of withdrawal will be reported and followed up to 30 days following the study treatment.

7.6 Subject Pregnancy within Follow Up Period

A. In the case of pregnancy, hysteroscopy will not be performed; however, as much of the remaining visit data as possible should be collected.

B. The Investigator and study coordinator should make every attempt to obtain basic pregnancy outcome information and complete the applicable case report form.

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

Subjects will be considered lost to follow up after 3 attempts to contact the subject have been made and all visits have been completed for all subjects enrolled at the site. It is recommended that at least one attempt to contact the subject be made via certified mail or other type of tracked courier service. Attempts to contact the subject should be documented in the subject study record and noted on the study exit form..

# 8 STUDY INVESTIGATORS

## 8.1 Study Sites

Up to 12 study sites may participate in this study worldwide.

## 8.2 Investigator Selection

A. Investigators will be selected based upon interest in participation as well as expertise in minimally invasive gynecological surgery. All investigators will have received device training prior to performing the procedure.

B. Selection criteria will include

1) Experience with hysteroscopic and laparoscopic surgery and electrosurgery
2) General proficiency with ultrasound
3) Availability of hysteroscopic equipment capable of capturing digital video
4) Access to a patient population with symptomatic fibroids that is sufficient to meet enrollment goals
5) Availability of a study coordinator with sufficient time to dedicate to study
6) Willingness to comply with all study requirements imposed by the protocol, Investigator Agreement, EC or equivalent review board, and local regulations as applicable
7) Not on the FDA debarment list or otherwise restricted or disqualified as a clinical investigator by the FDA or other regulatory authority

## 8.3 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.

## 8.4 Investigator Agreement and Discontinuation

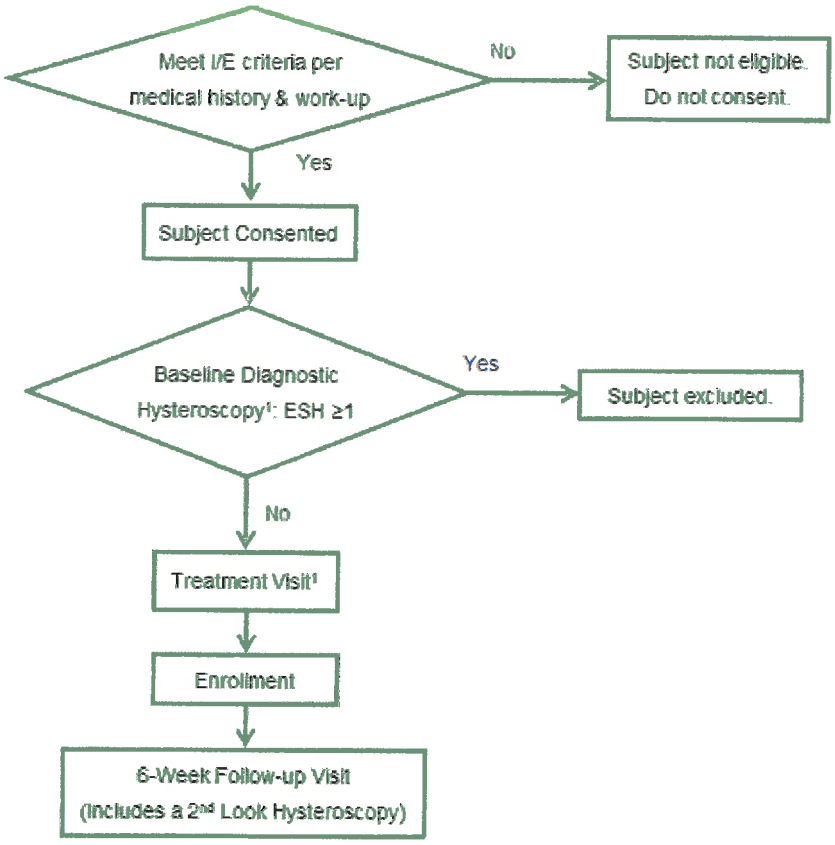
Prior to participation in the study, all investigators must sign the Investigator Agreement, which outlines the Investigator's obligations in the study. The sponsor may elect to discontinue, or suspend, the Investigator's participation in the study for reasons including but not limited to poor study compliance, lack of compliance with applicable regulations or EC requirements, or insufficient recruitment of study subjects.

# 9 STUDY FLOW AND VISIT SCHEDULE

**Table 2 Schedule of Screening and Study Assessments**

| Assessment | Consent | Baseline and Treatment | | Follow up |
|---|---|---|---|---|
| | | Baseline | Treatment | 6 wks |
| Informed Consent | X | | | |
| Demographics | | X | | |
| Transvaginal sonography | | X[1] | | |
| Hysteroscopic assessment of uterine cavity | | X[1] | | X |
| Sonata Treatment & Procedure Assessments | | | X[1] | |
| Adverse events | | | X | X |
| EQ-5D | | X | | X |
| OTE and Subject Satisfaction | | | | X |
| Return to normal daily activity/Treatment Recovery Questionnaire | | | | X |
| Pregnancy and pregnancy outcome / surgical reintervention* | | | | X |

* If subject undergoes hysterectomy, operative and pathology reports shall be forwarded to study sponsor
[1] As per routine medical care




[1] As per routine medical care

**Figure 1 Study Flowchart**

## 9.1 Consent and Enrollment

### A. Candidate Identification

All patients at the Investigational Sites with a complaint of symptomatic fibroids will be asked about their interest in study participation. For those patients who express an interest to participate, patient selection criteria in the Sonata System Operator's Manual will be reviewed against existing medical history and the results of any standard clinical work-up to assess potential eligibility.

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, the study's follow-up schedule, and the diagnostic hysteroscopy at 6 weeks post treatment. If the patient understands

the risks and benefits, and still wishes to participate, she will be asked to sign the informed consent form.

B. Screening/Baseline Assessments
Screening assessments include the following as shown in Table 2

1) Subject demographics and gynecological history
2) Height and weight
3) EQ-5D
4) Transvaginal ultrasound (TVUS) to assess the number, size, and FIGO classification of fibroids (as per routine medical care).
5) Diagnostic hysteroscopy per routine medical care is performed to document presence/absence of intrauterine synechiae and if present, the ESH score is determined. Diagnostic hysteroscopy will be captured on digital video and submitted per study's data collection process.
6) If ESH score ≥1, the subject is no longer eligible for participation and the study exit form will be completed. The subject may receive treatment for her fibroids with the Sonata System if desired.

9.2 Treatment

A. Once the subject has been deemed eligible for trial participation and baseline data have been obtained, the subject can be scheduled to undergo treatment with the Sonata System.

B. The Sonata System is a CE-marked device which is used within its intended purpose (per routine medical care). The treatment shall be performed in accordance with the Sonata System Operator's Manual. Sponsor representatives may assist the Investigator (generally one to three individuals) and may be present during the procedure to provide equipment support if needed as well as for proctoring and general observation.

C. The use of intrauterine adhesion barriers or post-procedure intrauterine devices/systems is not permitted

D. Concomitant intrauterine procedures (e.g., hysteroscopic myomectomy, metroplasty, polypectomy) and ablation of a type 0 myoma are not permitted as part of this study

E. Treatment and Recovery Assessments
The following data will be collected on the day of the treatment prior to discharge:

1) Whether any concomitant procedures were performed in violation of protocol
2) Number and FIGO type of fibroids ablated
3) Location of fibroids ablated
4) The number of ablations performed per treated fibroid

5) The size of the smallest and largest fibroids ablated

9.3 Follow-up

A. Follow-up visit will occur in accordance with Table 3 below. The day of the treatment with the Sonata System represents Day 0. Study visits that do not occur within the below time window will be considered protocol deviations.

**Table 3 Follow-up Visit Windows**

| Visit | Allowed Visit Date Range |
|---|---|
| 6-Week Follow-up | ± 2 week |

B. The measurements and evaluations that will occur at this follow-up visit are provided below (6-Week Follow-up Visit ± 2 weeks).

1) Pregnancy/Pregnancy Outcomes
Subjects will be asked if they have become pregnant since the treatment visit. If so, hysteroscopy will not be performed. Pregnancy outcome will be recorded.

2) Subject Satisfaction
Subjects will be asked to provide their opinion regarding their satisfaction with the treatment.

3) Return to Normal Daily Activity
Subjects will be asked to submit their completed Treatment Recovery Questionnaire (Appendix A).

4) EQ-5D Questionnaire
Subjects will be asked to complete the EQ-5D questionnaire (Appendix B).

5) Overall Treatment Effect (OTE)
Subjects will be asked to complete the OTE questionnaire (Appendix C).

6) Additional intrauterine procedures
If any additional intrauterine procedures have been performed since treatment with the Sonata System, the procedure performed and the date of the procedure will be recorded. Diagnostic hysteroscopy will not be performed in these subjects.

7) Diagnostic hysteroscopy
Subjects will undergo a post-treatment second look hysteroscopy to assess for the presence or absence of intrauterine synechiae which, if present, will then be scored using the ESH scoring system. Diagnostic hysteroscopy will be captured on digital video and submitted per study's data collection capture process..

8) Surgical Reintervention
Subjects will be asked if they have undergone any surgical procedure to treat their heavy menstrual bleeding since treatment with the Sonata System. If so, the procedure performed and the date of reintervention are

recorded. Diagnostic hysteroscopy will not be performed in these subjects.

9) Adverse Events
Subjects will be asked if they have experienced any untoward medical occurrences since treatment with the Sonata System, including increase in frequency or severity of symptoms relative to baseline. Events will be recorded on the Adverse Event case report form if they are deemed related to a device or procedure in accordance with the procedures outlined later in this protocol.

# 10 RISK/BENEFIT ANALYSIS

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

## 10.1 Potential Risks

A patient is eligible for participation in this study only if the patient and physician have already selected the Sonata System for treatment of fibroids. The Sonata System is a CE-marked device which is used within its intended purpose.

Risks associated with the Sonata procedure: As with any standard medical care procedure, the clinician should discuss with patients the potential risks related to the Sonata procedure as outlined in the Sonata System Operator's Manual.

Risks associated with the study specific second-look hysteroscopy at the 6-Week Follow-up Visit: potential procedural risks are the same as those associated with any diagnostic hysteroscopy procedure, including spotting and rare (<1%) uterine perforation, as well as any applicable risks associated with the anesthesia chosen for the procedure.[10] Risks associated with the second-look hysteroscopy are the same as those for the baseline hysteroscopy, and there are no incremental risks associated with subsequent hysteroscopies.

[10] Jansen FW, Vredevoogd CB, van Ulzen K, et al. Complications of hysteroscopy: a prospective, multicenter study. *Obstetrics and gynecology*. Aug 2000;96(2):266-70

10.2 Potential Benefits

The potential benefit to the subject due to her participation in this study is the early detection and treatment of any intrauterine adhesions possibly incited by radiofrequency ablation. Intrauterine adhesions can have a negative impact on fertility, while adhesiolysis can enhance fertility.[11] Regardless of pregnancy desire, detection of intrauterine adhesions by second-look hysteroscopy can lead to treatment of adhesion-related dysmenorrhea and hematometra, and also preserve the ability to adequately sample the endometrial cavity in the future.[12,13] Participation in the study will also contribute to knowledge regarding the impact of transcervical RF ablation of uterine fibroids on the potential development of uterine synechiae.

10.3 Risk/Benefit Analysis

The anticipated risk/benefit ratio of this study is favorable due to the low risks inherent with standard diagnostic hysteroscopy relative to the benefit of increased knowledge regarding the impact of transcervical RF ablation of uterine fibroids on the potential development of uterine synechiae. The rare risk of uterine perforation during second-look hysteroscopy at the 6-Week Follow-up Visit is outweighed by the potential benefits of early detection of intrauterine adhesions, such as the possibility of early treatment of adhesion-related issues and preservation of access to the endometrial cavity in the future.

# 11 ADVERSE EVENTS

Safety data collection and reporting will start once the subject is enrolled, all inclusion/exclusion criteria have been met, and the subject has been treated with the Sonata device.

11.1 Definitions[14]

A. Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including a clinically significant abnormal laboratory finding) in subjects, users or other persons whether or not related to the Sonata System.

1) This includes events related to the procedures involved.
2) For users or other persons this is restricted to events related to the Sonata System or it's procedure

[11] Deans R, Abbott J. Review of intrauterine adhesions. *J Minim Invasive Gynecol.* Sep-Oct 2010;17(5):555-69.
[12] Panayotidis C, Weyers S, Bosteels J, et al. Intrauterine adhesions (IUA): has there been progress in understanding and treatment over the last 20 years? *Gynecological Surgery.* 2009/09/01 2008;6(3):197-211.
13 Ahonkallio SJ, Liakka AK, Martikainen HK, et al. Feasibility of endometrial assessment after thermal ablation. *Eur J Obstet Gynecol Reprod Biol.* Nov 2009;147(1):69-71.
[14] Reference ANSI/AAMI/ISO 14155:2011

3) Increase in frequency or severity of symptoms relative to baseline are considered an adverse event if they are not related to a measured endpoint

NOTE:

- An elective surgical reintervention for HMB is not considered an adverse event.
- Presence of adhesions discovered during follow-up are not considered as an adverse event
- Inpatient admission does not constitute hospitalization for the purposes of this protocol as long as there are no reported adverse events associated with the stay

B. Serious Adverse Event (SAE)

1) AE that led to

(a) Death

(b) A serious deterioration in the health of the subject that either resulted in:

- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function, or
- An in-patient hospitalization, or prolongation of existing hospitalization, of more than 24 hours, or
- A medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

(c) Fetal distress, fetal death or congenital abnormality or birth defect

NOTE:

- 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.
- If recovery time from treatment with the Sonata System is no 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.

C. 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 Sonata System.

2) This definition includes any event that is a result of a use error or intentional misuse.

D. Device Deficiency

As this is a clinical trial utilizing a CE-marked device, device deficiencies ("incidents") are collected and reported by Gynesonics, Inc. according to Gynesonics' Complaint Handling system and per MEDDEV 2.12.1.

If the device deficiency involves an adverse event category as described in this protocol, the investigator shall notify the Sponsor by completing the adverse event or death case report form as applicable and must provide the Sponsor with all necessary documentation needed. If the device deficiency does not involve a reportable adverse event per this protocol, the investigator should notify the Gynesonics, Inc. Complaint Coordinator by emailing the information about the device deficiency to: regulatory@gynesonics.com

E. Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

F. Unanticipated Serious Adverse Device Effect (USADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

As this clinical trial is conducted according to the Sonata System's approved CE mark labeling, within its approved indications, and in accordance with its instructions for use, the Investigator and sponsor will follow the Medical Device Vigilance Guidelines (per MEDDEV 2.12.1) and report adverse events according to that guideline.

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

H. Relatedness

The determination of the level of relatedness of the adverse event to the Sonata device or Sonata procedure will be made according to the definitions below. Adverse events considered to be "Related", "Possibly Related", or "Not Related " to the Sonata System will be classified as an ADE or an SADE for purposes of statistical analysis.

1) Related
The adverse event was directly and clearly related to the Sonata System or procedure.

2) Possibly Related
The adverse event may have been related to Sonata System or procedure, but an alternative cause is equally likely.

3) Not Related
The adverse event was not related to the Sonata System or procedure.

Complications of procedures in the study are considered not related if the said procedures would have been applied to the subject also in the absence of the study device use/application.

I. Reportable Events to the Sponsor

AE data will be collected throughout the clinical study and will be reported to the Sponsor on a dedicated case report form. Reportable events to sponsor are considered:

a) All procedure and/or device related AEs (whether or not the event is considered serious).
b) Death events

In the event of subject death, Investigator will make reasonable effort to obtain a copy of the autopsy report and/or death summary. Investigator will determine the cause of death and its relationship to the device and or procedure. Investigator will record results on the Adverse Event Form and include copies of an autopsy report, if available, and/or a death summary with this form.

NOTE:
All events, unrelated to the device and/or procedure, except Death as noted above should not be reported to sponsor. Events considered to be SAE/SADE/USADE should be reported to Gynesonics at OPEN.safety@gynesonics.com as soon as possible after discovery of the event.

11.2 Principal Investigator responsibility - Safety reporting

The Investigator is responsible for reporting all SAEs and SADEs to the EC, according to ISO 14155, national regulations and EC requirements. The Investigator will forward a copy of this report to the Sponsor and file in site regulatory binder.

The Investigator will monitor all AEs until they are resolved, determined to be a chronic condition at the last follow-up visit or the subject is lost to follow-up. The Investigator will report all reportable serious AEs per this protocol (i.e., SAE/SADE/USADE) to the sponsor at OPEN.safety@gynesonics.com immediately after the study site personnel becomes aware of the event. Investigator will make all efforts to provide source documentation related to the event (e.g. hospitalization report, medical report, etc.).

11.3 Sponsor responsibility - Safety evaluation and reporting

Gynesonics will ensure that reportable events are reported to the relevant authorities as per ISO 14155, as well as other applicable local laws and regulations. The description of the adverse event, date of the adverse event, treatment and resolution of the reportable adverse events will be reported, as applicable, to the relevant authorities per regulations. Additional information may be requested by Gynesonics in order to support the reporting of AEs to regulatory authorities.

# 12 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

## 12.1 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 questionnaires
6) Source document worksheets
7) Case report forms
8) Adverse event reports to sponsor
9) Adverse reports to EC
10) Image files, including TVUS, IUUS, MRI (if performed)
11) Monitoring logs
12) EC approval for protocol
13) EC approval for informed consent
14) EC approval for subject materials
15) Annual report to sponsor and EC
16) Final report to sponsor and EC
17) Records of deviations, violations, and amendments

## 12.2 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

12.3 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 study 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.

# 13 STUDY MANAGEMENT

Study management will occur in accordance with Gynesonics standard operating procedures, ISO 14155: other relevant standards, regulations, and guidance documents. Several key components of study management are discussed separately below.

13.1 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).

13.2 Study Amendments

A. 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 EC. Changes may not be implemented until approval is obtained.

B. Administrative changes: If changes are non-substantive, a simple notification of amendment will be submitted to the EC.

13.3 Monitoring Plan

A. Gynesonics employees or representatives will monitor the study to ensure adherence to ISO 14155, good clinical practices and other applicable regional laws and regulations.

B. Study-related data will be reviewed with the sponsor's clinical research personnel or designated representatives to ensure compliance with the clinical protocol, ISO 14155, international regulations, and specific EC requirements. Data will be reviewed remotely and during on-site visits. Monitoring objectives include, but are not limited to:

(a) Verification that informed consent has been obtained for all subjects prior to initiation of study-specific screening assessments

(b) Assessment of compliance to the protocol, any amendment(s), applicable regulations, and EC requirements

(c) Review of completed case report forms in comparison to source documentation to ensure:

- that case report forms are accurate, complete, and up to date,
- that all source documentation is attributable, legible, contemporaneous, original, and accurate, and
- that clinical investigations records are stored and maintained appropriately

(d) Verification that open action items from a previous visit are closed

(e) 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.

(f) Verification that only authorized individuals are participating in the clinical investigation

(g) 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. Monitoring visits will occur at the frequency specified in the monitoring plan.

13.4 Data Management Plan

A. Date Entry

Data collected for the study will be entered into a web-based system through electronic Case Report Forms (eCRFs) by each study site. The Electronic Data Capture (EDC) system maintains a complete electronic audit trail. The design and specification of eCRFs as well as edit checks will be in accordance with the study requirements.

B. Database Lock

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.

13.5 Study Discontinuation

A. The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator. Premature termination is possible for reasons including but not limited to:

1) If no positive decision is obtained with regard to the research or if the judgment of the 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 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.

13.6 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.

# 14 STATISTICAL CONSIDERATIONS

The objective of the study is to characterize intrauterine adhesiogenesis after treatment with the Sonata System. As such, the study is not statistically powered and the sample size of up to 60 subjects is adequate to meet the study objective.

Subjects who were treated with the Sonata System but meet the following criteria will be excluded from the analysis:

- Become pregnant during the post-procedure study follow up period
- Undergo additional intrauterine procedures or any surgical procedure to treat their heavy menstrual bleeding during the post-procedure study follow up period

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.

Subject demographics and clinically relevant baseline variables will be tabulated. The number of adhesions and ESH scores will be tabulated. A summary of adverse events, and study deviations will be provided.

# 15 ADMINISTRATIVE REQUIREMENTS

## 15.1 Ethics Committee Approval

Before commencement of the study, each investigator must provide Gynesonics Inc. with written documentation of 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.

## 15.2 Competent Authority

Regulatory approval from the Competent Authority is not generally required for post-market studies of CE-marked devices used within their intended use. Gynesonics Inc. is responsible for obtaining regulatory approval for the study from the relevant Competent Authority for countries in which Competent Authority is required.

# 16 PERSONNEL RESPONSIBILITIES

## 16.1 Site Principal Investigators

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 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 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

## 16.2 Sponsor

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

1) Select appropriately qualified Principal Investigators.
2) Ensure EC approval of protocol and informed consent, and that any future modification(s) required by the EC or regulatory authority are made and documented appropriately.
3) Obtain Investigator Agreement and curriculum vitae of all participating Investigators.
4) Confirm that a supply of devices is available in a timely manner for the clinical investigation; n

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, 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 the EC, and/or the investigators.
    (a) Unanticipated Adverse Device Effects
    (b) Withdrawal of EC approval
    (c) Current List of Investigators
    (d) Recalls and Device Disposition
    (e) Progress and Final Reports

16.3 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 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 and complete.
    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 if data was entered in error or prompted by a query.
    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 EC, if required

10) Required reports, notifications, submissions and correspondence are maintained in the investigator's files and are accurate and complete.

11) Subject withdrawal has been documented

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, study 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.