STATISTICAL ANALYSIS PLAN

Protocol Number:	CL 04502
SAP Number	CL 04502-004
Study Title:	Evaluation of the Gynesonics System for Transcervical Treatment of Symptomatic Uterine Fibroids with Radiofrequency Ablation under Integrated Intrauterine Sonography Guidance
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Prepared by:	[redacted]

Approved by:

[redacted]

[redacted] Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

REVISION HISTORY

Revision	Date	Change
[redacted]	[redacted]	[redacted]
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2. LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
ADE	adverse device effect
eCRF(s)	electronic case report form(s)
DMP	Data Management Plan
e.g.	*exempli gratia* (for example)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
HMB	Heavy Menstrual Bleeding
ICH	International Conference on Harmonization
LOCF	last observation carried forward
N	number (sample size)
OTE	Overall Treatment Effect
PBAC	Pictorial blood loss assessment chart
PP	per-protocol
SAE(s)	serious adverse event(s)
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	standard deviation
UFS-QOL	Uterine fibroid symptom and quality of life

3. INTRODUCTION

The Gynesonics VizAblate® System is an intrauterine ultrasound-guided radiofrequency (RF) ablation system for the treatment of symptomatic uterine fibroids using a minimally invasive transcervical approach. VizAblate is suitable in an inpatient or outpatient setting, and is intended to provide focal treatment of symptomatic fibroids responsible for HMB. This Statistical Analysis Plan (SAP) describes the analytical methods to be used to assess the safety and effectiveness of the VizAblate System in the treatment of symptomatic uterine fibroids.

4. STUDY OBJECTIVES

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

5. INVESTIGATIONAL PLAN

5.1 Overall Study Design

The study is designed as a prospective, longitudinal, multicenter, single-arm cohort study with the subject serving as her own control.

5.1.1 Schedule of Screening Assessments

Table 1: 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 and SIS OR TVUS and hysteroscopy *(to confirm location & size of fibroids, assess for the presence of adenomyosis)*				X	
Hemoglobin level				X	
Cervical GC and chlamydia testing				X	
Urine or serum hCG				X	X
Serum creatinine			X		
Hemostasis assessment			X		
ce-MRI (screen MRI). *MRI's will be forwarded to a central reader.*				X	
UFS-QOL Questionnaire				X	
EQ-5D Questionnaire				X	
Birth control assessment	Ongoing				
Concomitant medications	Ongoing				
Adverse events	Ongoing				
Final eligibility assessment					X

5.1.2 Schedule of Study Visits and Assessments

Table 2: Schedule of Study Visits and Assessments

Assessment	Baseline	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		
EQ-5D	[Screening assessment]				X	X	X	X	X
UFS-QOL	[Screening assessment]				X	X	X	X	X
Vital signs as per screening		X							
Urine/serum hCG, (<24 hours pre-procedure)		X							
Venous thromboembolism risk classification		X							
Birth control adherence		X	X	X	X	X	X		
VizAblate Treatment & Procedure Assessments *Procedure & discharge times, pain VAS & tolerance, anesthesia and concomitant medications*		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 *Update to medical history and symptoms*			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

5.2 Selection of Study Population

5.2.1 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 ≤ 6 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 relevent total, irrespective of size.
5) Have at least one fibroid that indents the endometrial cavity.
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 with contraceptive foam, 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. Only monthly cyclic combined contraceptive steroids will be acceptable as oral contraception). 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 Protocol 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

5.2.2 Exclusion Criteria

1) Pregnancy, as determined by urine or serum hCG obtained within 24 hours prior to treatment with VizAblate
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 can not be treated for technical reasons (e.g. cervical fibroid)
12) Presence of an extrauterine pelvic mass
13) IUD/IUS in situ within the washout period specified in Protocol Appendix H prior to undergoing any screening procedures
14) Known prior fundal hysterotomy (e.g. classical c-section)
15) Previous endometrial ablation, uterine artery embolization, laparoscopic uterine artery occlusion, open/laparoscopic myomectomy or any other procedure for fibroids or heavy menstrual bleeding other than hysteroscopic myomectomy
16) Hysteroscopic myomectomy within 12 months prior to undergoing any screening procedures, or hysteroscopic 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 VizAblate Handpiece to the endometrial cavity or fibroids (eg, 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 > 400 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 < 75% fibroid enhancement by volume via contrast-enhanced MRI)

23) Previous pelvic irradiation

24) Hemoglobin level that does not meet the institutional presurgical requirement at time of treatment

25) Renal insufficiency [serum creatinine ≥ 1.5 mg/dL (132.6 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 Protocol 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 Protocol 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 Protocol Appendix J.

35) Uncontrolled hypertension lasting 2 years or more (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg that is not controlled with an antihypertensive drug regimen)

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

5.3 Treatments

The VizAblate System is intended for the transcervical treatment of symptomatic uterine fibroids, including those associated with HMB, under intrauterine ultrasound guidance.

5.4 Data Management

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.

5.5 Efficacy and Safety Variables

5.5.1 Co-Primary Efficacy Variables

5.5.1.1 Pictorial Blood Loss Assessment Chart (PBAC)

Subjects will be asked to assess menstrual bleeding using a PBAC menstrual diary. The PBAC is a visual representation of blood loss from which a numerical score is derived. The PBAC is detailed in Appendix D. PBAC scoring instructions are included in Appendix E.

5.5.1.2 Surgical Reintervention

Subjects will be asked to indicate whether there has been any surgical reintervention for the treatment of HMB since their last visit. The rate of surgical reintervention for HMB due to treatment failure will be evaluated throughout all assessment timepoints and at 12 months as a co-primary endpoint. Surgical reintervention for the treatment of HMB includes the following procedures:

a) Hysterectomy (abdominal, vaginal, laparoscopic)

b) Myomectomy (abdominal, vaginal, laparoscopic, hysteroscopic)

c) Uterine artery embolization

d) Magnetic resonance-guided focused ultrasound (MRgFUS) or similar focused ultrasound treatment

e) Endometrial ablation (nonresectoscopic, hysteroscopic)

5.5.2 Secondary Efficacy Variables

5.5.2.1 Total and Perfused Fibroid Volumes

Total and perfused fibroid volumes will be evaluated at baseline and at 12 months using contrast-enhanced MRI. The MRI's will be evaluated by a central reader.

5.5.2.2 Uterine Fibroid Symptom and Quality of Life (UFS-QOL)

The UFS-QOL is detailed in Appendix A. The Symptom Severity Score (SSS) and Health-Related Quality of Life Score (HRQL) are calculated from a subset of the UFS-QOL questionnaire. UFS-QOL scoring instructions are detailed in Appendix B.

5.5.2.3 Overall Treatment Effect (OTE)

Subjects will be asked to 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).

5.5.2.4 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".

5.5.2.5 EuroQOL EQ-5D

The EQ-5D should be completed during the subject's 3rd, 6th, and 12th menstrual cycles post-treatment, preferably on the first full day of bleeding. It should again be completed at 2 years and at 3 years post-treatment. 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.

5.5.3 Procedure Variables

Procedure information will be captured within the eCRF. The device insertion and removal times will be collected to facilitate the calculation of procedure time. Additionally, the time the subject entered the procedure room, exits the procedure room, was eligible for discharge, and was actually discharged will be collected. The procedure location will be captured (e.g. ambulatory care center, operating room, etc). The anesthesia and procedure-related medications, and number and size of each fibroid treated will also be captured, along with the number of ablations for each fibroid. In addtion, an eCRF will be created to capture device malfunctions.

5.5.3.1 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 visual analog scale.

5.5.3.2 Treatment Recovery Questionnaire

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.

5.5.3.3 Length of Stay (LOS)

The length of stay, in hours, will be assessed by recording the duration of the institutional stay from the start of procedure to discharge (time of insertion of device to time of 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.

5.5.4 Safety Variables

5.5.4.1 Adverse Events

Adverse events will be reported and classified by the Investigator using the specific medical diagnosis, or using signs, symptoms or abnormal laboratory values if no medical diagnosis can be identified.

5.5.4.2 Adverse Event Definitions

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 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. **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 VizAblate 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 an SAE.

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

E. **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 Investigator's Brochure.

5.5.4.3 Adverse Event Evaluations

Each adverse event in the study will be evaluated by the investigator as to its severity, its relationship to the study device and to the procedure, and whether it was anticipated in the investigational plan. The distinction between an AE, an SAE, and a UADE will be made according to the definitions given above. Gynesonics is responsible for the classification of adverse events. In case of disagreements in which the investigator's evaluation is that the event is more serious and/or more related, both opinions will be included in adverse event reports.

5.5.4.3.1 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:

1) Definitely Related: The adverse event was directly and clearly related to the VizAblate device or procedure

2) Probably Related: The adverse event may have been related to the VizAblate device or procedure. Alternative causes are possible but are less likely

3) Possibly Related: The adverse event may have been related to the VizAblate device or procedure, but an alternative cause is equally likely

4) Unlikely to be Related: The adverse event may have been related to the VizAblate device or procedure, but an alternative cause is more likely

5) Definitely Not Related: The adverse event was not related to the VizAblate device or procedure

NOTE: If any adverse event is considered to be "possibly", "probably" or "definitely" related to the use of the study device, that event will be classified as an ADE or an SADE for purposes of statistical analysis.

5.5.4.3.2 Severity of Adverse Events

Investigators will also be asked to assess the severity of all adverse events. The following definitions will be used:

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 medication or a medical evaluation; signs or symptoms are transient.

2) Moderate: Interferes with the subject's usual activity and requires symptomatic treatment.

3) Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

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.

5.6 Statistical Methods

All statistical processing will be performed using SAS® unless otherwise stated.

Continuous variables will be summarized descriptively using number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum. Categorical variables will be summarized descriptively using frequency counts and percentages.

Analyses presented for the Full Analysis Set[1] (FAS) will be considered primary. Analyses performed on the Per-Protocol (PP) will be secondary and supportive.

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[1] International Conference on Harmonization (ICH) – E9 Statistical Principles for Clinical Trials

5.6.1 Analysis Populations

The FAS population will be comprised of all study subjects who were treated and who do not meet any of the following criteria:

- Become pregnant during the 12-month post-procedure study period;
- Are diagnosed with a medical condition that would make assessment of menstrual bleeding invalid or unreliable.

The safety population will be comprised of subjects who were treated and have post-baseline information.

The per-protocol (PP) population will include subjects who complete 12 months of follow-up without study protocol violations. The PP population will include subjects from the FAS population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Did not complete a 12 month PBAC;
- Are associated with protocol violations that are considered to influence the endpoint under evaluation;

Subjects who discontinue the study due to a device/procedure-related adverse event (AE) or documented lack of efficacy (without surgical reintervention) will be included in the PP population, with missing data imputed as failure for the 12-month menstrual blood loss (MBL) endpoint.

5.6.2 Subject Disposition

The number of subjects included in each analysis population (FAS, Safety, PP) will be summarized, as well as the reasons for exclusion from each population. The number of subjects enrolled, completed, and discontinued (including the reasons for discontinuation) will be summarized.

5.6.3 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized descriptively for the FAS, PP and safety populations. Demographic variables will include variables such as age, race, ethnicity, height, and weight. Baseline characteristics will include variables such as pre-treatment MBL, fibroid volume and uterine volume.

5.6.4 Efficacy Analyses

Efficacy evaluations will be summarized descriptively, by visit.

5.6.4.1 Primary Efficacy Analysis

Table 3 describes the two co-primary endpoints. Each subject will be determined to be a Success or Failure per the subject success criteria. For the endpoint of Reduction in Menstrual Blood Loss, the count and percentage of subjects with Success and Failure will be summarized, along with the 95% exact confidence interval for the percent successes. The rate of surgical reintervention during 12 months, along with 95% confidence interval, will be determined using Life-Table methods. Each endpoint has a pre-specified study success criterion, as described in Table 3. Study success is achieved if both of study success criteria are met.

Table 3: Co-Primary Endpoints and Success Criteria

Co-Primary Endpoint	Test Method	Subject Success Criteria[a]	Study Success Criteria
Reduction in MBL at 12 months	Modified pictorial blood loss assessment chart (PBAC)	≥ 50% reduction in PBAC score, and a final PBAC score < 250	LCL of the percentage of subject success ≥ 45%
Rate of surgical reintervention for HMB due to treatment failure at 12 months	Surgical reintervention for HMB due to treatment failure	No surgical reintervention for HMB due to treatment failure at 12 months	LCL of the percentage of subject success ≥ 75%

[a] 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.

5.6.4.2 Secondary Efficacy Analysis

There are six secondary endpoints:

- Change in total fibroid volume from Baseline to 12 months
- Change in perfused fibroid volume from Baseline to 12 months
- Change in UFS-QOL from Baseline to 12 months
- OTE at 12 months
- Subject satisfaction at 12 months
- Change in EQ-5D from Baseline to 12 months

Secondary endpoints will be summarized using descriptive statistics.

5.6.5 Procedure Summaries

The following procedure related information will be summarized using descriptive statistics:

- Subject pain and tolerance of procedure
- Time to return to daily activities
- LOS (start of procedure to discharge)

- Time from entry into procedure room to discharge
- Procedure time
- Device malfunctions
- Procedure location (site of service)
- Number of fibroids treated
- Size of fibroids treated
- Number of ablations per fibroid
- Anesthesia and procedure-related medications
- Pain medication and narcotic use during recovery

5.6.6 Safety Analyses

5.6.6.1 Adverse Events

Procedure safety will be assessed by recording all AEs that occur on the day of the treatment procedure. Longer-term safety will be assessed by recording at each follow-up visit any untoward medical occurrence since baseline. Each AE will be assessed for severity and relationship to study device and/or procedure. In addition to evaluating procedural and longer-term safety, subjects who become pregnant after the procedure will be asked to report any pregnancy complications.

AEs will be classified by onset date into the following time periods:

- Day 0 (procedure day)
- Days 1-6 post-op (1^{st} week)
- Days 7-30 post-op (1^{st} month)
- Days 0-30 (aggregate of all AEs during 1^{st} month)
- Days 31-90
- Days 91-180
- Days > 180

Descriptions of AEs will include the date of onset, the date the AE resolved, stabilized, or returned to baseline, the severity of the AE, and the outcome. All reported AEs will be summarized by the number of subjects reporting AEs, severity, seriousness, and relationship to the VizAblate device and/or procedure. Summaries will also be presented for device-related AEs, procedure-related AEs, and AEs by anesthesia type administered to the subject.

AEs will be summarized both by subject incidence rate and event incidence rate. In addition, AEs will be summarized by severity and relationship to the VizAblate procedure and/or device, such that each subject will be counted only once for each AE by using the AE with the highest severity/greatest relationship within each category.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim given by the Investigator, start date, stop date, severity, and VizAblate procedure-relatedness. The AE onset will also be shown relative (in number of days) to the day of the VizAblate procedure. The sponsor is responsible for classifications of adverse events; in case of disagreements between the sponsor and the investigator in which the investigator's opinion is that the event is more serious and/or more related, both opinions will be included in adverse event reports.

Serious adverse events (SAEs) will be tabulated by subject. In addition, a list of subjects who discontinued from the study and a list of subjects who experienced SAEs will also be provided.

5.6.7 Determination of Sample Size

SAS® PROC POWER was used to calculate the following sample sizes. The co-primary endpoint of Reduction in MBL at 12 months will be analyzed using 95% exact confidence intervals. In order to claim study success, the lower limit of the 95% confidence interval must exceed the pre-specified threshold (described in the table below).

Table 4: Determination of Sample Size

Co-Primary Endpoint	Lower Confidence Limit Success Criterion	Assumed Subject Success Rate	N to Achieve 90% Power
Reduction in MBL at 12 months	≥45%	60%	125
Rate of surgical reintervention for HMB due to treatment failure at 12 months	≥75%	90%	75

To account for an assumed 20% subject dropout rate (subjects lost to follow-up), a sample size of at least 125 and up to 150 treated subjects will be enrolled.

5.6.8 Statistical/Analytical Issues

5.6.8.1 Adjustments for Covariates

No adjustments for covariates are planned.

5.6.8.2 Handling of Dropouts or Missing Data

Reduction in MBL at 12 Months

Missing 12-month menstrual blood loss data will be imputed using last observation carried forward (LOCF). Subjects which undergo surgical reintervention to manage fibroid symptoms prior to 12 months will be excluded from the Reduction in Menstrual Blood Loss analysis.

Surgical Reintervention for HMB due to Treatment Failure at 12 Months

Life-Table methods will be used to calculate the success rate and 95% confidence interval for the rate of surgical reintervention during 12 months. Therefore, subjects that are discontinued prior to 12 months for reasons other than surgical reintervention will be considered censored.

Sensitivity Analyses

Sensitivity analyses will also be conducted to examine the impact of missing data. A worst-case analysis (all missing data imputed as failures) and best-case analysis (all missing data imputed as successes) will be performed. In addition, a tipping point analysis will be performed.

Secondary Endpoint Analyses

No imputations will be made for missing secondary endpoint data.

5.6.8.3 Interim Analyses and Data Monitoring

No interim analyses are planned.

Adverse events occurring during the study will be reviewed by the Study's Medical Advisory Board quarterly. If it is determined that the continuation of the investigational study presents an unreasonable risk to subjects, the study or portions of the study which present that risk will be modified to eliminate the risk or terminated. The terminated study will not be resumed without approval of the EC and any other applicable governing regulatory agencies.

5.6.8.4 Multicenter Studies

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 minimum of 7 subjects will be enrolled for any investigator. Investigational sites enrolling fewer than 7 subjects will be combined, within country, using the following process. The investigator with the smallest enrollment will be combined with the investigator with the largest enrollment. If there is a further need to combine data (still fewer than 7 subjects), then the data of the investigator with the second smallest enrollment will be combined, and so on. Once 7 subjects have been achieved, the process will continue to until all investigators with less than 7

subjects have been included in a group containing 7 or more subjects. The process of combining investigator data that have insufficient subjects will result in redefining the groups of investigators for the purposes of investigating pooling. These combined groups will be referred to as "analysis centers".

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. The MBL endpoint will be analyzed using a logistic regression. The surgical reintervention endpoint will be analyzed using Life-Table methods.

5.6.8.5 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed for the co-primary endpoints, since both primary endpoints are required to be met to claim overall study success.

5.6.8.6 Examination of Subgroups

The co-primary endpoints will be summarized by baseline PBAC, fibroid load and International Federation of Gynecology and Obstetrics (FIGO). Specifically, subjects will be classified based on baseline PBAC scores of 150-200, >200-300, >300-400 and >400-500. Subjects will be classified based on the largest treated fibroid, as 1 cm - 2 cm, > 2 cm - 3 cm, > 3 cm - 4 cm, > 4 cm. Subjects will also be classified based on total treatable fibroid burden, where total treatable fibroid burden will be summed across all fibroids of type 1, 2, 3, 4, 2-5 that are 1 cm or more in size. Total treatable fibroid burden will be classified as <= 50 cc, > 50 cc - 100 cc, > 100 cc - 150 cc, > 150 cc - 200 cc, and > 200 cc.

In addition, change in fibroid volume will be summarized for subgroups of fibroids. Fibroids will be classified based on diameter (1 cm - 2 cm, > 2 cm - 3 cm, > 3 cm - 4 cm, > 4 cm), volume (<= 20 cc, > 20 cc - <=40 cc, > 40 cc - <= 60 cc, > 60 cc - <= 80 cc, > 80 cc - <= 100 cc, and > 100 cc), and type.

The subgroup analyses described above are exploratory. No labeling claims will be pursued based on the results of these analyses.

5.7 Changes in the Conduct of the Study or Planned Analyses

No changes to planned analyses.

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