Prospective Feasibility Study Evaluating EchoMark LP Placement and EchoSure Measurements for Subjects Requiring Arteriovenous Fistulae

Protocol Number: IDE-F1-2021

National Clinical Trial (NCT) Identified Number: NCT04896476

IDE Number: G210264

Principal Investigator: [redacted]

Protocol
Version 9.0

July 27, 2023

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STATEMENT OF COMPLIANCE

The Sonavex feasibility clinical trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable United States Code of Federal Regulations (CFR). The Principal Investigator will assure no deviations or changes to the protocol take place without prior agreement from Sonavex, the sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained prior to participant enrollment. Amendments to the protocol will require review and approval by the IRB before any changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who have previously provided consent.

1. ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CEC	Clinical Events Committee
CFR	Case Report Form
CKD	Chronic Kidney Disease
CPU	Central Processing Unit
DSMB	Data Safety Monitoring Board
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
ICH GCP	International Conference on Harmonization Good Clinical Practice
IRB	Institutional Review Board
PHI	Personal Health Information
PI	Principal Investigator
QC	Quality Control
RVT	Registered Vascular Technologist
SAE	Serious Adverse Event
SOC	Standard of Care

Abbreviation	Definition
SOP	Standard Operating Practices
UADE	Unanticipated Adverse Device Effect
US	United States

2. PROTOCOL SUMMARY

STUDY TITLE	Prospective Feasibility Study Evaluating EchoMark LP Placement and EchoSure Measurements for Subjects Requiring Arteriovenous Fistulae.
INVESTIGATIONAL DEVICE	EchoMark LP is a bioresorbable implant used as ultrasound marker for marking an arteriovenous fistula. The EchoSure System for AVF is a diagnostic ultrasound system. EchoSure and its transducer are intended for use in clinical examinations of arteriovenous fistulae and other blood vessels that are marked with an EchoMark LP implant. As a system, EchoMark and the EchoSure System for AVF provides measurements and information about blood flow, including volumetric flow rate, diameter, and depth, for assessing upper arm arteriovenous fistulae throughout the maturation period.
OBJECTIVES	To evaluate the feasibility and safety of the EchoMark LP and the EchoSure diagnostic ultrasound system for assessing AV fistula blood flow, diameter and depth.
STUDY DESIGN	Prospective, multi-center, single-arm, non-blinded feasibility clinical trial
SUBJECT POPULATIONS	Subjects undergoing new upper arm autologous arteriovenous fistula creation who require hemodialysis
NUMBER OF SUBJECTS	Up to 20 subjects will be enrolled for up to 365 days. Each site can enroll up to 3 “roll-in” subjects. Roll-in subjects will be consecutive and must

	be identified as roll-in subjects prior to the EchoMark LP implantation and will not count toward the total enrollment of 20 subjects.
NUMBER OF CLINICAL SITES	Up to 6 sites within in the United States will be evaluated, qualified, and selected for participation.
PROCEDURE AND FOLLOW-UP:	All subjects that receive an EchoMark LP will be evaluated at the following time-points: • 15 days (+/- 7 days) • 30 days (+/- 7 days) • 60 days (+/- 15 days) • 90 days (+/- 15 days) • 120 days (+/- 15 days) • 150 days (+/- 15 days) • 180 days (6 month) (+/- 15 days) • 12 Month (1 Year) (+/- 15 days) • 15 Months (+ /- 15 days) • 18 Months (+/- 15 days) • 24 Months (+/- 15 days) Except for the 180 day (6 month), 12 month (1 year), 15 Month, 18 Month, and 24 Months visits, each visit will include a physical exam, Duplex scan, EchoSure scan, and assessment for adverse events. The monthly EchoSure scans will be suspended after the 120-day (4 month) visit or once radiographic maturation is achieved, whichever is longer, but clinical follow-up and Duplex will continue per the above schedule. The 180-day (6-month) and 12 month (1 year)visits will include a physical examination, Duplex scan for patency, and an assessment for adverse events. The 15 Month, 18 Month, and 24 Month visits will include capture of medical history since the last visit, a duplex scan, information on any fluid collection observed on the Duplex scan, and an assessment for any adverse events. EchoSure scans will be completed by study personnel who do not have prior ultrasound training and are representative of non-expert users. Subjects that are consented but do not receive the EchoMark LP will be considered a screen failure, and can be replaced.
PRIMARY ENDPOINT	The primary safety and feasibility endpoints are as follows: **Primary Safety:**

	Composite of new major device related adverse events (MAEs) at 30 days post EchoMark LP implantation, as adjudicated by the Clinical Events Committee (CEC), including: • Device or procedure-related death • Device related infection • Device related interventions • Device related hospitalizations • Fistula failure • Fistula rupture • Aneurysm After the close of the final 90-day visit window, all evaluable subjects will be summarized and expansion to a pivotal trial will be requested under a new IDE. **Primary Feasibility (Technical Success):** Rate of Technical Success defined as the successful implantation of the EchoMark LP implant and the ability to determine blood flow, diameter and depth measurements using the EchoSure diagnostic ultrasound system. Technical success will be assessed from baseline to 4 months.
OBSERVATIONAL ASSESSMENTS	The following observational analyses will be performed and/or summarized: • Comparison of EchoSure and duplex measurements of flow, diameter, and depth. Only duplex images that pass a quality control check by an independent RVT will be included in the assessment. • Comparison of EchoSure depth measurements to Independent Reviewer measured depth results. • Time to radiographic maturation is defined as the number of days from baseline procedure to date of radiographic maturation (date of ultrasound imaging, as adjudicated by the CEC). Radiographic maturation is defined as a fistula with volume flow of 500mL/min and 5mm diameter. • Time to clinical maturation defined as the number of days from baseline procedure to date of clinical maturation. Clinical maturation is defined as 75% of dialysis sessions with successful 2 needle cannulation. Date of clinical maturation is defined as first date of the 4-week window when clinical maturation is achieved. • Radiographic maturation success rate defined as the percentage of subjects that achieve radiographic maturation (as determined by the physician and adjudicated by the CEC) by end of study.

Radiographic maturation is defined as a fistula with 500mL/min and 5mm diameter.

- Clinical maturation success rate is defined as the percentage of subjects that achieve clinical maturation by end of study. Date of clinical maturation is defined as first date of the 4-week window when clinical maturation is achieved.
- 6-month patency rate as defined by the status (yes/no) of an arteriovenous dialysis access with detectable blood flow through and beyond the anastomosis shown by either an imaging modality or physical examination (presence of a palpable thrill or audible bruit along some point of the arteriovenous dialysis access beyond the arteriovenous anastomosis).
- 12-month patency rate as defined by the status (yes/no) of an arteriovenous dialysis access with detectable blood flow through and beyond the anastomosis shown by either an imaging modality or physical examination (presence of a palpable thrill or audible bruit along some point of the arteriovenous dialysis access beyond the arteriovenous anastomosis).
- Occurrence of events occurring within 30 days of implantation that require reinterventions (open or endovascular), hospitalizations, or prolongation of existing hospitalization.
- Occurrence of reported reduction of blood flow of blood flow that prevents the ability to cannulate or requires further assessment and/or intervention from baseline procedure to 12 months.
- Occurrence of reported inability to cannulate fistula beginning once the fistula is deemed radiographically and clinically mature to 12 months.
- Occurrence of the development of steal syndrome from baseline to 12 months.
- Occurrence of bleeding requiring surgical intervention (including PRBC transfusion) from baseline to 12 months.
- Occurrence of infiltration requiring procedural intervention from baseline to 12 months.
- Occurrence of hematoma requiring procedural intervention from baseline to 12 months.
- Occurrence of the inability to use the EchoSure component of the system, from baseline to 4 months, due to:
    - Migration of the EchoMark device
    - Early resorption of the EchoMark device as defined as breakdown of the EchoMark shape prior to 4 months from index procedure.
- Occurrence of pain related to the study devices from baseline to 12 months.
- Occurrence of infection (not limited to infection requiring implant explantation) from baseline to 12 months.

	• Occurrence of infection confirmed by either implant explantation or purulent fluid on pathologic assessment during incision and drainage beginning at baseline to 12 months. • Composite of new major device related adverse events (MAEs) at 12 months post EchoMark LP implantation, as adjudicated by the Clinical Events Committee (CEC). The proportion of subjects with device success and free from device- and/or procedure-related SAEs (per CEC adjudication) at 12 months. The summaries for each individual safety data point will also be provided, including: o Device or procedure-related death o Device related infection o Device related interventions o Device related hospitalizations o Fistula failure o Fistula rupture o Aneurysm
OVERSIGHT	A Data Safety Monitoring Board (DSMB) will be employed to provide safety oversight. A Clinical Events Committee (CEC) will be employed to provide adjudication of endpoints. An Independent RVT will be employed to adjudicate and perform a quality check of Duplex imaging. The Independent RVT will not review any measurements from the EchoSure system.
INCLUSION CRITERIA	1. Males or non-pregnant, non-breastfeeding females ≥ 18 years of age but < 85 years of age at the time of informed consent 2. Subject is able and willing to provide written informed consent prior to receiving any non-standard of care, protocol specific procedures 3. Subject is willing and capable of complying with all required follow-up visits 4. Subject and/or Care Team agree that the distance and transportation resources from the subject's home to the clinic are reasonable for study participation and compliance 5. Subject has an estimated life expectancy > 18 months 6. Subject is ambulatory (cane or walker are acceptable) 7. Subjects presenting for upper arm autologous arteriovenous fistula creation 8. Vein diameter > 2.5 mm at the antecubital fossa via imaging 9. Artery diameter > 3 mm via imaging 10. Subject is not participating in another investigational clinical trial that has not met its primary endpoint. Participation in a post-market registry is acceptable.

EXCLUSION CRITERIA	1. Subject is receiving a forearm fistula. 2. Subject has history of Steal Syndrome 3. Subject who is immunocompromised or immunosuppressed 4. Subject has had three previous failed AV fistulae for hemodialysis access 5. Subjects expecting to undergo major surgery within 60 days from the EchoMark LP implantation. 6. Known or suspected active infection on the day of the index procedure. 7. Subjects who had infection(s) in the 30-day window prior to EchoMark placement to reduce the likelihood of partially treated infections that can seed the device and fistula. 8. Subjects with diagnosed bleeding disorder, thrombocytopenia (platelet count <50,000), hypercoagulability, and history of recurrent deep vein thrombosis not related to AV access. 9. Subjects with active malignancy. 10. Subjects with a history of poor compliance with the dialysis protocol. 11. Subjects with a known or suspected allergy to any of the device materials. 12. Subjects with an existing fistula or graft. 13. Subjects who are pregnant, plan to become pregnant, or are breastfeeding.

Table 1: Schedule of Events

Study Requirement	Screening / Enrollment	Index Procedure		Follow-Up at Vascular Surgeon Office/Clinic										
			Discharge	15 days ±7 Days	30 Days ±7 Days	60 Days ±15 Days	90 Days ±15 Days	120 Days ±15 Days	150 Days ±15 Days	180 Days ±15 Days	12 Month ±15 Days	15 Month ±15 Days	18 Months ±15 Days	24 Months ±15 Days
Informed Consent	X													
Inclusion / Exclusion Criteria	X													
Blood Culture for Bacteremia	X													
Demographics	X													
Medical History and Most Recent Kt/V, CBC, Serum chemistry, Calcium, Phosphorous, Magnesium, Total Protein, Albumin, PTH	X			X	X	X	X	X	X	X	X	X	X	X
Relevant Medications	X			X	X	X	X	X	X	X	X	X	X	X
Physical Examination / Vital Signs	X	X	X	X	X	X	X	X	X	X	X			
Fistula Creation		X												
EchoMark LP Implantation		X												

External EchoMark Measurements			X	X	X	X	X	X	X	X	X			
Duplex Scans	X		X	X	X	X	X	X	X	X	X	X	X	X
EchoSure Scans*			X	X	X	X	X	X	X					
Cannulation Log, including attempts				X	X	X	X	X	X	X	X			
AE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
End of Study														X

** Note: The monthly EchoSure scans will be suspended after the 120 day (4 month) visit or once radiographic maturation is achieved, whichever is longer. Patients will continue to be followed monthly with physical examination, Duplex, and AE monitoring until the 180-day timepoint. If radiographic maturation is never achieved, patients will be followed until either the fistula is abandoned, or the patient reaches the 180-day timepoint. The 180-day timepoint is meant to assess patency via Duplex and is meant for AE monitoring.

3. INTRODUCTION

3.1. Device Description

Overview

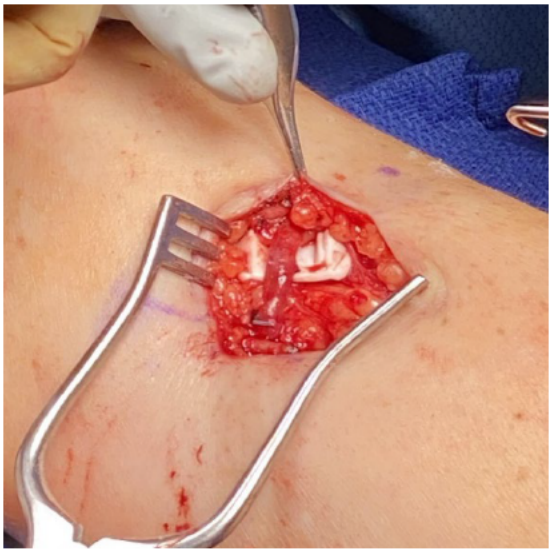
EchoMark/EchoMark LP is an ultrasound marker for marking an arteriovenous fistula. The EchoSure diagnostic ultrasound system and its transducer are intended for use in clinical examinations of arteriovenous fistulae and other blood vessels that are marked with an EchoMark/EchoMark LP implant. The system provides measurements and information about blood flow, and conduit diameter, and depth.

EchoMark

EchoMark is an implantable, echogenic, bioresorbable fiducial marker comprised [redacted] The EchoMark product line comes in two sizes, EchoMark and EchoMark LP, for physicians to select from. A photo of both sizes compared to a United States Quarter is shown below as **Figure 1**.

[redacted]).

The EchoMark is implanted under the vessel of interest during an open surgical procedure. In the context of arteriovenous fistulae, EchoMark implantation will occur during standard open fistula creation procedures through the same incision used for vascular access creation. The surgeon will place the EchoMark LP under the outflow vein of the fistula after the anastomosis of the vein to the artery has been completed. The vessel will sit in the channel of the EchoMark between its two peaks, as shown in **Figure 2**, [redacted] he EchoMark will be secured in place with 3-0 or 4-0 Prolene or equivalent non-resorbable sutures. The EchoMark can be prepared for securing by pre-loading the implant with non-resorbable sutures. The sutures should be driven through at least two corners of the device at bumper on the lateral edges of the implant at least 1mm from any edge of the EchoMark. [redacted]



[redacted] a check is performed to ensure that the devices is outside of the elbow articulation zone, not impinging the elbow motion, secure, and that there is no impingement of the vessel. Afterwards, the incision is closed using standard technique.

[redacted] Both features provide localization and orientation information about the marked vessel when scanned with the EchoSure ultrasound system that facilitate ultrasound data collection for the quantification of marked vessel's volumetric blood flow rate, diameter and depth.

EchoSure for AVF

EchoSure is a portable semi-automated diagnostic ultrasound imaging device that includes the EchoSure Ultrasound, the EchoSure AVF Application (software) and the EchoSure Probe. [redacted] such that the user simply needs to place the probe in the general region of the target rather than in a precise location. [redacted] hese features enable health care personnel without ultrasound experience to quickly and reliably position the EchoSure probe for a successful scan without consideration of technique. A photo of the full EchoSure system is shown in **Figure 3**.

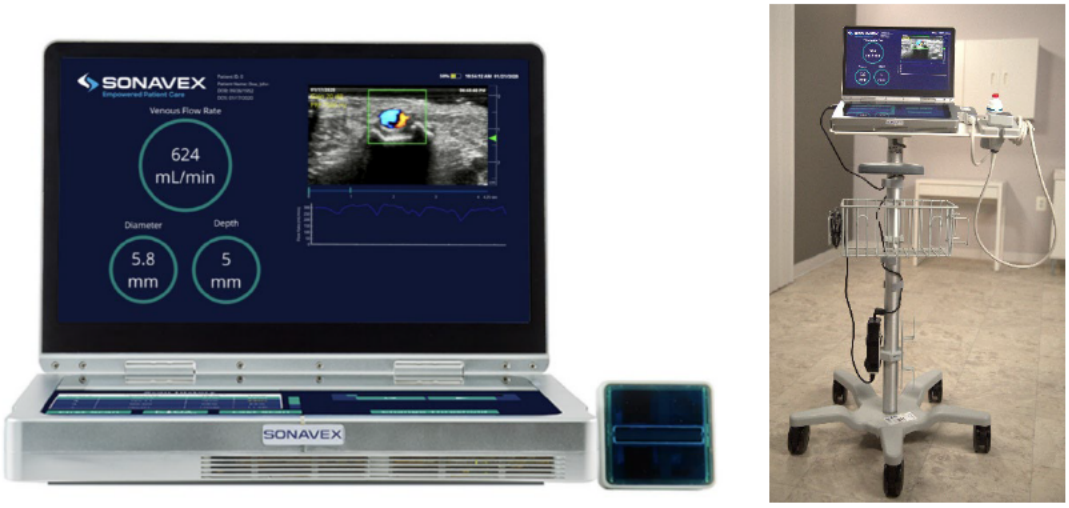


Figure 3 Closeup Photo of EchoSure and EchoSure Probe (left). Photo of full EchoSure system on roll stand (right).

The EchoSure AVF Application is designed with a simple user interface and workflow that walks the user through the scanning process with step-by-step instructions. [redacted] With each scan, EchoSure AVF automatically calculates and reports volumetric flow, diameter and depth of

the AVF. Scan results are presented to the user graphically and with tabulated historical results so changes in flow, diameter and depth can be tracked over time.

3.2 Product Development

[redacted]

3.3 Intended Use

EchoMark is intended to be implanted by the surgeon during upper arm open fistula creation under the outflow vein of the fistula, approximately 3cm away from the anastomosis. EchoSure is intended for use by healthcare personnel, with or without ultrasound training, in dialysis clinics or other clinical settings.

3.4 Indications for Use

The EchoMark/EchoSure System provides measurements and information about blood flow, including volumetric flow rate, diameter, and depth, for assessing upper arm arteriovenous fistulae throughout the maturation period.

3.5 Preliminary Investigations

Introduction

[redacted]

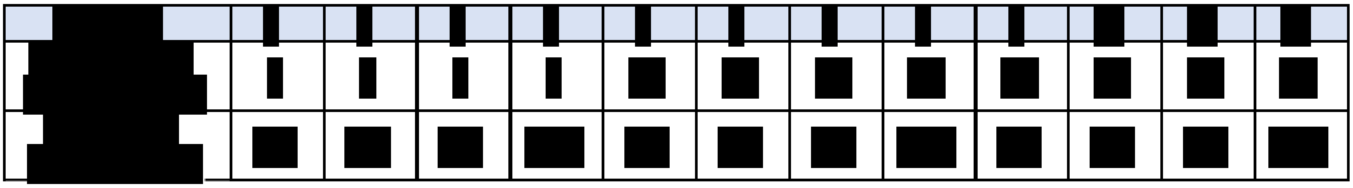
Benchtop Performance Data

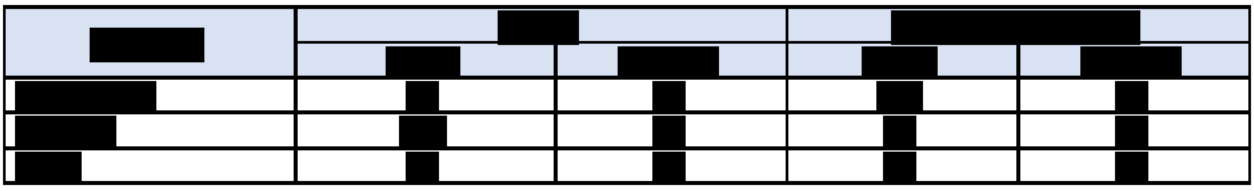
Purpose

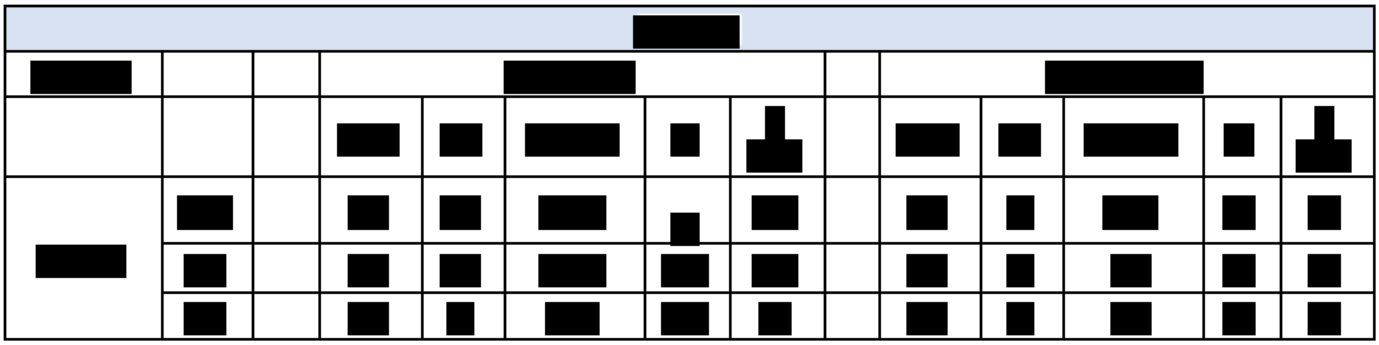
[redacted]

Test Procedure

[redacted]







[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ISO 10993 biocompatibility testing was performed on the EchoMark device. Results from the tests indicate that the device is non-toxic, non-sensitizing, non-mutagenic and non-irritating therefore biocompatible for its intended use.

EchoSure Probe

Sonavex has also performed extensive biocompatibility testing on EchoSure Probe. Biocompatibility testing of the EchoSure Probe devices was conducted in accordance with ISO 10993 series standards and EP/USP guidance documents as applicable. Additional guidance for the performance of these tests comes from the U.S. FDA June 2016 Guidance Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". All tests were conducted in compliance with applicable requirements in the good laboratory practice (GLP) regulations in 21 CFR 58. The specific studies include:

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ISO 10993 biocompatibility testing was performed on the EchoSure Probe. Results from the tests indicate that the device is biocompatible for its intended use.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

[redacted]

Summary of Outcomes Compared to Literature

In order to evaluate the longer-term impact on outcomes, maturation rates were also evaluated for the subjects in the studies. A total of 34 fistula patients were followed to the first maturation assessment or longer. A summary of the outcomes for EchoMark patients are included below alongside cited literature for non-EchoMark AV fistula patients.

	Sonavex EchoMark Patients[1]	Sonavex EchoMark (>90-day postop)[2]	Woodside 2018 (USRDS Data)	Robbin 2018 (HFM Study)	Chan 2018
Number of Patients/AVFs	34	30	45,087	587	146
% Mature	73.5%	83.3%	64%	72%	72%
% Failed	11.8%	16.7%	36%	28%	28%
% Outcome Not Yet Known*	14.7%	N/A	N/A	N/A	N/A

* A maturation determination has either not yet been determined or not yet communicated to Sonavex.

[1] All patients who underwent a first maturation assessment.

[2] All patients with a maturation outcome assigned or who are at least 90 days post-surgery. Though the national average time to maturation is over 6 months, out of caution, patients who received their AV fistula procedure more than 90 days ago were assigned as 'failure.'

Note: A total of 7 patients had follow-ups occurring after the study was suspended on January 7. These results were communicated to Sonavex verbally and represent 2 mature AVFs, 1 failed AVF, and 4 'outcome not yet known.'

The exact binomial method was used for EchoMark patients with 90-day follow-up to estimate the 95% confidence interval for maturation success. Centered around the 83.3% successful maturation rate, the 95% CI is [65.3% – 94.4%]. Thus, the existing sample size appears adequate to demonstrate that maturation success in the EchoMark patient population is in line with recent large AVF cohort studies[3,4,5,6,7]. Based on the results above, Sonavex has no reason to believe that EchoMark introduces additional risk to AV fistula patients. In fact, given historic average maturation times of 6-9 months it is likely that many of the patients in "outcome not yet known" may become successes, pushing the maturation success to a level higher than other recent large multicenter reports.

[redacted]

4. OBJECTIVES AND ENDPOINTS

4.1 Objectives

The primary objective of this study is to evaluate the feasibility and safety of the EchoMark and the EchoSure diagnostic ultrasound system for assessing AV fistula blood flow, diameter, and depth.

4.2 Study Endpoints

4.2.1 Primary Safety Endpoints

Composite of new major device related adverse events (MAEs) at 30 days post EchoMark implantation, as adjudicated by the Clinical Events Committee (CEC) including:

- Device or procedure-related death
- Device related infection
- Device related interventions
- Device related hospitalizations
- Fistula failure
- Fistula rupture
- Aneurysm

After the close of the 90-day visit window, all evaluable subjects will be summarized and expansion to a pivotal trial will be requested under a new IDE.

4.2.2 Primary Feasibility (Technical Success):

Rate of Technical Success defined as the successful implantation of the EchoMark implant and the ability to determine blood flow, diameter and depth measurements using the EchoSure diagnostic ultrasound system from baseline to 4 months.

4.2.3 Observational Assessments

The following observational assessments will be performed and/or summarized:

- Comparison of EchoSure and duplex measurements of flow, diameter, and depth. Only duplex images that pass a quality control check by an Independent RVT will be included in the assessment.
- Comparison of EchoSure depth measurements to Independent Reviewer measured depth results.

- Time to radiographic maturation is defined as the number of days from baseline procedure to date of radiographic maturation (date of ultrasound imaging, as adjudicated by the CEC). Radiographic maturation is defined as a fistula with volume flow of 500mL/min and 5mm diameter.
- Time to clinical maturation defined as the number of days from baseline procedure to date of clinical maturation. Clinical maturation is defined as 75% of dialysis sessions with successful 2 needle cannulation for 4 weeks. Date of clinical maturation is defined as first date of the 4-week window when clinical maturation is achieved.
- Radiographic maturation success rate defined as the percentage of subjects that achieve radiographic maturation (as determined by the physician and adjudicated by the CEC) by end of study. Radiographic maturation is defined as a fistula with volume flow of 500mL/min and 5mm diameter.
- Clinical maturation success rate is defined as the percentage of subjects that achieve clinical maturation by end of study. Date of clinical maturation is defined as first date of the 4-week window when clinical maturation is achieved.
- 6-month patency rate as defined by the status (yes/no) of an arteriovenous dialysis access with detectable blood flow through and beyond the anastomosis shown by either an imaging modality or physical examination (presence of a palpable thrill or audible bruit along some point of the arteriovenous dialysis access beyond the arteriovenous anastomosis). [8]
- 12-month patency rate as defined by the status (yes/no) of an arteriovenous dialysis access with detectable blood flow through and beyond the anastomosis shown by either an imaging modality or physical examination (presence of a palpable thrill or audible bruit along some point of the arteriovenous dialysis access beyond the arteriovenous anastomosis).
- Occurrence of events occurring within 30 days of implantation that require reinterventions (open or endovascular), hospitalizations, or prolongation of existing hospitalization.
- Occurrence of reported reduction of blood flow that prevents the ability to cannulate or requires further assessment and/or intervention from baseline procedure to 12 months.
- Occurrence of the reported inability to cannulate fistula beginning once the fistula is deemed radiographically and clinically mature to 12 months.
- Occurrence of the development of steal syndrome from baseline to 12 months.
- Occurrence of bleeding requiring surgical intervention (including PRBC transfusion) from baseline to 12 months.
- Occurrence of infiltration requiring procedural intervention from baseline to 12 months.

- Occurrence of hematoma requiring procedural intervention from baseline to 12 months.
- Occurrence of the inability to use the EchoSure component of the system, from baseline to 4 months, due to:
    - Migration of the EchoMark device
    - Early resorption of the EchoMark device as defined as breakdown of the EchoMark shape prior to 4 months from index procedure.
        - EchoMark will continue to be monitored throughout the duration of the study.
- Occurrence of pain associated with the study devices from baseline to 12 months.
- Occurrence of infection (not limited to infection requiring implant explantation) from baseline to 12 months.
- Occurrence of infection confirmed by either implant explantation or purulent fluid on pathologic assessment during incision and drainage from baseline to 12 months.
- Composite of new major device related adverse events (MAEs) at 12 months post EchoMark LP implantation, as adjudicated by the Clinical Events Committee (CEC). The proportion of subjects with device success and free from device- and/or procedure-related SAEs (per CEC adjudication) at 12 months. The summaries for each individual safety data point will also be provided, including:
    - Device or procedure-related death
    - Device related infection
    - Device related interventions
    - Device related hospitalizations
    - Fistula failure
    - Fistula rupture
    - Aneurysm

5. STUDY DESIGN

5.1 Overall Design

This is a prospective, multi-center, single-arm, non-blinded clinical trial designed to evaluate the feasibility and safety of the Sonavex EchoMark and the EchoSure in subjects undergoing new upper arm autologous arteriovenous fistula creation who require hemodialysis. The trial will enroll up to 20 subjects in up to 6 clinical sites in the United States. Each site can enroll up to 3 “roll-in” subjects. Roll-in subjects will be consecutive, must be identified as roll-in subjects prior to the EchoMark implantation, and will not count toward the total enrollment of 20 subjects.

5.2 Blinding

The data from EchoSure will not be used in clinical care. The study investigators will be blinded to EchoSure results and comparison of EchoSure measurements to Duplex measurements until the end of the study.

5.3 End of Study

All enrolled subjects will exit the study when all study related activities and visits are completed, but no later than 24 months.

6. STUDY POPULATION

6.1 Clinical Sites

It is important to select the appropriate clinical sites for this trial. Investigators should be credible and experienced, and the sites should experience a high enough volume of subjects undergoing upper arm autologous arteriovenous fistula creation for hemodialysis.

It is estimated that up to 6 clinical sites including hospitals and surgical centers in the United States will enroll in this trial. All follow up visits included in this study where the EchoSure device is used will be conducted at the vascular surgeon's office/clinic.

6.2 Determination of Study Eligibility

All subjects will be required to sign the Institutional Review Board–approved informed consent form for the study.

Upon satisfying inclusion and exclusion criteria, a clinical history and signing the informed consent form, a subject will be eligible for enrollment in the trial.

6.3 Inclusion Criteria

Subjects will be included if all the following inclusion criteria apply:

1. Males or non-pregnant, non-breastfeeding females ≥ 18 years of age but < 85 years of age at the time of informed consent
2. Subject is able and willing to provide written informed consent prior to receiving any non-standard of care, protocol specific procedures
3. Subject is willing and capable of complying with all required follow-up visits
4. Subject and/or Care Team agree that the distance and transportation resources from the subject's home to the clinic are reasonable for study participation and compliance
5. Subject has an estimated life expectancy > 18 months
6. Subject is ambulatory (cane or walker are acceptable)
7. Subjects presenting for upper arm autologous arteriovenous fistula creation
8. Vein diameter > 2.5 mm at the antecubital fossa via imaging
9. Artery diameter > 3 mm via imaging

10. Subject is not participating in another investigational clinical trial that has not met its primary endpoint. Participation in a post-market registry is acceptable.

6.4 Exclusion Criteria

Subjects will be excluded if any of the following exclusion criteria apply:

1. Subjects receiving a forearm fistula.
2. Subject has history of Steal Syndrome.
3. Subject who is immunocompromised or immunosuppressed.
4. Subject has had three previous failed AV fistulae for hemodialysis access
5. Subjects expecting to undergo major surgery within 60 days from the EchoMark implantation.
6. Known or suspected active infection on the day of the index procedure.
7. Subjects who had infection(s) in the 30-day window prior to EchoMark placement to reduce the likelihood of partially treated infections that can seed the device and fistula
8. Subjects with diagnosed bleeding disorder, thrombocytopenia (platelet count <50,000), hypercoagulability, and history of recurrent deep vein thrombosis not related to AV access
9. Subjects with active malignancy
10. Subjects with a history of poor compliance with the dialysis protocol
11. Subjects with a known or suspected allergy to any of the device materials
12. Subjects with an existing fistula or graft
13. Subjects who are pregnant, plan to become pregnant, or are breastfeeding.

6.5 Strategies for Recruitment and Retention

The clinical research personnel will screen and attempt to enroll subjects in clinical settings scheduled for an upper arm autologous arteriovenous fistula creation who meet the study criteria. Qualified research personnel will be responsible for obtaining informed consent. The prospective participants will be informed the study is solely voluntary and that they can choose to not enroll or exit the study at any time without consequence to the quality of their care or services provided. Prospective participants will be provided with adequate time to make an informed decision and will be invited to ask questions.

6.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but never have the EchoMark implanted. A minimum set of screen failure information is required including demographics, screen failure details, and eligibility criteria. Screen failures can be replaced.

7. STUDY INTERVENTION

7.1 EchoSure Scan Requirements

The EchoSure scans will be conducted at the vascular surgeon's (investigator's) office/clinic by a member of their staff that does not have formal ultrasound training and has been designated and trained as study personnel. Appropriate staff members to conduct the EchoSure scans include the study research coordinator(s), nurses, nursing assistants, or medical technicians. Prior to starting study activities, each site will designate at least one staff member without previous ultrasound training to conduct the EchoSure scans. These designated EchoSure users will be trained on the use of the EchoSure system and how to fill out the EchoSure case report form, including the blinding of the investigator, during Site Initiation Visits. The designated EchoSure users will be included in the study delegation log of authority and a copy their CV/resume will be included in the site's study regulatory binder. No other study personnel will operate the EchoSure system.

The follow-up EchoSure scans will be conducted by the designated EchoSure user without the investigator and without the sonographer/RVT conducting the Duplex exam in the room, either during the routine work-up prior to the surgeon seeing the patient or after. The EchoSure results for flow, and vessel depth and diameter are shown as numerical values on the screen of the EchoSure device. After each scan, the EchoSure user will transcribe these values onto the case report form. The EchoSure data will not be included elsewhere in the patient's medical record. The CRF data will be entered in to an EchoSure master data spreadsheet by a data manager. This master data spreadsheet will not be available to investigators. While historical EchoSure scans and data are stored on the EchoSure system, the system requires a username and password to login. Only designated EchoSure users will be given login credentials. The investigator's will not be provided with login credentials, so they will not be able to log in to the system to conduct EchoSure scans or view any of the EchoSure measurement data.

7.2 Duplex Scan Requirements

The Duplex exams will be conducted by certified sonographers or registered vascular technologists (RVT), or physicians experienced in vascular ultrasound exams who have been trained on the study's Duplex data collection protocol (defined in Section 7.4, pg 36 – 39, of the Investigator's Brochure). All study personnel will be instructed during training that the sonographer/RVT must not be in the room during the EchoSure scans. During the Duplex exam, the sonographer/RVT will fill out the Duplex Follow-Up CRF which includes transcribing the numerical values for flow and vessel depth and diameter that result from the Duplex exam. The saved Duplex data (specific images with caliper measurements and calculations as outlined in the study Duplex protocol) and the CRF will be sent to an Independent RVT for quality checks. An Independent RVT will verify the quality of Duplex images and measurements following defined specifications and key-in verified numerical values for flow and vessel depth and diameter into a Duplex master data spreadsheet. This master data spreadsheet will not be available to the investigators.

7.3 Pre-Procedure Requirements

Once informed consent is obtained the subject is enrolled in the study. The subject will undergo the following procedures:

- Demographics
- Vital Signs
- Medical History to include the most recent Kt/V, CBC, Serum Chemistry, Calcium, Phosphorous, Magnesium, Total Protein, Albumin, PTH
- Relevant medications
- Duplex scan to assess the blood flow, depth and diameter of the target vessels.
- Duplex scan to assess the Brachial Artery for flow and diameter.
- Blood culture to confirm absence of bacteremia.

7.4 Study Procedure

All subjects will undergo a physician exam prior to their arteriovenous fistula creation per the institution's standard of care. After the fistula creation is completed, but prior to closure, the EchoMark will be implanted under the outflow vein and secured in place using 3-0 or 4-0 Prolene or equivalent non-resorbable sutures. The EchoMark is to be secured a minimum of 3 cm away from the anastomosis. Procedure details and outcomes will be collected, including:

- Inflow Artery Diameter
- Outflow Vein Diameter
- Length of vessel from anastomosis to the closest edge of the EchoMark
- Adverse Events
- Procedure Success

7.5 Post-Procedure Through Discharge

Subjects will be followed through discharge. The subject will be evaluated for flow by physical exam to include assessment of palpable thrill and audible bruit and will be monitored for adverse events. The subject will undergo a duplex scan, capturing the flow rate, diameter, and depth when feasible. Additionally, an external measurement of each EchoMark corner location will be completed. The EchoMark will be located with palpitation and each corner will be measured independently to the antecubital fossa.

7.6 Pre-Maturation Follow-up at 15, 30, 60, 90, 120, 150 Days

Subjects will have follow-up visits at 15 (+/- 7 days), 30 (+/- 7 days), 60 (+/- 15 days), 90 (+/- 15 days), 120 (+/- 15 days), and 150 (+/- 15 days) days from the baseline procedure, including a physical exam, duplex imaging, EchoSure scan, external EchoMark measurement, medical history, and adverse event monitoring. The EchoSure scans will be suspended after the 120 day (4 month) visit or once radiographic maturation is achieved,

whichever is longer. Radiographic maturation is defined as 500mL/min and a 5 mm diameter. The monthly clinical follow-up and duplex imaging will continue per the follow-up schedule. The physical exam will include assessing the fistula for bruit and thrill. The medical history will include all interventions, cannulation history including any attempts, and the most recent Kt/V, CBC, Serum Chemistry, Calcium, Phosphorous, Magnesium, Total Protein, Albumin, PTH. EchoSure scans will be completed by study personnel who do not have prior ultrasound training, are representative of non-expert users, and have been delegated on the delegation of authority log. Duplex and EchoSure scans will include:

- A total of three (3) EchoSure scans performed at the site of the EchoMark. Volume flow, diameter, and depth data to be recorded.
- A total of three (3) limited DUS scans performed at the site of the EchoMark. DUS will be performed in transverse Bmode and longitudinal view. Volume flow, diameter, depth, and distance from scan area to anastomosis will be recorded.
- A total of three (3) limited DUS scans performed at the cannulation zone in transverse Bmode and longitudinal view. Volume flow, diameter, and depth, will be recorded.
- The 9 Duplex images will be de-identified and undergo quality control checks performed by an Independent RVT.
- A duplex exam of the fistula from the EchoMark location and beyond to assess for the presence of stenotic lesions. If a lesion is present, capture and save an image showing a longitudinal view of the fistula segment with the stenosis, note the location of the stenosis in relation to the anastomosis and EchoMark, and track the stenosis as an adverse event.
- A duplex scan of the brachial artery to assess flow and diameter, capture a PW image showing the flow and diameter measurements.

7.7 Post-Maturation Follow-up at 150 Days if Radiographic Mature

The EchoSure scans will be suspended after the 120 day (4 month) visit or once radiographic maturation is achieved, whichever is longer. Radiographic maturation is defined as fistula diameter ≥ 5mm, fistula flow ≥ 500 mL/min. If radiographic maturation has been achieved before the 150-day follow-up visit, the subject will not switch to the Post Maturation follow-up schedule until the 150 Day visit when the EchoSure scans are suspended. Post-Maturation follow-up visits will include a physical exam, medical history review, Duplex scan, external EchoMark measurement, and adverse event monitoring. The physical exam will include assessing the fistula for bruit and thrill. The medical history will include all interventions, cannulation attempts, and the most recent Kt/V, CBC, Serum Chemistry, Calcium, Phosphorous, Magnesium, Total Protein, Albumin, PTH, Duplex scans will include:

- Assessment of patency (flow/no flow adjudicated by the CEC)

- Limited DUS scan performed at the site of EchoMark to determine EchoMark visibility including:
    - 1 BMode, transverse view of EchoMark at center
    - 1 BMode, transverse view of EchoMark at distal edge
    - 1 BMode, Transverse view of EchoMark at proximal edge
    - 1 BMode, Longitudinal view centered over vessel showing full length of EchoMark
- A duplex exam of the fistula from the EchoMark location and beyond to assess for the presence of stenotic lesions. If a lesion is present, capture and save an image showing a longitudinal view of the fistula segment with the stenosis, note the location of the stenosis in relation to the anastomosis and EchoMark, and track the stenosis as an adverse event.
- A duplex scan of the brachial artery to assess flow and diameter, capture a PW image showing the flow and diameter measurements.

7.8 180 Day and 12 Month (+ 15 Days) Follow-up

All subjects will have follow-up visit at 180 days and 12 months after baseline procedure. Follow-up visits will include a physical exam, medical history review, Duplex scan, external EchoMark measurement, and adverse event monitoring. The physical exam will include assessing the fistula for bruit and thrill. The medical history will include all interventions, cannulation attempts, and the most recent Kt/V, CBC, Serum Chemistry, Calcium, Phosphorous, Magnesium, Total Protein, Albumin, PTH, Duplex scans will include:

- Assessment of patency (flow/no flow adjudicated by the CEC)
- Limited DUS scan performed at the site of EchoMark to determine EchoMark visibility including:
    - 1 BMode, transverse view of EchoMark at center
    - 1 BMode, transverse view of EchoMark at distal edge
    - 1 BMode, Transverse view of EchoMark at proximal edge
    - 1 BMode, Longitudinal view centered over vessel showing full length of EchoMark.
- A duplex exam of the fistula from the EchoMark location and beyond to assess for the presence of stenotic lesions or a fluid collection. If a lesion is present, capture and save an image showing a longitudinal view of the fistula segment with the stenosis, note the location of the stenosis in relation to the anastomosis and EchoMark, and track the stenosis as an adverse event. If a fluid collection is present, capture and save an image noting the location from the anastomosis and the size and volume.
- A duplex scan of the brachial artery to assess flow and diameter, capture a PW image showing the flow and diameter measurements.

7.9 15 Month, 18 Month, and 24 Month (+ 15 Days) Follow-up

All subjects who are willing to reconsent to longer-term follow-up will have a follow-up visit at 15 months, 18 months, and 24 months after baseline procedure. Follow-up visits will include a captures of medical history since the last visit, Duplex scan, and adverse event monitoring. The Duplex scans will include:

- Limited DUS scan performed at the site of EchoMark to determine EchoMark visibility including:
  - 1 BMode, transverse view of EchoMark at center
  - 1 BMode, transverse view of EchoMark at distal edge
  - 1 BMode, Transverse view of EchoMark at proximal edge
  - 1 BMode, Longitudinal view centered over vessel showing full length of EchoMark
- A duplex exam of the fistula from the EchoMark location and beyond to assess for the presence of a fluid collection. If a fluid collection is present, capture and save an image noting the location from the anastomosis and the size and volume.

7.10 Fistula Outside of the EchoMark

If the subject's fistula is deemed to be outside of the EchoMark, an adverse event form will be completed and adjudicated by the CEC. The subject will remain in the study. The EchoSure scans will be suspended. The subject will complete the follow-up schedule as scheduled. Each follow-up visits will include a physical exam, medical history review, Duplex scan, external EchoMark measurement, and adverse event monitoring. The physical exam will include assessing the fistula for bruit and thrill. The medical history will include all interventions, cannulation attempts, and the most recent Kt/V, CBC, Serum Chemistry, Calcium, Phosphorous, Magnesium, Total Protein, Albumin, PTH, Duplex scans will include:

- Depth, Diameter and Volume Flow at/near the EchoMark
- Assessment of patency (flow/no flow adjudicated by the CEC)
- Limited DUS scan performed at the site of EchoMark to determine EchoMark visibility including:
  - 1 BMode, transverse view of EchoMark at center
  - 1 BMode, transverse view of EchoMark at distal edge
  - 1 BMode, Transverse view of EchoMark at proximal edge
  - 1 BMode, Longitudinal view centered over vessel showing full length of EchoMark
- A duplex exam of the fistula from the EchoMark location and beyond to assess for the presence of stenotic lesions. If a lesion is present, capture and save an image showing a longitudinal view of the fistula segment with the stenosis, note the location of the stenosis in relation to the anastomosis and EchoMark, and track the stenosis as an adverse event.
- A duplex scan of the brachial artery to assess flow and diameter, capture a PW image showing the flow and diameter measurements.

The subject will follow the same 180-day and 12-month visit follow-up visit as described in Section 7.8 7.8 180 Day and 12 Month (+ 15 Days) Follow-up

7.11 Fistula Failure

If the subject's fistula is deemed a failure and abandoned by the investigator, a fistula failure case report form will be completed recording the reasoning for the failure. The subject will remain in the study and receive monthly telephone calls to monitor for adverse events and physical assessments of the EchoMark at all standard of care visits. The subject will complete the 180-day and 12 months visit as scheduled to undergo a physical exam, medical history review, adverse event monitoring, and duplex examination of the EchoMark and exit the study.

7.12 EchoMark Explantation

If the EchoMark is removed, the subject will be followed until the event is resolved. A case report form will be completed to track the reasoning, procedure details, and outcomes. The subject will be monitored with the institution's standard of care, including physical exam and possibly ultrasound. The event will be tracked until the symptoms are resolved and the subject will exit the study.

8. RISK AND BENEFIT ASSESSMENT

The study involves the creation of an arteriovenous fistula, therefore the risks of participating in this research include the risks inherently associated with a standard AV fistula creation which may include bruising, numbness, tingling and/or coolness in the extremity, thrombosis, stenosis, failure to mature, additional interventions, venous hypertension, swelling, irritation or pain, bleeding/hemorrhage, hematoma, seroma, wound problem, fever, steal syndrome, ischemia, embolism, infection, increased risk of congestive heart failure, nerve damage, vessel damage, pseudoaneurysm, compartment syndrome, heart problems such as arrhythmias, burns, problems due to sedation or anesthesia, sepsis, allergic reaction, or death.

With the implantation of any foreign material such as a radiologic marker (EchoMark), there is risk of allergic reaction, infection, inflammation, migration, or extrusion. Given the biocompatibility data collected by the company and the extensive prior use of the material in medicine, the probability of such risk is low. The safety of the device for general use has already been evaluated by the FDA during the clearance process for EchoMark and there has been a prior multicenter study in AV fistula patients that has shown maturation success rates that were in line with recent literature. There is also a possibility that the fistula may slide out of the EchoMark, which may prevent the EchoSure device from measuring the flow, diameter and depth accurately. When the EchoMark implant is secured properly the likelihood of this risk is low and standard of care methods for assessing the fistula are still available making the severity low. There is risk that the ultrasound scan may create mild discomfort for the subject on the wound site. The likelihood and severity of this risk is low.

Prior experience in the AV population captured adverse events including infection and seroma. All subjects are to be closely monitored for signs of an infection or seroma. If the subject begins to exhibit signs of infection, inflammation or extrusion, a clinical decision will be made by the team if the risk from the implantable device requires removal of the device. In these cases, the implantable device will be removed, and the subject will be monitored with the institution's standard of care, including physical exam and possibly ultrasound. The event will be tracked until the symptoms are resolved.

There is potential risk of loss of subject confidentiality in the event of a data breach. Protections are in place to minimize the risk. No protected health information (PHI), such as subject names, medical record numbers, or other identifying information which could be linked to a subject will be stored in the database. A subject ID number will be assigned to medical record information stored in the database. Information linking the subject ID to subject PHI will be store separately in a secure location, accessible to study personnel only.

Participation in the clinical study does not provide any guarantee of benefit to the subject. However, the study follows existing Standard of Care with additional touchpoints. The study involves at least monthly post-op visits with the physician, providing the ability to detect any issues that may arise from the study and can then be addressed in a timely fashion. Second, subjects will receive additional care above and beyond the Standard of Care, including extra physical examinations and ultrasound assessments.

9. ADVERSE EVENTS

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

9.1 Serious Adverse Event

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, in subject hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Unanticipated Adverse Device Effects (UADE)

A UADE is considered "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated

serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

9.3 Severity of an Adverse Event

For adverse events (AEs) the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

9.4 Relationship to the Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Possibly Related - There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study device). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "Related."
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.5 Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At study visits, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator is to report all SAEs to the study sponsor within 24 hours of first recognition of the event. Additionally, any device malfunctions, failures, and/or explants are to be reported to the sponsor within 24 hours of first recognition of the event.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

10. STUDY DISCONTINUATION AND WITHDRAWAL**Discontinuation and Closure**

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reasoning for the

termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

The DSMB will meet at least every three months to assess the safety and efficacy data of the study. The DSMB will operate under the rules of an approved charter and each meeting must include a recommendation to continue or to terminate the study and whether the DSMB has any concerns about participant safety. Additionally, an emergency meeting of the DSMB may be called at any time by the DSMB chairperson should questions of patient safety arise.

10.2. Withdrawal

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons pregnancy, significant study intervention non-compliance, clinical adverse event (AE), laboratory abnormality, or other medical condition or situations such that continued participation in the study would not be in the best interest of the participant.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Forms (CRFs). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, and will not be replaced.

10.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

1. The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit and ascertain if the participant wishes to and/or should continue in the study.
2. Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone

calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11. STATISTICAL ANALYSIS

11.1. Sample Size Considerations

This is a feasibility study and accordingly there is not a pre-specified null hypothesis to be tested against for the study endpoints. Data collected from this study will provide preliminary device safety and effectiveness data for the use of the EchoMark/EchoSure System in patients receiving arteriovenous fistulae for hemodialysis access. Descriptive statistics will be reported for the study data. Inferential statistical analysis will be conducted in an exploratory manner. The sample size for this study is planned to be up to 20 subjects at up to 4 investigational sites, with data points collected at multiple timepoints for each subject.

Statistical methods for the study are outlined below.

11.2. Data Analysis Plan

11.2.1 General Principles

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4, SAS Institute Inc. Cary, NC), STATA (version 16, StataCorp, College Station, TX) or other widely accepted statistical or graphical software. All statistical analysis will be conducted by an independent statistician.

Descriptive statistics will be used to present the data and to summarize results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values. In general, data for all study subjects combined will be presented. The primary analysis for all baseline characteristics and study outcomes will include all available data for all enrolled subjects. Individual data will be presented in subject listings.

Summaries of the following endpoints present the number and percentage of unique subjects within an event, unless specified otherwise: protocol deviations; subject status; adverse events. Thus, multiple occurrences of the same event are counted only once per subject, unless specified otherwise.

11.2.2 Subject Disposition

The number and percentage of subjects screened, screen failure, enrolled, treated, and completed will be summarized. Screen failure percentage is calculated from number of screened subjects and other percentages are calculated among number of enrolled subjects. A subject will be considered enrolled once they have signed the study patient

informed consent form. Subjects who discontinue from the study will be summarized with reason and listed by their primary reason for discontinuation.

11.2.3 Study Conduct

Protocol deviations from the investigation plan will be summarized by deviation type as well as total. Protocol deviations by investigational site will also be provided.

11.2.4 Analysis Samples

The primary and observational analysis samples will include all enrolled subjects with successful EchoMark LP implantation.

11.2.5 Analysis of Population Demographics, Baseline and Procedural Characteristics

Descriptive statistics will be summarized for baseline demographics, medical history, baseline disease characteristics, and procedural characteristics.

11.2.6 Analysis of Primary Safety Endpoint

For the composite primary safety endpoint, the proportion of subjects with device success and free from device- and/or procedure-related SAEs (per CEC adjudication) at 30 days. The summaries for each individual safety data point will also be provided.

11.2.7 Analysis of Primary Feasibility (Technical Success)

Definition of feasibility endpoints are described in Section 4.2.

For composite endpoints, i.e., technical success and implantation success, the number and percentage of subjects with success will be summarized. Descriptive statistics for components of each endpoint will also be provided.

11.2.8 Analysis of Observational Endpoints

Observational endpoints are defined in Section 4.2.

For discrete endpoints, the number and percentage of subjects with success will be summarized. Descriptive statistics for components of each endpoint will also be provided.

For continuous variables (e.g., volume flow, depth, and diameter), results will be summarized with the with the numbers of observations, means, medians, standard deviations, minimums, and maximums. Change from baseline will be included using these same descriptive statistics.

11.2.8.1 Comparison of EchoSure volume flow, diameter and depth to Duplex values:

The degree of correlation between paired EchoSure values and Duplex values that pass the quality checks by an Independent RVT will be analyzed.

The comparison data points are:

- EchoSure vessel depth at EchoMark vs Duplex vessel depth at EchoMark
- EchoSure vessel diameter at EchoMark vs Duplex vessel diameter at EchoMark
- EchoSure volume flow at EchoMark vs Duplex volume flow at cannulation zone (standard of care)

All Duplex volume flow, depth and diameter data points will undergo quality checks performed by an Independent RVT to qualify for inclusion in the comparison analyses. The quality checks will assess if the Duplex data was collected per protocol and meet defined requirements that ensure a uniform technique.

Duplex volume flow data points that do not pass the quality checks will not be included in the analysis. The paired EchoSure flow values for failing Duplex values will also not be included.

Duplex diameter and depth values that do not pass the quality checks will be corrected by an Independent RVT. The corrected Duplex depth and diameter data points will be included in the analysis along with their paired EchoSure values.

All sites and their sonographers will be trained on the Duplex data collection protocol and quality requirements. Each site will be required to submit a set of images for quality checks by an Independent RVT as a part of site qualification.

Degree of correlation between paired EchoSure values and Duplex values (volumetric flow, vessel diameter, vessel depth, etc.) that pass quality checks will undergo the following analyses:

- Pearson Correlations to assess correlation
- Bland Altman testing using percentages will be used to assess for bias and the limits of agreement
- Distribution of correlation percentage between EchoSure and Duplex values

Additional statistical analyses may be conducted as deemed necessary.

11.2.8.2 Comparison of EchoSure depth measurements to Independent Reviewer measured depth results.

All EchoSure images will be adjudicated for the reported depth measurements. An Independent Reviewer will manually measure the vessel depth on the EchoSure images. The Independent Reviewer will only receive anonymized EchoSure images.

Degree of correlation between paired EchoSure values and the Independent Reviewer values (depth) will undergo the following analyses:

- Pearson Correlations to assess correlation.
- Bland Altman testing using percentages will be used to assess for bias and the limits of agreement.

- Distribution of correlation percentage between EchoSure and Independent Reviewer values.

Additional statistical analyses may be conducted as deemed necessary.

11.2.8.3 Time to Radiographic Maturation

Time to radiographic maturation is defined as the number of days from baseline procedure to date of radiographic maturation (date of ultrasound imaging).

Radiographic maturation is defined as fistula diameter ≥ 5mm, fistula flow ≥ 500 mL/min as assessed by physician based on ultrasound imaging and adjudicated by CEC.

11.2.8.4 Time to Clinical Maturation

Time to clinical maturation is defined as the number of days from baseline procedure to date of clinical maturation (first date of 4-week window with 75% successful 2 needle cannulation).

Clinical maturation is defined as 75% of dialysis sessions with 2 needle cannulation for 4 weeks.

11.2.8.5 Radiographic Maturation Success Rate

Radiographic maturation success rate is defined as the percentage of subjects that achieve radiographic maturation by end of study.

Radiographic maturation is defined as fistula diameter ≥ 5mm, fistula flow ≥ 500 mL/min as assessed by physician based on ultrasound imaging and adjudicated by CEC.

11.2.8.6 Clinical Maturation Success Rate

Clinical maturation success rate is defined as the percentage of subjects that achieve clinical maturation by end of study.

Clinical maturation is defined as 75% of dialysis sessions with 2 needle cannulation for 4 weeks.

11.2.8.7 6-Month Patency Rate

6-month patency rate is defined as the percentage of subjects that have patent access at 6 months if both radiographic and clinical maturation definitions have been met.

6-month patency rate as defined by the status (yes/no) of an arteriovenous dialysis access with detectable blood flow through and beyond the anastomosis shown by either an imaging modality or physical examination (presence of a palpable thrill or audible bruit along some point of the arteriovenous dialysis access beyond the arteriovenous anastomosis).

11.2.8.8 12-Month Patency Rate

12-month patency rate is defined as the percentage of subjects that have patent access at 12 months if both radiographic and clinical maturation definitions have been met.

12-month patency rate as defined by the status (yes/no) of an arteriovenous dialysis access with detectable blood flow through and beyond the anastomosis shown by either an imaging modality or physical examination (presence of a palpable thrill or audible bruit along some point of the arteriovenous dialysis access beyond the arteriovenous anastomosis).

11.2.8.9 30-day occurrence of Interventions or Hospitalizations

Occurrence of events occurring within 30 days of implantation that require reinterventions (open or endovascular), hospitalizations, or prolongation of existing hospitalization

11.2.8.10 Occurrence of Events:

Occurrence is defined as the overall number of each event listed below that occur in the defines time period.

- Occurrence of reported reduction of blood flow that prevents the ability to cannulate or requires further assessment and/or intervention from baseline to 12 months.
- Occurrence of reported inability to cannulate fistula beginning once the fistula is deemed radiographically and clinically mature to 12 months.
- Occurrence of the development of steal syndrome from baseline to 12 months.
- Occurrence of bleeding requiring surgical intervention (including PRBC transfusion) from baseline to 12 months.
- Occurrence of infiltration requiring procedural intervention from baseline to 12 months.
- Occurrence of hematoma requiring procedural intervention from baseline to 12 months.
- Occurrence of the inability to use the EchoSure component of the system, from baseline to 4 months, due to:
    - Migration of the EchoMark device
    - Early resorption of the EchoMark device as defined as breakdown of the EchoMark shape prior to 4 months from index procedure.
- Occurrence of pain caused by the study devices beginning at baseline to 12 months.
- Occurrence of infection (not limited to infection requiring implant explantation) beginning at baseline to 12 months.

- Occurrence of infection confirmed by either implant explantation or purulent fluid on pathologic assessment during incision and drainage beginning at baseline to 12 months.

11.2.8.11 Composite of new major device related adverse events (MAEs) at 12 months

The proportion of subjects with device success and free from device- and/or procedure-related SAEs (per CEC adjudication) at 12 months. The summaries for each individual safety data point will also be provided. Composite of new major device related adverse events (MAEs) at 12 months post EchoMark LP implantation, as adjudicated by the Clinical Events Committee (CEC), including:

- Device or procedure-related death
- Device related infection
- Device related interventions
- Device related hospitalizations
- Fistula failure
- Fistula rupture
- Aneurysm

11.2.9 Interim Analysis

An interim analysis will be conducted when the last subject enrolled reaches the 90 day follow-up visit.

Informal interim analyses may be performed if deemed necessary by CEC, DSMB, or Sponsor. The Sponsor may access the study data at any time during the study, as necessary for engineering and safety reporting purposes.

11.2.10 Handling of Missing Data

Data will only be absent from analyses of study outcomes in the event that they were not available for collection. In general, missing values in any of the endpoints will not be inputted when summarizing these endpoints using descriptive statistics.

12. REGULATORY, ETHICAL, AND OVERSIGHT CONSIDERATIONS

12.1. Informed Consent Process

Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or approved study personnel will explain the research study to the participant and answer any questions that may arise. Each study candidate that meets the study inclusion/exclusion criteria will be advised in detail regarding the purpose, procedure, and potential risks of the study, their rights as research participants, and the requirements for participation is this study. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that if they decline to participate in this study the quality of their medical care will not be adversely affected.

12.2. Confidentiality and Privacy

Participant confidentiality and privacy will strictly be enforced by all participating investigators, staff, and the sponsor. This confidentiality is extended to cover the clinical information relating to participants. Therefore, all study documentation, data, and other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Sonavex. This will not include the participant's contact or identifying information. Individual participants and their research data will be de-identified and assigned a unique study identification number. The study data entry and study management systems used by clinical sites and by Sonavex staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

12.3. Study Device Use and Instruction

The EchoMark is an implantable ultrasound marker for identifying a surgical site in soft tissue. The implants are composed of a polymeric bioabsorbable material and feature two peaks which are easily distinguishable on an ultrasound image. [redacted]

12.3.1 Preparation

Prepare the EchoMark by pre-loading non-resorbable sutures into at least two corners of the EchoMark. The sutures should be 3-0 or 4-0 Prolene or equivalent non-resorbable sutures.

12.3.2 Implantation

After mobilizing the vein from the underlying muscle fascia layer,

Implant the EchoMark beneath the outflow vein so that there is 3cm of length, at minimum, between the anastomosis and the closest edge of the device. Ensure that the EchoMark is placed proximal to the patient's elbow crease and out of the elbow bending area. The vessel should run in a straight line through the EchoMark channel. Check for vessel or any other tissue structure impingement due to EchoMark placement prior to securing. Reposition the implant until optimal configuration is achieved.

Secure the EchoMark in place to prevent future movement using 3-0 or 4-0 Prolene or equivalent non-resorbable sutures.

12.3.3 Post-Procedure

With the implantation of any foreign material such as EchoMark, there is risk of allergic reaction, infection, inflammation, migration, or extrusion. There is also a possibility that the fistula may slide out of the EchoMark, which may prevent the EchoSure device from measuring the flow, diameter and depth accurately. When the EchoMark implant is secured properly the likelihood of this risk is low.

All subjects will undergo adverse event monitoring, physical exam, duplex scan, EchoSure scans, and a medical history review to including all interventions, laboratory results, and cannulation attempts. Additionally, a physical measurement of each EchoMark corner will be measured to assess for migration. If the subject begins to exhibit signs of infection, inflammation or extrusion, a clinical decision will be made if the EchoMark requires removal.

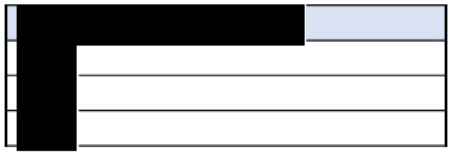
12.4. Device Accountability

All study devices will be provided to the PI by Sonavex after being tested, released, and shipped according to appropriate standards. The PI and/or designee is responsible for the secure storage of and controlled access to the study devices and accountability. The study device shall not be dispensed to any person who is not a consented study subject under this protocol.

12.5. Future use of Data

Data collected for this study will be analyzed and stored within a password protected database. After the study is completed, the de-identified, archived data will be stored in a password protected database for use by other researchers including those outside of the study. Permission to retain and future use of the data will be included in the informed consent.

12.6. Key Roles and Study Governance



12.7. Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including vascular surgeons and interventional nephrologists. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least every three months to assess safety and efficacy data of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

The Clinical Events Committee (CEC) will be responsible for adjudication of reported clinical events for the EchoMark and EchoSure Feasibility Clinical Study, including assessing radiographic maturation and any adverse events. The CEC is a well-recognized group of experts including vascular surgeons and interventional nephrologist who are independent from the study and free of conflicts of interest. The CEC will operate under the

rules of an approved charter that will be written and approved at the organizational meeting. The CEC will meet at least once a month. The CEC confirms that an event took place, ensures accurate counting, assessing, rating, etc. of events. The CEC will adjudicate and provide a final analysis of all safety endpoints and all reported events including and EchoMark/EchoSure (device) related adverse events.

12.8. Duplex Quality Assessment

An independent registered vascular technologist (RVT) will assess the quality of the duplex images.

The Independent RVT will receive only anonymized duplex scans during the study period, and will not receive any EchoSure scans. The Independent RVT will provide the following analyses to assess the quality of the duplex scans:

Quality Assessments & Measurements:

- B-Mode
    - Check accuracy of cursor placement for all caliper measurements of vessel depth and diameter
    - Correct caliper measurements that do not meet acceptance criteria
- Pulse Wave (PW) – Volume Flow Measurements
    - Check PW settings accuracy of cursor placement, angle and sample gate settings
        - Measure angle offset if acceptance criteria not met
    - Identify unacceptable volume flow measurements when acceptance criteria not met

12.9. Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of study participants are protected, that the reported trial data is accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

All selected monitors will be designated by the sponsor and will have the proper education and qualifications to perform the monitoring duties.

The basic operations to be performed by the monitors will include:

1. A pre-investigation visit to confirm

    a. the investigator(s) and research site are prepared

    b. the investigator(s) is(are) aware of the applicable responsibilities.

    c. the study staff is adequately qualified, educated, and/or trained to conduct the study

2. Periodic or interim visits to review and confirm

a. regulatory documentation for compliance with all applicable regulations and requirements

b. all changes to research have been submitted and approved by the IRB

c. the continued adequacy of the facility and its resources for the conduct of the study

d. the investigator is following the protocol

e. the study team membership and delegation of responsibilities are current and IRB approved

3. Close-out monitoring to

a. reconcile any outstanding regulatory documentation issues

b. resolve outstanding research participant matters

c. correct any residual data-queries

d. An inspection of a portion, but not excluding all, of the research subject record for

1. proper informed consent procedures
2. subject eligibility, with source documentation to confirm
3. protocol compliance
4. data integrity, consistency, and correctness
5. safety reporting
6. protocol deviations are noted and reported

Monitors will be responsible for the generation and distribution of a written report identifying the monitoring findings including:

1. What regulatory compliance issues were observed and corrected
2. What research record deficiencies were noted and corrected

12.10. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed and enforced at each site.

Quality control (QC) procedures will be implemented beginning with the data entry and data QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in

compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities

12.11. Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study.

Clinical data and clinical laboratory data will be entered into an electronic 21 CFR Part 11-compliant data capture system (EDC). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the sponsor company. This will not include the participant's contact or identifying information. Individual participants and their research data will be de-identified and assigned a unique study identification number. The study data entry and study management systems used by clinical sites and by company staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.12. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or the International Conference on Harmonization Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. A deviation log will be kept up-to-date throughout the study.

12.13. Coverage of Subject Expenses

Subjects will be compensated for their travel expenses and time during follow-up visits associated with completing the protocol requirements. The subjects will be compensated a flat rate for each follow-up visit and $100.00 for the 12 month visit. The compensation schedule is included in each site's informed consent form.

12.14. Publication and Data Sharing

Study updates and results will be communicated to the investigators and the sponsor.

A study report will be developed within 6 months after the last subject enrolled has exited the study. The study report will be distributed to the sponsor, investigators, and to all parties implicated in the study. Study results may be submitted for publication in scientific journals and as presentations at congresses.

12.15. Conflicts of Interest

Any conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

13. REFERENCES

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