Vis-Rx Prime Micro-Imaging Catheter

Clinical Evaluation Study

("Vis-Rx Prime Clinical Study")

Sponsor

Gentuity, LLC
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1 General

1.1 Introduction

This evaluation is a prospective, single-arm, unblinded, multi-center clinical evaluation assessing the safety and imaging capabilities of the Gentuity® High-Frequency Optical Coherence Tomography (HF-OCT) System ("Gentuity Imaging System") with the Vis-Rx Prime Micro-Imaging Catheter ("Vis-Rx Prime Catheter"), collectively called the "Gentuity device". The device will be used in patients who are candidates for Percutaneous Coronary Intervention (PCI) procedures. The purpose of the study is to collect clinical data that can be used to support a future product regulatory submission in Europe. The Gentuity Imaging System that will be used under this investigation plan is the same product that is FDA cleared. There are no modifications to the cleared Gentuity Imaging System. The Vis-Rx Prime Catheter has not been reviewed by the FDA. In the United States, FDA does not require clinical data as part of the product 510(k) Premarket Notification review process. This protocol is similar to the Vis-Rx Post-Market Evaluation ("Vis-Rx PME") protocol (NCT04533503) which was conducted to collect data which was later used for product regulatory submission in Europe.

Three (3) to five (5) clinical centers will use HF-OCT imaging to participate in the study. Between 30 to 70 subjects will be enrolled and undergo HF-OCT imaging. This clinical evaluation study is expected to begin in May 2024 and conclude by April 2025. The sites, investigators, and research staff will be selected based on their established experience using various intracoronary HF-OCT imaging technologies in patients who are candidates for PCI.

System and catheter performance will be rated by the treating clinical users on a Likert scale at the end of each case to provide feedback.

Study participants' HF-OCT images will be anonymized, collected, and provided to a core laboratory to analyze the Clear Image Length (CIL), attained for each acquired HF-OCT image.

1.2 Regulatory Status & Non-Significant Risk Determination

The Gentuity Imaging System first received its initial U.S. Food and Drug Administration clearance (K192922) on February 20, 2020. The system was cleared with the Vis-Rx Micro-Imaging Catheter. The Gentuity Imaging System with the Vis-Rx Catheter Indications for Use Statement is:

> *The Gentuity® HF-OCT Imaging System with Vis-Rx® Micro-Imaging Catheter is intended for intravascular imaging and is indicated for use in coronary arteries in patients who are candidates for transluminal interventional procedures. The Vis-Rx Micro-Imaging Catheter is intended for use in vessels 1.3 to 6.0 mm in diameter. The Vis-Rx Micro- Imaging Catheter is not intended for use in a target vessel that has undergone a previous bypass procedure.*

The Vis-Rx Prime Catheter is the next generation micro-imaging catheter that will eventually replace the commercialized Vis-Rx Catheter. The Vis-Rx Prime Catheter also operates on the same FDA cleared Gentuity Imaging System. Both catheters share the exact same Indications for Use Statement and intent-to-treat population as well as a similar design and manufacturing process. The Vis-Rx Prime

Catheter is primarily being designed to reduce the manufacturing and material costs associated with the Vis-Rx Catheter. Additionally, minor changes to its design are also being implemented. This includes a modified catheter tip design that will improve the deliverability of the catheter by reducing potential friction.

The Gentuity Imaging System that will be used under this investigation plan is the same product that is FDA cleared. There are no modifications to the cleared Gentuity Imaging System. The Vis-Rx Prime Catheter has not been reviewed by the FDA. In the United States, FDA does not require clinical data as part of the product 510(k) Premarket Notification review process. The protocol is similar to the Vis-Rx Post-Market Evaluation ("Vis-Rx PME") protocol (NCT04533503) which was conducted to collect data that would be used for EU submission.

For the purposes of this research study, Gentuity has classified the Vis-Rx Prime Catheter as a Non-Significant Risk (NSR) device, and that the device does not meet the definition of a Significant Risk (SR) device. As a result of this decision, the protocol does not require an Investigational Device Exemption. This decision is based on Gentuity determining the Vis-Rx Prime Catheter does not meet FDA's definition of an SR device under 21 CFR 812.3(m).

The rationale for this NSR decision is based on meeting the following regulations:

1. The device is not an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject. The catheter is placed in the artery for several minutes to obtain an image of the artery, after which it is removed.
2. The device is not purported or does not represent to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject. The device is used as a diagnostic tool and is not intended to allow direct diagnosis or monitoring of a patient. The device is intended for imaging of the coronary artery.
3. The device is not for use of substantial importance in the diagnosis, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject. The device is intended for intravascular imaging and is indicated for use in coronary arteries in patients who are candidates for transluminal interventional procedures (e.g., stent placement). It is not required that a physician use HF-OCT, in comparison, where angiography is required to perform PCI procedures. There are multiple types of additional imaging modalities that a physician may choose to use as part of evaluating a patient's arteries (e.g., HF-OCT, IVUS, MRI, CT).
4. The device does not present a potential for serious risk to the health, safety, or welfare of a subject.

There are no anticipated changes to the contraindications, warnings, and caution statements as well as expected product complications and risks associated with use of the Vis-Rx Prime catheter when compared to the Vis-Rx Catheter. As a result, similar Instructions for Use apply to use of the new Vis-Rx Prime Catheter.

1.3 Identification of the Evaluation

This evaluation is entitled the “Vis-Rx Prime Micro-Imaging Clinical Evaluation Study”, or “Vis-Rx Prime Clinical Study”.

The sponsoring organization of this clinical evaluation is:

Gentuity, LLC
142 North Road, Suite G
Sudbury, MA 01776

The sponsor has designated the following point(s) of contact for questions or communication regarding this clinical evaluation:

Sharon Timberlake, Vice President, Clinical, Quality & Regulatory Affairs
Telephone: (978) 538-8192
Email: stimberlake@gentuity.com

Gentuity will appoint additional trained clinical research personnel as a point of contact which will be communicated to the participating sites throughout the study duration.

1.4 Synopsis of the Evaluation

Study Title	Vis-Rx Prime Micro-Imaging Catheter Clinical Evaluation Study (Vis-Rx Prime Clinical Study)
Product	Gentuity® HF-OCT Imaging System with Vis-Rx Prime® Micro-Imaging Catheter
Indications for Use	The Gentuity High-Frequency Optical Coherence Tomography (HF-OCT) Imaging System with Vis-Rx Prime Micro-Imaging Catheter is intended for intravascular imaging and is indicated for use in coronary arteries in patients who are candidates for PCI. The Vis-Rx Prime Micro-Imaging Catheter is intended for use in vessels 1.3 to 6.0 mm in diameter. The Vis-Rx Prime Micro- Imaging Catheter is not intended for use in a target vessel that has undergone a previous bypass procedure.
Study Aim	This clinical evaluation is to assess the performance of the Gentuity HF-OCT Imaging System with the Vis-Rx Prime Micro-Imaging Catheter in a real-world setting.
Study Objectives	To evaluate the clinical and technical performance in the target patient population. Clinical performance will be determined by interventional cardiologist operator evaluation and technical performance will be determined by an objective measurement of HF-OCT image clarity. Safety will be evaluated based on reported adverse event rates.
Study Design	This is a single arm, unblinded, multi-center, clinical evaluation that will be performed at 3 to 5 investigational sites in the United States with subjects who undergo HF-OCT imaging as part of their cardiac catheterization procedure. This study will evaluate a range of device operators (interventional cardiologists) as well as patients and vessels consistent with the product labeling. The operator evaluation will be determined post use of the device using a Likert Grading Scale. Clear Image Length of the acquired HF-OCT image will be measured by an independent core lab. Safety will be monitored through the interventional procedure and Adverse Events that are potentially related to either the device or the procedure will be recorded, evaluated and analyzed. Device malfunctions will also be handled according to the Gentuity Complaint Handling Process.
Study Population	Patients in the cardiac catheterization lab who are candidates for PCI.
Investigative Sites	3 to 5 centers in the United States
Sample Size	30 to 70 imaged subjects

Clinical Performance Endpoint	The performance endpoint includes the following four categories: ▪ Catheter preparation ▪ Catheter deliverability ▪ Image quality ▪ Overall performance Data collected at the end of each procedure. The criteria will be graded on a 5-point Likert Scale with the objective of a mean score of greater than 3 for each category, where 3 is acceptable.
Safety Endpoint	Safety will be determined based on adverse event data. The primary endpoint for safety is the incidence rate for each HF-OCT Imaging procedure related adverse event observed in the study. The overall rate and severity of adverse events will be analyzed based on the total number of catheters used for the HF-OCT procedures performed.
Technical Endpoint	A median Clear Image Length for the acquired HF-OCT pullback images greater than 35 mm, as evaluated by an independent core lab.
Inclusion Criteria	The evaluation inclusion criteria are aligned with the Instructions for Use and include: ▪ Patients 18 years of age or older ▪ Patients willing and able to provide written informed consent to participate in evaluation ▪ Patients who are candidates for transluminal interventional procedures for their coronary arteries (also known as PCI)
Exclusion Criteria	All exclusion criteria align with the Instructions for Use contraindications, and include patients who have the following conditions: ▪ Bacteremia or sepsis ▪ Major coagulation system abnormalities ▪ Severe hemodynamic instability or shock ▪ Acute renal failure ▪ Disqualified for Coronary Artery Bypass Graft surgery ▪ Disqualified for Percutaneous Coronary Intervention ▪ Patients currently enrolled in another study to evaluate an investigational device or medication ▪ Any target vessel which has undergone a bypass procedure The lesion-specific exclusion criteria assessed from angiography are: ▪ Total occlusion ▪ Coronary artery spasm ▪ Large thrombus (as visible under angiography)
Follow Up Procedure/Visit	No further subject follow-up assessments or visits are required following the transluminal interventional procedure.

2 Devices

2.1 Intracoronary Optical Coherence Tomography (HF-OCT) Imaging

Patients who suffer from Coronary Artery Disease (CAD) might undergo Percutaneous Coronary Intervention (PCI) procedures as a means to assess their atherosclerotic lesions and treat the severe blockages that reduce the supply of oxygenated blood to the myocardial muscle of the heart. PCI procedures are guided by angiography, but this approach is limited because it depicts a 2-D projection of the arterial lumen ('shadow-gram') with low resolution (~100-200 µm) without providing detailed information on three-dimensional vessel morphology including features such as atherosclerotic plaques, calcium deposits, vessel trauma, and other similar findings. Intravascular imaging has been developed to overcome the limitations of angiography and includes video angioscopy, intravascular ultrasound (IVUS), and intravascular optical coherence tomography (HF-OCT).

HF-OCT is an imaging modality that is analogous to ultrasound imaging but uses near-infrared light instead of sound waves. It is estimated that over 100,000 HF-OCT imaging procedures are now performed each year in the coronaries[1]. Extensive clinical data has been acquired on the current HF-OCT platforms that indicates adequate safety, efficacy, and value in obtaining the HF-OCT images for coronary disease evaluation and treatment planning[2].

Coronary HF-OCT systems use a broad-bandwidth light source with a central wavelength of ~1300 nm, where the bandwidth provides the high resolution afforded by HF-OCT (typically 10-20 µm) and the central wavelength is chosen to minimize light scattering and increase imaging depth into tissue. It is also non-ionizing and low power (a few milliwatts) and therefore inherently safe for tissue exposure.

Similar to IVUS and even radar, HF-OCT obtains depth (ranging) information by measuring the time-of-flight of the reflected signal from the vessel wall and surrounding tissue. Optical coherence tomography improves localization of the returned signal due to the much shorter wavelength of the imaging light when compared to ultrasound wavelengths and provides resolutions approximately an order of magnitude better than ultrasound.

Coronary HF-OCT catheters use a rotating fiber optic core with attached distal optics, all encased within a miniature cross-section, elongated sheath. The distal most section of the sheath is transparent for optimal light transmission and collection. The optical catheter collects and returns light scattered from the coronary tissue to the HF-OCT system which then analyzes the returned light to create the three-dimensional image. Coronary HF-OCT imaging is usually performed with a coinciding delivery of contrast media to the target vessel to temporarily displace the obscuring blood from the imaging field. HF-OCT imaging runs ('pullbacks') are typically completed within 1-3 seconds and cause little or no patient discomfort.

The Gentuity HF-OCT console and Vis-Rx Prime Catheter are shown in **Figure 1** and **Figure 2**.

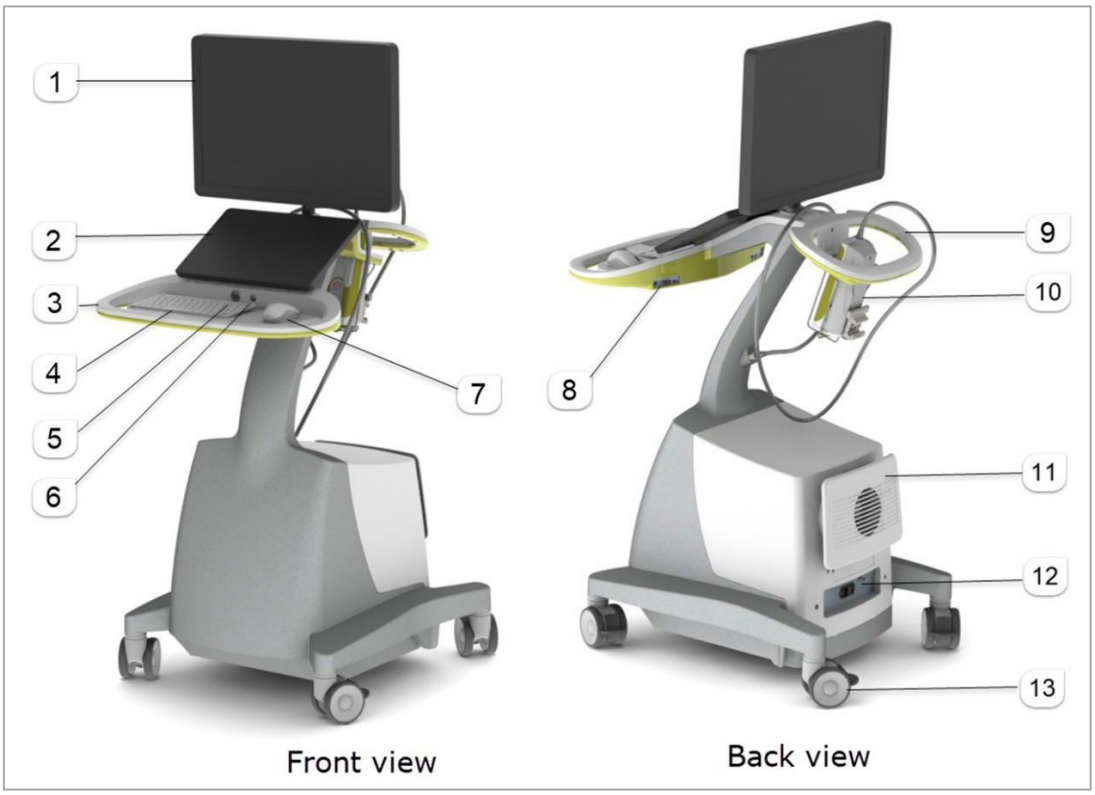
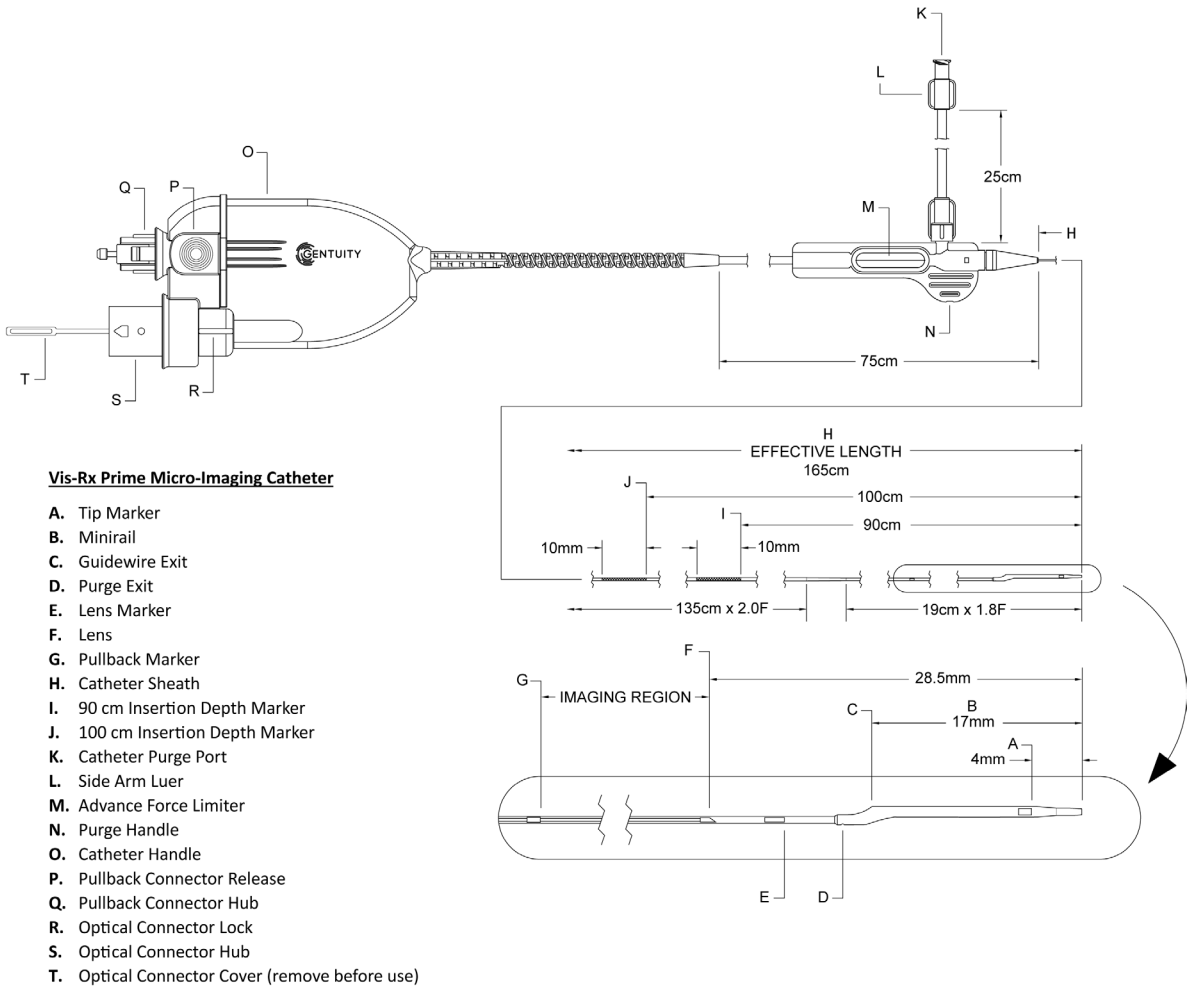


Figure 1: Gentuity HF-OCT console, including PIM.

ID	Name of Component	Description and Features
1	Monitor, 24 inches	Primary image display for sterile operator.
2	Monitor, Touchscreen, 15.6 inches	Primary image and interface display for the non-sterile operator.
3	Front Handle	Integrated front handle for transporting the system and for table-side positioning.
4	Keyboard	Standard keyboard for data entry.
5	USB port	Used for exporting patient data from the system to a USB drive for storage and archiving.
6	On/Standby button	Used to turn the system on or place in standby mode.
7	Mouse	Pointing and selecting device.
8	Input/Output	Video, USB, Ethernet, other I/O.
9	Rear Handle/PIM Cable Wrap	Integrated rear handle for transporting the system and PIM cable storage for transport.
10	Probe Interface Module (PIM)	Bedside connection to catheter. Contains bed rail mount, Start/Stop buttons, catheter pull-back drive and catheter rotation drive.

11	Access Cover and Power Cord Wrap	Provides protection for and access to internal components. Contains cooling fan. Also provides storage space for AC power cable during transport.
12	Power	Switched and fused AC mains power inlet and grounding terminal (POAG).
13	Caster	High quality medical casters with wheel locks for mobile transport and fine positioning.
Key Internal Components		
Optical Engine Assembly		Contains the Swept Source, reference arm, detector, and visible red aiming beam.
Computer Assembly		Contains the system medical grade power supply, mother board, processor, memory, mass storage, digitizer, frame grabber and graphic processing unit.



Vis-Rx Prime Micro-Imaging Catheter

- **A.** Tip Marker
- **B.** Minirail
- **C.** Guidewire Exit
- **D.** Purge Exit
- **E.** Lens Marker
- **F.** Lens
- **G.** Pullback Marker
- **H.** Catheter Sheath
- **I.** 90 cm Insertion Depth Marker
- **J.** 100 cm Insertion Depth Marker
- **K.** Catheter Purge Port
- **L.** Side Arm Luer
- **M.** Advance Force Limiter
- **N.** Purge Handle
- **O.** Catheter Handle
- **P.** Pullback Connector Release
- **Q.** Pullback Connector Hub
- **R.** Optical Connector Lock
- **S.** Optical Connector Hub
- **T.** Optical Connector Cover (remove before use)

Figure 2: Vis-Rx Prime Catheter

2.2 Gentuity HF-OCT Imaging System

The Gentuity HF-OCT console and Vis-Rx Prime Catheter are shown in **Figure 1** and **Figure 2**.

The Gentuity HF-OCT Imaging System with Vis-Rx Prime Micro-Imaging Catheter consists of a cart-mounted computer and optical engine placed inside an ergonomically designed mobile console. It includes two monitors, keyboard, mouse, and cord storage as well as external interfaces to the system. It also includes the Probe Interface Module (PIM), which provides the interconnection between the

Gentuity System and the Vis-Rx Prime catheter. The cart is equipped with two display monitors: one for the console operator (Touchscreen 15.6”), and the other for the physician (24”).

The Vis-Rx Prime Micro-Imaging Catheter is the next generation of the FDA-cleared Vis-Rx Catheter operating on the same Gentuity Imaging System. Both catheters share the same Indications for Use Statement and intent-to-treat population as well as a similar design and manufacturing process. The Vis-Rx Prime Catheter includes a modified catheter tip design to improve the deliverability of the catheter by reducing potential friction. The new rapid exchange tip is also intended to ensure smooth deliverability over the guidewire.

The single-use Vis-Rx Prime Micro-Imaging Catheter (See Figure 2) attaches to the PIM. The catheter uses a rotating fiber optic core with attached distal optics (i.e., imaging lens), all encased within a miniature cross-section, elongated plastic sheath. The distal most section of the sheath is transparent, allowing for optimal near-infrared light transmission and collection. During image acquisition the lens is rotated and retracted within the outer sheath to create a longitudinal vessel image volume. Contrast media is delivered to the target vessel to temporarily displace the obscuring blood from the imaging field during the image acquisition. The HF-OCT imaging runs (pullbacks) are completed within 1 or 2 seconds.

During the image acquisition period the lens is rotated and retracted within the outer sheath to create a longitudinal vessel image volume. The imaging frame rate that can be achieved is determined by the rotational speed of the imaging core as well as by the A-line rate.

2.3 Scope of the Evaluation

The devices under evaluation will be the Gentuity HF-OCT Imaging System and the next generation Vis-Rx Prime Catheter (collectively called the 'Gentuity Device').

The interventional cardiology procedure for this clinical evaluation will involve cardiac catheterization, with a planned PCI to treat an atherosclerotic lesion per hospital site standard-of-care and the discretion of the interventional cardiologist user or operator. The PCI will begin with the standard-of-care diagnostic angiography and allow for use of any other intravascular imaging or lesion assessment according to the standard PCI clinical assessment and treatment decisions. The interventional cardiologist can utilize the Gentuity Device according to their device labeling and as it aligns with established clinical guidelines for intracoronary imaging throughout the course of the PCI procedure.

3 Justification of the Evaluation

The Gentuity Device improves upon existing intravascular HF-OCT systems by offering a smaller catheter which is able to access and image coronary arteries both pre- and post-intervention. It captures up to 100 mm of vessel segment in a single one- or two-second pullback.

Gentuity has designed the next generation Vis-Rx Prime Catheter to reduce the manufacturing and material costs associated with the Vis-Rx Catheter. Additionally, minor changes to its design have been implemented including a modified catheter tip design that will improve the deliverability of the catheter by reducing potential friction.

With the introduction of the Vis-Rx Prime Catheter, the purpose of this study is to collect clinical data for the Gentuity Device that can be used to support a future product regulatory submission in Europe. Although the Vis-Rx Prime Catheter has not been reviewed by the FDA, in the United States, FDA does not require clinical data as part of the product 510(k) Premarket Notification review process. The Gentuity Imaging System that will be used under this investigation plan is the same product that is FDA cleared. There are no modifications to the cleared Gentuity Imaging System.

4 Risks and Benefits

4.1 Benefits

The subjects who participate in the clinical evaluation may potentially benefit from more thorough atherosclerotic lesion assessment during their PCI treatment procedure using intracoronary HF-OCT imaging to evaluate their lesion. While intracoronary HF-OCT imaging is used routinely in select standard-of-care PCI procedures, it is not used in all PCIs.

Overall, advancement of medical and scientific knowledge that may benefit future or repeat patients may be realized from this evaluation.

4.2 Risks

The standard-of-care PCI procedure introduces certain risks to the patient, and any intravascular imaging technology utilized during PCI also carries certain risks. The risks to patients who undergo intracoronary HF-OCT imaging with the Gentuity HF-OCT Imaging System and Vis-Rx Prime Micro-Imaging Catheter can be found in the instructions for use and are similar to those of other available

intracoronary HF-OCT imaging platforms.

5 Objectives of the Evaluation

The aim of this clinical evaluation is to assess the performance of the Gentuity HF-OCT Imaging System with the Vis-Rx Prime Micro-Imaging Catheter in a real-world setting. The objective is to evaluate the clinical and technical performance in the target patient population.

This evaluation will collect safety and performance data for the system in a real-world clinical setting in patients who are candidates for PCI, including coronary angiography images and HF-OCT imaging both pre- and post-intervention. To objectively evaluate the performance of the Gentuity system, clear image length will be determined by an independent core lab experienced in reading HF-OCT intravascular images. The target median clear image length is based on a meta-analysis of 64 randomized controlled trials that found an average coronary lesion length of 17 ± 4 mm[3,4]. The target clear image length includes two standard deviations above the average coronary lesion length, plus two 5 mm “landing zones”, one proximal and one distal to the stent, which should provide ample margin to image the full target lesion and demonstrate efficacy of the technology. Further, the performance of the Gentuity HF-OCT products will be rated by clinicians experienced with using other HF-OCT imaging technologies to guide PCI procedures. The evaluation results will be used by Gentuity to prepare for its wider clinical use, and to support further regulatory approvals.

5.1 Clinical Performance Endpoint

Clinical performance will be determined by the interventional cardiologist clinical operator based on a 5-point Likert-scale rating evaluation following each PCI case. The rating evaluation includes the following four categories, with individually scored criteria as listed, which are consistent with the Vis-Rx Prime Catheter product specifications:

Category 1, Preparation:

- Ease of handling product packaging.
- Ease of making PIM-catheter connection.
- Ease of purging.

Category 2, Deliverability:

- Ease of loading onto the guidewire.
- Ease of navigation to imaging region.
- Visibility of radiopaque markers.
- Ease of withdrawal over guidewire.

Category 3, Image Quality:

- Lumen visualization.
- Stent visualization.
- Overall image quality.

Category 4, Overall Performance:

- Image acquisition workflow (pullback).
- Console screen layout.
- Overall ability to visualize and assess acquired images.

The above criteria will be graded on the following 5-point Likert Scale as evaluated by the interventional cardiologist clinical operator:

5: Excellent; 4: Good; 3: Acceptable; 2: Poor; 1: Unacceptable.

The objective is a mean score above 3 for each of the four categories defined above.

5.2 Technical Performance Endpoint

Technical performance will be determined by an objective measurement of image clarity performed on the acquired HF-OCT pullback images by an independent core lab following the PCI case. The technical endpoint is the length measurement of image clarity in each pullback, known as the Clear Image Length (CIL, in millimeters). The objective is that pullbacks acquired in this evaluation have a median CIL greater than 35 mm.

The 35 mm target CIL arises from the following factors:

1. Average lesion length:
   The average atherosclerotic lesion length is 17 mm, with a standard deviation of 4 mm per the citations[3,4], which included an analysis of over 100,000 patients.
2. Standard deviation of lesion length:
   Two standard deviations (8 mm) have been added to the average lesion length to account for 98% of the lesions likely to be imaged using HF-OCT in the enrolled subject population.
3. Landing zones:
   Intracoronary imaging convention for PCI procedures involves imaging “landing zones” or “reference segments” of healthy vessel distal and proximal to the target atherosclerotic lesion prior to treating with stent implantation. The assessment and measurements performed on these 5 mm long landing zones often help determine the size of the stent implanted in the lesion. Therefore, the goal is to acquire a clear image of both the distal and proximal landing zones in the HF-OCT pullback image.
4. Calculation of CIL objective:
   17 mm + 2*(4 mm standard deviation) + 2*(5 mm landing zone) = 35 mm.

Participating subjects are anticipated to have an average of 1.6 implanted stents per the meta-analysis cited previously[3]. Key results from this meta-analysis are excerpted:

- Angiographic features of included patients 150 arms with 102,735 patients.
- Length of lesion in mm (median ± SD) 17 ± 4.
- Number of stents for patients (median, min–max) 1.6 (1–2).

Participating clinical operators might use the Gentuity HF-OCT imaging technology to assess more than one atherosclerotic lesion in participating subjects, thereby imaging more lesions or vessels with HF-

OCT than there are subjects enrolled in this evaluation. Furthermore, each lesion can be imaged with HF-OCT multiple times throughout the PCI procedure, beginning with pre-intervention to visualize the lesion characteristics, later post-intervention following stent deployment to assess stent expansion and determine if stent struts are well-apposed to the vessel wall, and to determine if further stent expansion is necessary. The number of HF-OCT pullbacks performed in an eligible lesion is at the discretion of the operator and in consideration of intravascular imaging guidelines. It is therefore expected that this evaluation will collect more HF-OCT pullback images than enrolled subjects. This will provide an adequate sample of HF-OCT pullback images for CIL statistical analysis in the target patient population (Section 7.2).

Following the conclusion of each PCI case, the acquired HF-OCT pullback images will be anonymized and transferred to an independent core lab experienced in analysis of clinical intracoronary HF-OCT pullback images. The core lab will analyze each HF-OCT pullback according to pre-determined criteria for image clarity, and each pullback will receive a CIL score.

5.3 Safety Endpoint

Safety will be determined based on adverse event data. The primary endpoint for safety is the incidence rate for each HF-OCT Imaging procedure related adverse event observed in the study. The overall rate and severity of adverse events will be analyzed based on the total number of catheters used for the HF-OCT procedures performed. Design of the Evaluation

5.4 General

This is a prospective, single-arm, unblinded, multi-center clinical evaluation assessing the safety and imaging capabilities of the Gentuity High-Frequency Optical Coherence Tomography (HF-OCT) System and the Vis-Rx Prime Micro-Imaging Catheter for use in PCI procedures.

The evaluation will be conducted at 3 to 5 centers and will enroll between 30 and 70 subjects who will undergo HF-OCT imaging. A conservative estimate of the number of achieved pullbacks was used to test the robustness of the statistical model. In this case, each subject is expected to yield 1.3 imaging pullbacks during the PCI procedure (as compared with an expected mean of 1.6 stents per patient from Section 5.2), for an expected total of at least 39 HF-OCT imaging pullbacks in the evaluation. The sample will reflect a range of clinical operators as well as patients and vessels consistent with the labeling for the device.

The clinical performance endpoint is the 5-point Likert scale rating by the interventional cardiologist clinical operator following each PCI case. The objective is a mean rating of greater than 3 for each of the four categories, where 3 is considered acceptable. Refer to section 5.1 for further details of the clinical performance evaluation.

The technical performance primary endpoint is that the acquired HF-OCT pullback images have a median Clear Image Length (CIL) of greater than 35 mm, as measured by an independent core lab experienced in analysis of intracoronary HF-OCT images. The target of 35 mm CIL is based on the

average and standard deviation of atherosclerotic lesion length and the convention of imaging a distal and proximal landing zone that serves as a reference of the neighboring healthy vessel.

5.5 Devices

The Gentuity High-Frequency Optical Coherence Tomography (HF-OCT) Imaging System Console and the Vis-Rx Prime Micro-Imaging Catheter are the devices subject to evaluation. Please, refer to Section 2.2 of this evaluation protocol for further details. There are no comparator or control devices in this evaluation. Other medical devices may be used as part of PCI standard-of-care at the discretion of the interventional cardiologist clinical operator, including guidewires, stents, angioplasty balloons, etc.; none of these devices shall be investigational or involved in another clinical study or evaluation.

5.6 Subjects

In general, this evaluation is intended to enroll “all comers” for standard-of-care PCI treatment procedures who also meet the Indications for Use for the Gentuity HF-HF-OCT Imaging System and Vis-Rx Prime Micro-Imaging Catheter at the participating centers during the time of subject screening and enrollment. The subjects eligible for enrollment and participation in this clinical evaluation are those that meet all the below inclusion criteria, none of the below exclusion criteria, and who provide written informed consent for participation prior to their PCI procedure. The evaluation inclusion and exclusion criteria are aligned with the cleared Indications for Use, repeated here:

The Gentuity HF-OCT Imaging System with Vis-Rx Prime Micro-Imaging Catheter is intended for intravascular imaging and is indicated for use in coronary arteries in patients who are candidates for transluminal interventional procedures. The Vis-Rx Prime Micro-Imaging Catheter is intended for use in vessels 1.3 to 6.0 mm in diameter. The Vis-Rx Prime Micro-Imaging Catheter is not intended for use in a target vessel that has undergone a previous bypass procedure.

5.6.1 Inclusion Criteria

The subjects who are screened and enrolled should meet all the following inclusion criteria:

- Patients 18 years of age, or older.
- Patients willing and able to provide written informed consent to participate in evaluation.
- Patients who are candidates for transluminal interventional procedures for their coronary arteries (also known as PCI).

5.6.2 Exclusion Criteria

The subjects who are screened and enrolled should have none of the conditions, history, or anatomy as described in the following general exclusion criteria, which are contraindications of the Gentuity HF-OCT Imaging System and Vis-Rx Prime Micro-Imaging Catheter according to the instructions for use.

- Bacteremia or sepsis.
- Major coagulation system abnormalities.
- Severe hemodynamic instability or shock.
- Acute renal failure.

- Disqualified for Coronary Artery Bypass Graft (CABG) surgery.
- Disqualified for PCI procedure.
- Patients currently enrolled in another study to evaluate an investigational device or medication.
- Any target vessel which has undergone a bypass procedure.

5.6.2.1 Lesion-specific exclusion criteria

Enrolled subjects will be screened for lesion-specific exclusion criteria during the PCI procedure using diagnostic angiography. Subjects that undergo HF-OCT imaging and target atherosclerotic lesions that are imaged should have none of the following lesion-specific conditions or anatomy, which are contraindications of the Gentuity HF-OCT Imaging System and Vis-Rx Prime Micro-Imaging Catheter according to the Instructions for Use.

- Total occlusion.
- Coronary artery spasm.
- Large thrombus (as visible under angiography).

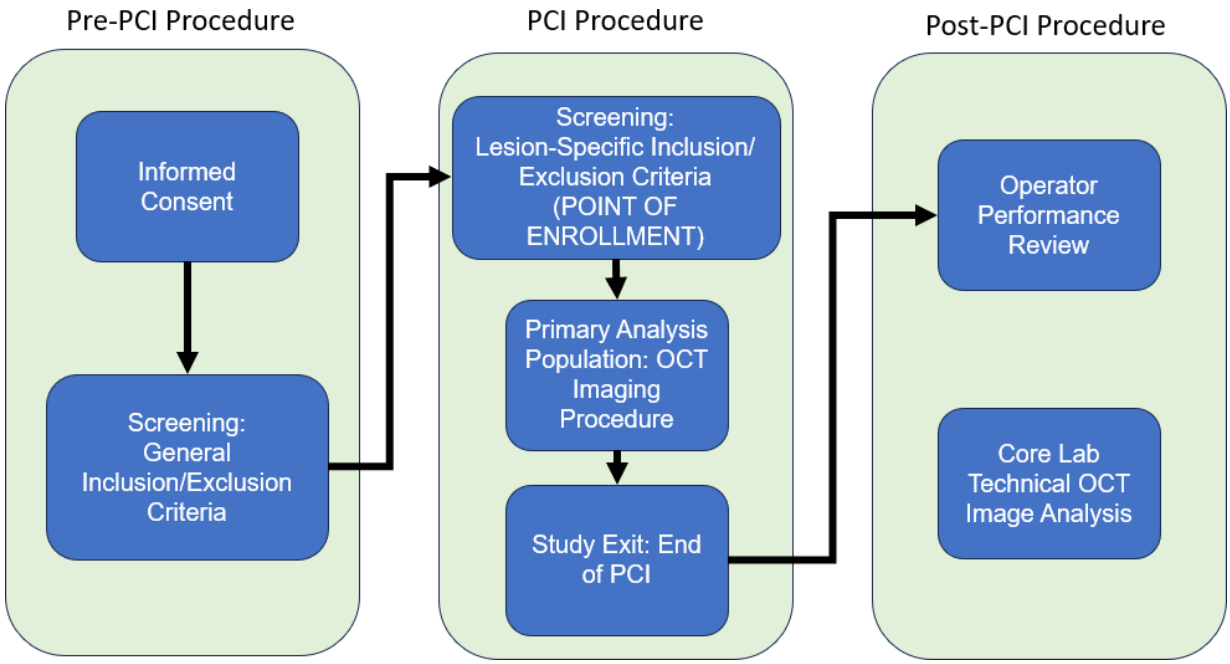


Figure 3: Participating subject procedural flow chart, from informed consent through study exit, including post-PCI data collection and image analysis.

5.6.3 Duration of Participation

Each participating subject is expected to be in the evaluation from the time of providing written informed consent through the course of their PCI procedure. Details on the point of enrollment, evaluation exit, and withdrawal are all described in the sections below. The progression of a subject's participation in the evaluation is shown in the flow chart described in **Figure 3**.

5.6.4 Point of enrollment

Patients will be considered enrolled in this clinical evaluation if –

a) Written informed consent has been obtained, AND
b) The patient meets all the inclusion criteria, none of the general exclusion criteria and none of the lesion-specific exclusion criteria after diagnostic angiography.

Patients that do not qualify for the study based on the inclusion/exclusion criteria will be considered screen failures.

5.6.5 Primary Analysis Population

Several exclusion criteria apply to characteristics of the target lesion(s) which can only be assessed and confirmed during the PCI following the diagnostic angiography. Only subjects who undergo HF-OCT imaging will be included in the Primary Analysis Population. The start of the HF-OCT imaging procedure is considered the introduction of the Vis-Rx Prime Imaging Catheter into the hemostatic valve which corresponds to its insertion into the subject's bloodstream.

Any patient that is consented and screened, but who does not undergo the HF-OCT imaging procedure, will not be included in the Primary Analysis Population.

The evaluation will include between 30 and 70 HF-OCT imaged subjects in the Primary Analysis Population.

5.6.6 Evaluation exit

Subjects are exited from the evaluation following the completion of their PCI. There are no follow-up assessments or visits.

5.6.7 Withdrawal

Subjects can voluntarily withdraw from the screening process or discontinue the evaluation at any time during their participation, which begins following written informed consent and continues until the completion of their PCI procedure.

The clinical operator can also decide to withdraw a subject from the evaluation if he or she determines that it is in the best interest of the subject to cease participation.

5.7 Procedures

The use of the Gentuity HF-OCT imaging technology in this clinical evaluation is intended to align with the standard-of-care use of other intracoronary imaging technologies, including other available HF-OCT imaging platforms and IVUS as well. Gentuity HF-OCT imaging can be used at various times during the typical PCI procedure to assess or visualize the atherosclerotic lesion or the administered interventional treatment such as a coronary stent. The use of other FDA-cleared intravascular lesion assessment technology, such as Fractional Flow Reserve (FFR) for physiological analysis, is not restricted.

5.6.8 HF-OCT Imaging Steps

The steps in the Gentuity HF-OCT imaging procedure include the following:

1. Preparation of the HF-OCT System Console according to the User Manual.
2. Selection of pullback parameters on the HF-OCT System Console. The following are recommended for optimal HF-OCT imaging for this study:
    a. Pullback length 100 mm
    b. Flush media: 100% (undiluted) contrast media
3. Preparation of the Vis-Rx Prime Micro-Imaging Catheter according to the Instructions for Use.
4. Preparation of contrast media flush according to the Instructions for Use.
5. Positioning the Vis-Rx Prime lens marker distal to the target lesion in order to acquire an HF-OCT pullback image of the distal landing zone, the target lesion, and the proximal landing zone.
6. Administration of contrast media flush to clear blood from lesion during image acquisition.
7. Initiation of the imaging pullback when blood clearance is obtained and subsequent image acquisition.
8. Post-acquisition image playback and review for lesion assessment and measurements.

Following the PCI procedure, the interventional cardiologist operator will complete the Likert-scale performance assessment to provide product feedback.

6 Statistical Analysis Plan

6.1 Introduction

The study features a prospective, single arm, unblinded, multi-center design. The study will enroll between 30 and 70 subjects who will undergo HF-OCT imaging at 3-5 participating centers. The objective of this study is to evaluate the clinical and technical performance in the target patient population. The clinical performance will be measured by the operator's subjective evaluations of catheter preparation, catheter deliverability, overall catheter ease of use, and image quality. The technical performance will be measured by an objective measurement of the length of clarity in each HF-OCT pullback or Clear Image Length (CIL, in millimeters).

The Gentuity HF-OCT can capture up to 100 mm of vessel segment in a single pullback. The study's primary hypothesis states that the true population median CIL is greater than the reference standard of

35 mm, such that a one-sample comparison of median to a reference CIL standard or μ_0 can be expressed as the following:

H_0: $\mu = \mu_0$ vs. H_1: $\mu \neq \mu_0$, where μ_0 = 35 mm was chosen per the analysis of Section 5.2

The test will be accomplished by a one-sample two-sided exact Wilcoxon signed-rank test with 0.05 type I error rate. The data support $\mu > \mu_0$ if the two-sided p-value is less than 0.05 and the estimate of μ is greater than μ_0.

For all enrolled subjects who are included in the Primary Analysis Population, clinical data, and collected HF-OCT images will be retained and analyzed for technical performance. For subjects who were consented and enrolled but who were screening failures during the PCI procedure via lesion-specific exclusion criteria, any clinical data collected prior to PCI will not be included in the evaluation demographic, medical history, or PCI details analyses.

For all enrolled subjects and cases that involve HF-OCT imaging, the clinical operator will be interviewed to evaluate the Gentuity HF-OCT technology for its clinical performance in catheter preparation, catheter deliverability, image quality, and overall performance.

The following sections describe the plans for statistical analysis of the evaluation results. The statistical analysis plan is based on the minimum enrollment into the Primary Analysis Population, which is 30 subjects.

6.2 Sample Size Calculation

The study plans to enroll and image at least 30 subjects with the HF-OCT imaging technology, and up to 70 subjects. Conservatively, each participating subject is expected to have an average of 1.3 imaging pullbacks, for an anticipated total of approximately 39 imaging pullbacks (or more) captured with HF-OCT in the evaluation. The number of HF-OCT pullbacks performed in an eligible lesion is according to the discretion of the operator and in consideration of intravascular imaging guidelines. It is therefore expected that this evaluation will collect at least 39 HF-OCT pullback images. For the purpose of power calculation, we assume that 39 HF-OCT pullback images will be obtained from the minimum of 30 subjects. Another reasonable assumption to make in this case is that these 39 pullback images are statistically independent. The argument for statistical independence lies in the fact that CIL is very dependent on the details of the artery shape, the local flow, and the positioning of the guide catheter which delivers the flush. These factors yield a great deal of variability in the resulting CIL measurements even among vessels from the same subject.

The power analysis was performed using SAS/STAT PROC POWER and mean-based paired t-test, while the actual analysis will be median, or rank based due to abnormality in the skewed CIL data distribution. To compensate for the methodology difference, a Wilcoxon adjustment factor was applied. This adjustment factor to the sample size is based on an assumed data distribution[5]. The adjusted sample size N_W is equal to: $N_W = N_T/WW$, where N_T is the unadjusted sample size using the paired t-test and WW is the Wilcoxon adjustment factor for the assumed data distribution and has a range between 2/3 and π/3. A conservative decision was made to use the adjustment factor resulting in the largest adjusted sample size N_W.

The Gentuity HF-OCT technology is designed with a longer, 100 mm pullback length. It is expected that about 20% of the pullbacks will be in the 75 mm range. Setting the expected mean CIL at 45 mm and a target reference CIL of 35 mm (corresponding to an effect size 10 mm), standard deviation of 17 mm, 5% type 1 error rate, a study with 38 vessels will provide more than 80% power for the above hypothesis testing[6].

Table 1: Various effect size, standard deviation, and sample size to attain approximately 80% power.

Effect Size $\Delta = \mu - \mu_0$	SD in Δ	Unadjusted Sample Size (N_T)	Adjusted Sample Size (N_w)	Power
6	10	24	36	80.4%
7	12	27	40	81.6%
8	14	27	40	81.5%
9	16	27	40	80.3%
10	17	25	38	80.6%
11	19	26	39	81.0%
12	21	27	40	81.5%

6.3 Remarks About Statistical Analysis

All the analyses will be performed using SAS statistical software, version 9.4 or higher, primarily PROC FREQ for categorical data and PROC UNIVARIATE for continuous data. For categorical variables, subject counts and percentages will be generated. For continuous variables, mean, standard deviation, median and range will be generated. Two-sided p-values of less than 0.05 will be considered as statistically significant. Analyses will be based on the observed data only. Missing data will not be imputed. Multiple comparison adjustment will not be performed.

6.4 Baseline Analysis

Subject demographic variables will be summarized descriptively. Medical history findings and PCI details will be tabulated. Protocol deviations will be listed.

6.5 Clinical Performance Analysis

The performance endpoints consist of the following four previously identified categories (Section 5.1):

- Catheter preparation
- Catheter deliverability
- Image quality
- Overall performance

Subjective criteria within these categories will be evaluated and rated using the 5-point Likert scale by the interventional cardiologist clinical operator. The performance endpoints will be analyzed by mean and standard deviation. As the Likert scale evaluation will be conducted following the PCI case of each enrolled subject, the performance evaluation sample will be equivalent to the number of enrolled

subjects who underwent HF-OCT imaging. The primary performance objective is to achieve a mean rating of greater than 3 (or acceptable) for the above four categories. No inferential statistical analysis will be performed for these clinical performance endpoints.

Three (3) to five (5) centers will enroll subjects, and there may be multiple interventional cardiologist clinical operators at each participating center. Therefore, there will be a range of clinical operators who evaluate the performance of the Gentuity HF-OCT Imaging System and Vis-Rx Prime Catheter in a range of PCI cases.

6.6 Technical Performance Analysis

The clear image length analysis will be conducted on HF-OCT pullbacks acquired in this evaluation by an independent core lab experienced with intracoronary HF-OCT imaging analysis. A clear image frame has at least 270° of visible lumen. CIL is the extent of clear image frames in a given pullback, measured in millimeters. The acquired pullbacks will reflect a range of coronary arteries, atherosclerotic lesions, and procedural timepoints. These factors result in a great deal of variability in the CIL measurements even among pullbacks from the same subject. Consequently, for these CIL data, it is reasonable to utilize statistical methodologies normally suitable only for independent observations. The primary analysis will be performed using SAS/STAT PROC UNIVARIATE and features an exact one-sample two-sided Wilcoxon signed-rank test using “CIL minus 35” as outcome. The data will reject the null hypothesis and support Gentuity HF-OCT’s claim of superiority to the reference standard if the two-sided p-value is less than 0.05 and the median CIL estimate greater than 35 mm.

6.7 Safety Endpoint Analysis

Safety endpoint analysis will be determined based on adverse event data. The primary endpoint for safety is the incidence rate for each HF-OCT Imaging procedure related adverse event observed in the study. The overall rate and severity of adverse events will be analyzed and reported as a percentage based on the total number of catheters used for the HF-OCT procedures performed.

6.8 Procedural Error and Device Malfunctions

It is possible that a procedural error may occur that will lead to a pullback image being captured that has no or only partial clear imaging. For example, the injector pump (if used) had insufficient contrast media to clear the vessel, the bedside manifold was set such that delivered contrast media was not directed into the guide catheter and vessel, or the guide catheter became mis-aligned with the target artery prior to flush delivery. If such errors occur, they will be noted in the Case Report Form, the HF-OCT pullback will be repeated (at the operator’s discretion), and the pullback with the procedural error will not be included in the statistical analysis. Any procedural errors will be described in the final report.

The investigational device malfunctions will be recorded and detailed on the Device Malfunction Case Report Form. Document malfunctions that occur at setup and during use of the device will be collected.

7 Data Management

The collection and handling of subject clinical data will comply with regulatory guidelines and the Sponsor's Standard Operating Procedures (SOPs). All steps and actions taken regarding data management and quality assurance will be documented in the Sponsor's SOPs and data management plan.

Subject demographic, medical history, PCI details, and the Likert-scale performance evaluation will be collected via paper Case Report Forms (CRFs). The clinical data will be reviewed and approved by the clinical operator following the PCI and performance evaluation interview. The CRFs will collect only de-identified information. The data will be identified using methods to ensure HIPAA compliance (e.g., study participant ID). Following the PCI, clinical performance evaluation, and completion and approval of the CRFs, the collected data, including HF-OCT and coronary angiography images, will be transferred to Gentuity for data monitoring and clinical performance analysis.

HF-OCT images will be exported from the Gentuity HF-HF-OCT Imaging System Console in an anonymized format onto a USB drive. The anonymized HF-OCT image files will be transferred in a 21 CFR Part 11 compliant manner from the participating center to the core lab for later CIL image analysis. In addition, Gentuity will collect an anonymized copy of the pullback images. The CIL technical performance results will be entered into a CRF by the core lab and provided to the statistician for technical performance results analysis.

Centers and the core lab are responsible for retaining the primary data and records for this evaluation for a period of two years following the close-out of the study. The Sponsor should be contacted prior to the destruction of any records pertaining to this evaluation to ensure that they no longer need to be retained.

8 Amendments to the Evaluation

Amendments to this clinical evaluation protocol will be identified by protocol number and revision letter. All amendments will be accompanied by an addition to the revision history table on the cover page that identifies all substantial changes. The protocol reference number and revision letter will be placed on the title page and every subsequent page of an amendment.

A protocol amendment will not be implemented for enrollment of subjects before all necessary reviews and approvals have been obtained, including Sponsor approvals, clinical operator signatures, and local Institutional Review Board (IRB) approvals, as applicable.

9 Deviations from the Evaluation Protocol

Deviations to the informed consent process, inclusion or exclusion criteria, and evaluation procedures including the HF-OCT imaging and clinical performance evaluation will be identified and tracked to determine the potential impact on the evaluation results.

Deviations relating to subject informed consent and deviations resulting in safety events for the subject will be reported to the local IRB per their reporting policies.

10 Statements of Compliance

This evaluation will be conducted in compliance with international ethical and scientific quality standards, known as Good Clinical Practice (GCP), which includes review and approval by independent Institutional Review Boards (IRBs) before enrolling subjects, continuing review by IRBs, and obtaining and documenting informed consent of subjects prior to participation.

The study was designed to reflect GCP as outlined in International Organization for Standardization (ISO) 14155:2011. It will also be conducted in compliance with applicable local and national regulations, including FDA regulations (21 CFR Parts 11, 50, 54, and 56). It will furthermore be conducted in compliance with the International Council for Harmonization (ICH) Guideline E6 for GCP.

This clinical evaluation shall not begin until the required approvals are obtained from the applicable IRBs.

Subjects will not be paid to participate in the clinical evaluation. It is not expected that subjects will incur any additional cost due to their participation in the evaluation.

11 Informed Consent Process

Informed consent must be obtained in accordance with FDA regulations 21 CFR Part 50, 45 CFR Part 46, and ICH E6 Good Clinical Practice (GCP).

Each subject must sign and date the current version of the Informed Consent Form (ICF) as approved by the IRB prior to screening and enrollment in the evaluation. The subject will be provided with ample time and opportunity to ask about the details of the Gentuity HF-OCT devices and evaluation procedures in order to decide on whether to participate before informed consent is obtained. Coercion or undue influence of a subject for participation must be avoided and a subject's legal rights must not be waived.

An ICF will be provided to each prospective subject to include: an explanation of the evaluation; the expected benefits, risks, or inconveniences to them; an explanation of alternatives; Gentuity representative attendance of their PCI; provision of anonymized HF-OCT images to the Sponsor and core lab; and collection of de-identified clinical data. The ICF will contain non-technical language. Informed consent will be documented by the dated signatures of the subject and the individual obtaining informed consent. The clinical operator or designee will be responsible for obtaining informed consent.

12 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a clinical evaluation subject, users, or other persons, whether or not related to the evaluation device. An AE would be any unfavorable or unintended sign, symptom, or disease that appears or worsens during the subject's participation in this evaluation.

Subject safety will be monitored throughout a subject's participation in the evaluation, from the beginning of the HF-OCT imaging procedure when the Vis-Rx Prime Catheter is inserted into the hemostatic valve, and continuing through their exit from the evaluation at the conclusion of the PCI

procedure. Any Adverse Events will be assessed by the clinical operator according to their relatedness to the Gentuity HF-OCT imaging procedure, Vis-Rx Prime Micro-Imaging Catheter, or HF-OCT Imaging System.

Any observed AE will be documented on the Adverse Event CRF. Any AE deemed to be possibly, probably, or definitely related to the Gentuity HF-OCT procedure, Vis-Rx Prime Catheter, or Imaging System will be reported to the IRB and evaluated as a complaint by Gentuity per Gentuity's complaint handling process. Non-related AEs will be tracked until the subject exits the evaluation at the conclusion of their PCI. Related AEs will be tracked until they are resolved.

Each AE will be classified as either non-serious or serious. A Serious Adverse Event (SAE) is defined to be an AE that:

- Led to death.
- Led to serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Each AE will furthermore be classified as either anticipated or unanticipated. The anticipated AEs are listed in the Instructions for Use. Any unanticipated AEs will be further considered to determine if they may be an Unanticipated Serious Adverse Device Effect (USADE), which is defined to be a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Adverse events will be reported by diagnosis term, severity, and relatedness to the HF-OCT imaging procedure, Vis-Rx Prime Catheter, and HF-OCT Imaging System. Narratives will describe serious events and related events. Tabulation of procedure-emergent adverse events will be generated and stratified by diagnosis term. Similar tabulations will be generated for procedure or device related AEs that are classified as definitely, probably, or possibly related to the evaluation procedure or products.

13 Schedule of Assessments

Clinical Test	Baseline	Intra-Procedure	Post-Procedure
Informed Consent	X		
Initial Inclusion/Exclusion Screening	X		
Subject Demographics	X		
Medical History	X		
Transluminal Interventional Procedure History	X		
Coronary Angiography		X	
Lesion-Specific Screening		X	
HF-OCT Imaging and Pullback(s) Details		X	
Transluminal Interventional Procedure Details		X	
Device Malfunction (if applicable)		X	X
Likert-Scale Rating Evaluation			X
Adverse Event Assessment		X	
HF-OCT Image Upload			X
Coronary Angiography Upload			X
Case Report Form Upload			X

14 Revision History

Revision	ECO #	Date	Description of Change(s)
A	E04329	2/21/2024	Initial Release
B	E04435	4/19/2024	The name of the study has been updated to reflect the new commercial name for the Micro-Imaging catheter, which was changed from 'GenVue' to 'Vis-Rx Prime'. All references to 'GenVue' have been replaced with 'Vis-Rx Prime' in the CIP.
C	E04709	11/12/2024	Section 2.3 removed Arjun Bhat as primary study contact and added general statement about Gentuity contact personnel information throughout duration of study. Section 3.1 updated catheter drawing to reflect one pullback marker. Sections 6.0 clarified type of imaging to included angiography and HF-OCT imaging. Section 7.8 added language related to how device malfunction data will be collected. Section 8.0 added language to clarify collected data to include HF-OCT imaging and angiography. Section 13 added Schedule of Assessments table. Moved revision history from cover page to Section 14 Bibliography now Section 15

15 Bibliography

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