DE NOVO CLASSIFICATION REQUEST FOR ELLIPSYS VASCULAR ACCESS SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Percutaneous catheter for creation of an arteriovenous fistula for hemodialysis access. This device is a single use percutaneous catheter system that creates an arteriovenous fistula (AVF) in the arm of patients with chronic kidney disease who need hemodialysis.

NEW REGULATION NUMBER: 21 CFR 870.1252

CLASSIFICATION: II

PRODUCT CODE: PQK

BACKGROUND

DEVICE NAME: Ellipsys Vascular Access System (Ellipsys® System)

SUBMISSION NUMBER: DEN170004

DATE OF DE NOVO: January 10, 2017

CONTACT: Avenu Medical, Inc.
27123 Calle Arroyo, Suite 2101
San Juan Capistrano, CA 92675

INDICATIONS FOR USE

The Ellipsys® System is indicated for the creation of a proximal radial artery to perforating vein anastomosis via a retrograde venous access approach in patients with a minimum vessel diameter of 2.0mm and less than 1.5mm of separation between the artery and vein at the fistula creation site who have chronic kidney disease requiring dialysis.

LIMITATIONS

The sale, distribution, and use of the Ellipsys® System are restricted to prescription use in accordance with 21 CFR 801.109.

The Avenu Medical Ellipsys® System is intended to only be used by physicians trained in ultrasound guided percutaneous endovascular interventional techniques using appropriate clinical standards of care for fistula maintenance and maturation including balloon dilatation and coil embolization.

The Ellipsys® System is contraindicated for use in patients with target vessels that are < 2mm in diameter. The Ellipsys® System is contraindicated for use in patients who have a distance between the target artery and vein > 1.5mm.

The Ellipsys® System has only been studied for the creation of an AV fistula using the proximal radial artery and the adjacent perforating vein. It has not been studied in subjects who are candidates for surgical fistula creation at other locations, including sites distal to this location.

Additional procedures are expected to be required to increase and direct blood flow into the AVF target outflow vein and to maintain patency of the AVF. Care should be taken to proactively plan for any fistula maturation procedures when using the device.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Ellipsys® Vascular Access System is a catheter based system that is used to percutaneously create a vascular anastomosis between adjacent blood vessels using direct current (DC) thermal heating. The system consists of several components:

- Ellipsys Catheter
- Ellipsys Crossing Needle
- Ellipsys Power Controller

Ellipsys Catheter

The Ellipsys Catheter is a single-use, sterile, flexible catheter with a heating element on the distal tip. The catheter is tracked over a guidewire in the vein to the target anastomosis site. Then the distal tip components are extended, with part of the tip placed into the target artery, and the tip is retracted to approximate the vessels (i.e., pull the vessels together). Thermal energy is then delivered from the heating element on the tip to seal the vessels together and create an arteriovenous fistula (AVF). The figures below illustrate the catheter and its mechanism of action.

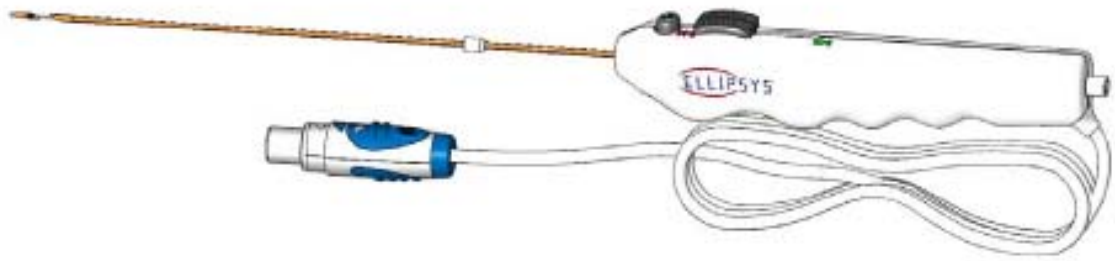


Figure 1: Ellipsys Catheter

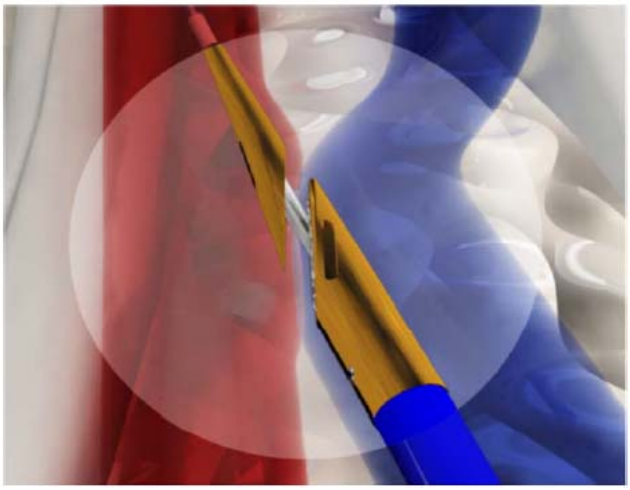


Figure 2: Ellipsys Catheter Position in Vasculature Prior to Activation

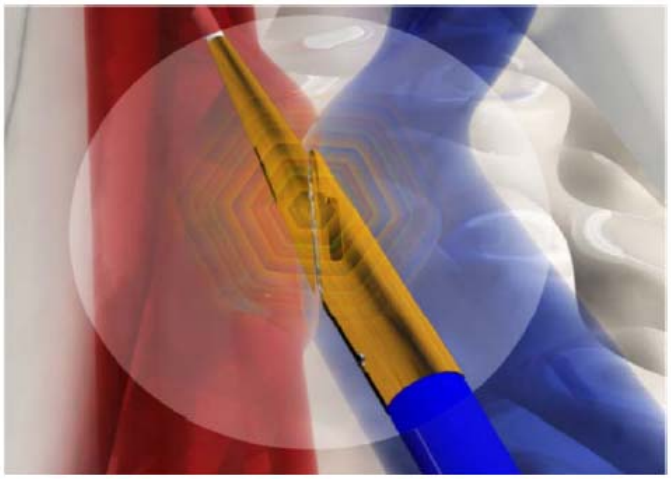


Figure 3: Creation of a Fistula with the Ellipsys Catheter

Ellipsys Crossing Needle

The Ellipsys Crossing Needle is a single use, sterile, telescoping needle that is used to cross from inside the vein into the artery at the target anastomosis site. When the inner needle is retracted, it has a round, atraumatic tip that can be positioned against the wall of the adjacent vessel prior to advancing the needle. The sharp needle tip housed within the cannula can be manually deployed a distance of 10mm by pushing forward on the inner hub of the handle. The Ellipsys Crossing Needle is compatible with a non-coated .014" guidewire and a 6F introducer sheath.

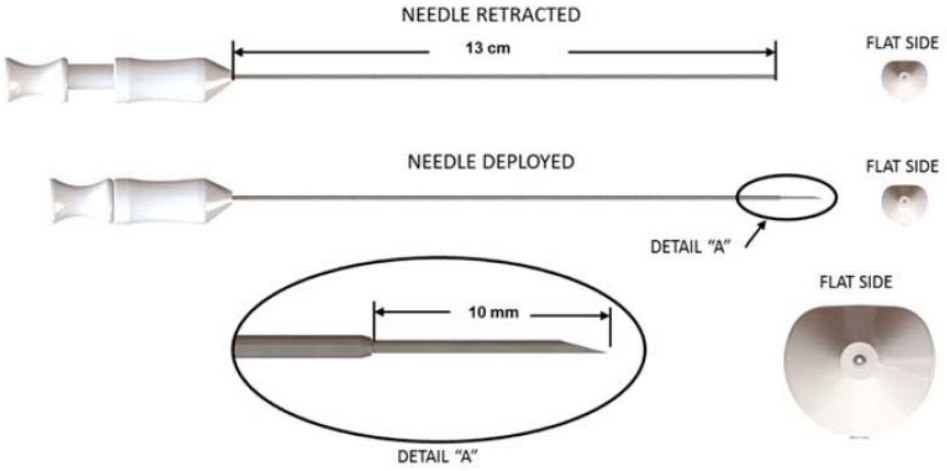


Figure 4: Ellipsys Crossing Needle

Ellipsys Power Controller

Unlike the other components, the Ellipsys Power Controller is a reusable, non-sterile device. This portable electronic console is powered with AC inputs, has internal control electronics, and a user interface display. The catheter can connect to the controller which provides the catheter with DC power (converted from AC power) and a closed loop temperature control of the distal heating element.

The Power Controller performs the following functions:

- Performs a start-up sequence to verify catheter function prior to insertion into the patient.
- Contains a visual display screen so the user can verify catheter functionality and start the thermal cycle.
- Controls the thermal cycle.
  - Applies DC energy to heat the catheter
  - Monitors the tip temperature of the catheter
  - Monitors the tip position of the catheter
  - Provides closed loop temperature control algorithm to ensure the temperature is maintained at the programmed parameter
- Stores patient ID, the process parameters and control calculations by the main controller board.
- Has a USB port to allow the user to externally export procedural data to a USB flash drive.

Figure 5: Ellipsys Power Controller

Please refer to the Instructions for Use for additional details.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Catheter and the Crossing Needle are externally communicating components that are in direct contact with circulating blood for a limited duration (b) (4) The biocompatibility testing summarized below was performed to demonstrate that these components are biocompatible for their intended uses. All tests passed.

The Power Controller is a non-patient-contacting component and was not tested.

Table 1: Biocompatibility Testing Summary

Test	Description (Method)
Cytotoxicity	MEM Elution Assay with L-929 Mouse Fibroblast Cells (ISO 10993-5)
Sensitization	Guinea Pig Maximization (ISO 10993-10)

Irritation	Intracutaneous Reactivity (ISO 10993-10)
Acute System Toxicity	Acute Systemic Injection (ISO 10993-11)
Hemocompatibility	ASTM Hemolysis Assay – Direct Contact & Extract Methods (ASTM Method F756-08)
	Complement Activation C3a and SC5b-9 Determination of SC5b-9 Terminal Chain Complex (TCC) and C3a-desArg Present in Normal Human Serum Through Enzyme Immunoassay (ISO 10993-4)
	In-vivo Thromboresistance (evaluated as part of the animal studies)
Pyrogenicity	Material-mediated Rabbit Pyrogen (USP Rabbit Pyrogen Test Procedure, Section 151)
	Endotoxin-mediated (LAL) (AAMI ST72)

SHELF LIFE/STERILITY

The shelf-life of the Ellipsys System has been established at 2 years based on accelerated aging testing equivalent to 2 years in accordance with *ASTM F1980 - 07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices*. Following 2X sterilization, environmental conditioning per ISTA 2A, distribution simulation per ASTM D4169, and accelerated aging, the devices were visually inspected for damage per ASTM F1886, bubble leak tested per ASTM F2096, and package seals were tested per ASTM F88. Aged devices also underwent repeat engineering bench testing to confirm acceptable performance.

The Ellipys Catheter and Crossing Needle are labeled as sterile and have a validated sterility assurance level (SAL) of 10^{-6}. The Ellipsys Catheter and Crossing Needle have been validated to be sterilized via ethylene oxide (EO). The sterilization cycle was validated using the (b) (4), and the EO and ECH residuals were shown to meet the limits specified by ISO 10993-7:2008.

The Ellipsys Power Controller is provided non-sterile and is labeled as such. The Power Controller user manual includes instructions for cleaning.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The electromagnetic compatibility and electrical safety of the Ellipsys System was evaluated by demonstrating compliance to the following standards:

Table 2: Electrical Performance Testing Summary

Standard	Name
IEC 60601-1:2005 + CORR. 1 (2006) + CORR. 2 (2007) +	Medical Electrical Equipment - Part 1: General Requirements For Basic Safety And Essential Performance

AM12012	
IEC 60601-1-2:2007	Medical Electrical Equipment - Part 1-2: General Requirements For Basic Safety And Essential Performance - Collateral Standard: Electromagnetic Disturbances - Requirements and Tests

MAGNETIC RESONANCE (MR) COMPATIBILITY

The Ellipsys System is intended as a temporary use device and has not been tested for MR compatibility.

SOFTWARE

The Ellipsys Power Controller software controls the catheter temperature. The controller also receives, analyzes, and adjusts the power output of the power control module to maintain the desired temperature. The controller reports the data via the user interface, archives recent process data for later analysis, and directs the user through most of the Ellipsys system, automating most functions. The software monitors the catheter for errors and provides alerts and instructions to the user if it cannot resolve the error automatically.

The Ellipsys Power Controller has a Moderate Level of Concern (LOC). Appropriate documentation was provided to support the validation of the Power Controller software for a Moderate LOC in accordance with FDA's 2005 guidance titled, "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*."

PERFORMANCE TESTING – BENCH

The Ellipsys System was subjected to a series of bench tests to assess its functional performance. These tests were performed on final, sterilized product. The engineering bench testing summarized in the table below was performed to demonstrate acceptable mechanical performance of the device for its intended use.

Table 3: Performance Testing (Bench) Summary

Test		Description/Acceptance Criteria
Ellipsys Catheter		
Dimensional Verification/Validation	Catheter Working Length	The working length of the catheter must be > 15cm
	6F Sheath Compatibility	The device must pass through a 6F sheath without excessive friction.
	0.014" Guidewire Compatibility	0.014" guidewire must pass through device lumen with ease.
	Hub/Tip Alignment	Hub must correctly identify the tip orientation; i.e., taper of heater element must face away from thumb tab.
Electrical Performance	Electrical Connection to Generator	Catheter connector shall only be connected to the generator in one orientation.
	Control Thermocouple Accuracy	Ambient Temperature: 700 ±10°F

	Base Thermocouple Accuracy	Ambient Temperature: 700 ±50°F
	Position Sensor Function	The voltage range for the position sensor corresponding to opening and closing of device shall have a 1-1.3 V voltage differential.
Tensile Strength		• Bonds/joints shall maintain mechanical integrity during use • Each bond/joint was tested against specifications based on the clinical use of the device
Simulated Use		• Catheter shall properly connect to the Power Controller. • Power Controller software shall run without errors or interruption when connected to the catheter. • Track device samples through vein/artery samples and activate device to create a fistula. • After simulated use, the pull force required to separate the vessels must be > 20g. • Device shall be free of damage.
Corrosion Resistance		Metallic components of the catheter intended for fluid path contact shall show no signs of corrosion.
Coating Integrity Testing		After simulated use in a clinically-relevant model, and subjecting the device to 2 heat cycles, the device coating shall not exhibit any damage or peeling when inspected under magnification.
Ellipsys Crossing Needle		
Dimensional Verification/Validation	Crossing Needle Working Length	The working length of the needle must be 13.0 ± 0.5 cm.
	6F Sheath Compatibility	The device must pass through a 6F sheath without excessive friction.
	0.014" Guidewire Compatibility	0.014" guidewire must pass through device lumen with ease.
	Needle Extension Length	Needle shall extend between 8-11mm.
	Needle Tip Orientation and Grind Profile	• Needle hub shall correctly indicate the position of the needle. • Needle tip shall be sharp, not bent or flattened, when inspected under magnification.
	Distal End of Outer Cannula Protrusion	• Distal end of cannula shall conform to drawing dimensions and needle shall not protrude from cannula when retracted. • Tip of cannula shall be free of debris or sharp edges when inspected under magnification.
Tensile Strength		• Bonds/joints shall maintain mechanical integrity during use. • Each bond/joint was tested against specifications based on the clinical use of the device.
Corrosion Resistance		The crossing needle shall show no signs of corrosion.
Ellipsys Power Controller		
Electrical Performance	Position Sensor Function	Position sensor shall have an accuracy of 3.0 ± 0.5mm.
	Electrical Connection to Catheter	The Power Controller shall connect to the catheter in only one orientation.

PERFORMANCE TESTING – ANIMAL &/OR CADAVER

Two main *in vivo* animal studies were conducted to demonstrate the feasibility and safety of the Ellipsys System. The studies are summarized in the table below.

Table 4: Summary of Preclinical Studies

Purpose	Methods	Results
Evaluate the acute and chronic safety, fistula blood flow characteristics, fistula patency, handling characteristics, and histopathological response at the treatment site and off-target tissue sites using the final device design. Perform gross comparison of fistulae created with the final device design compared to a previous device design to demonstrate equivalent fistula creation. Perform study according to Good Laboratory Practices.	• GLP • N=6 ovine models • Insert, track, deploy, and activate device to create bilateral arteriovenous fistulae in each animal. The original device design was used to create a fistula in one femoral artery and the final device design was used to create a fistula in the other femoral artery. • Acute and post-treatment assessments of device performance included needle and catheter access/removal, and anastomosis and sheath appearance. • Immediately after fistula creation, fistulae were evaluated by ultrasound to determine fistula diameter, patency, and fistula flow. • At 1, 7, and 30 days post-procedure, animals were evaluated for safety events (swelling, hematoma, thrombosis, etc.) and ultrasound was used to evaluate fistula diameter, patency, and fistula flow. • Gross necropsy, including external and internal examination of the fistulae, was performed at 30 days. • Histopathological examination of the fistulae and downstream organs such as the brain, heart, lungs, liver, spleen, and kidneys was conducted at 30 days to evaluate chronic safety of the fistula and any thromboembolic events. • All results from fistulae created with the final device design were compared to the fistulae	• All fistulae were successfully created. • Needle access/removal, catheter insertion/removal, anastomosis appearance, and sheath appearance were acceptable for all devices. • No procedural or handling differences were observed between the two device designs. • Intra-operative ultrasound demonstrated a focal seal zone around the circumference of all anastomoses. • All animals appeared normal at routine health assessments. • One unexpected death occurred due to anesthetic complications that occurred immediately post-sedation. • 7/10 fistulae (4/5 created using final device design) were patent at 7-day follow-up. Loss of patency was due to flow reduction due to thrombosis at fistula, though the adjacent vein and artery were patent in all cases. • There was no evidence of excessive submural bleeding, aneurysm, or loss of vessel approximation. • The fistula sizes and flow rates for both device designs were acceptable at 30 days. • Gross pathology supported the ultrasound findings. • Thermal necrosis, granulation tissue, mineralization and neointimal hyperplasia were localized to the tissue site as expected. • Vascular healing appeared to be normal for this type of device. • No evidence of safety concerns, such as thrombo-emboli, was observed in downstream organs.

	created with the previous device design to determine equivalence.	
Evaluate the ability to create an endovascular fistula, acute performance, and chronic safety in an animal model using an earlier design version of the device compared to surgical fistula creation. Following the study, no major changes were made to the electro-mechanical system involved in vessel access or energy delivery.	• Non-GLP • N=6 ovine models • Insert, track, deploy, and activate device to create a fistula in one of the femoral arteries of each animal. A surgical fistula was subsequently created in the other femoral artery of each animal. • Immediately after fistula creation, fistulae were evaluated by ultrasound to determine fistula diameter, patency, and fistula flow. • At 15 and 30 days post-procedure, ultrasound was used to evaluate fistula diameter, patency, and fistula flow. • Gross pathological examination and histopathological examination performed for N=3 animals at 15 days and N=3 animals at 30 days to evaluate safety and healing response.	• Procedural performance was acceptable for all devices. • 5/6 fistulae were successfully created. One fistula separated five minutes after the procedure, but no intervention was required and no clinical sequelae were observed. • All successfully created fistulae were patent at all follow-up evaluations, with acceptable fistula flow. • No adverse clinical events were observed in any animals. • No evidence of chronic tissue damage was observed. • No excessive inflammatory response, delayed healing or stenosis was observed. • Fistula performance appeared to be acceptable and comparable to the surgical control fistulae.

SUMMARY OF CLINICAL INFORMATION

The Ellipsys System was primarily supported by a pivotal study entitled the "Ellipsys Vascular Access System Clinical Trial." Details of the study design and selected clinical results are provided below.

Purpose: To demonstrate the safety and effectiveness of the Ellipsys Vascular Access System in creating a native AV fistula via percutaneous access to support future hemodialysis.

Design: The study was a non-randomized, prospective multi-center study conducted in the United States, in which a total of 117 subjects from 5 sites were enrolled to undergo creation of an AV fistula using the Ellipsys Vascular Access System. Patients who met the study criteria and had suitable vascular anatomy, as confirmed by pre-procedure ultrasound vascular mapping, were enrolled in the study.

Follow-up visits were scheduled at 24 hours, 1 week, 4 weeks, 90 days, 6 months and 1 year using the following standard of care assessments: vital signs, upper extremity vessel dimensions by ultrasound, post-procedure patency and flow rates, and adverse events.

All study data were monitored by an independent study monitor, and adverse events were adjudicated by an independent medical monitor.

Primary Endpoints:

1) Safety: The primary safety endpoint was the percent of subjects showing at least one of the following device-related serious adverse events (SAEs): vessel perforation, vessel dissection, and electrical shock during index; and embolization in a previously uninvolved arterial territory within 90 days (+/- 14 days) of the index procedure.

   The following definitions were used for the safety analyses in the study:

   - Adverse event (AE): any undesirable experience associated with the use of a medical product in a patient.

   - Serious adverse event (SAE): an AE or any untoward medical consequence that meets any of the following criteria:
     - Results in death.
     - Is life-threatening (i.e., an AE that, in the opinion of the investigator, places the subject at immediate risk of death).
     - Requires in-patient hospitalization or prolongs an existing hospitalization (hospitalizations for scheduled medical or surgical procedures to conduct scheduled treatments or routine examinations do not meet this criterion).
     - Results in persistent or significant disability or incapacity.
     - Is a congenital anomaly or birth defect in the infant/newborn of a mother that has been exposed to the research device.
     - It is considered by the investigator to be a significant medical event based on medical criteria (e.g., puts the subject at risk or may require medical or surgical intervention to prevent one of the aforementioned results).

   - Device-related adverse event: AE that is directly attributable to the use of the device.

   - Procedure-related adverse event: AE that is directly related to accessing the vessel prior to introducing the study device and creating the AV fistula.

2) Effectiveness: The primary effectiveness endpoint was the maturation success rate at the 90-day follow-up visit, with maturation defined as an access site intended for dialysis needle cannulation with venous diameter ≥ 4 mm, blood flow ≥ 500 ml/min.

Secondary Endpoints: Secondary endpoints consisted of the following:

- *Device Success Rate*: Percent of Ellipsys Vascular Access Systems that successfully created an AVF upon deployment.

- *Technical Success Rate*: Percent of access sites that demonstrated physical exam patency through clinic discharge;

- *Rapid Maturation Rate*: Percent of access sites that could sustain three 2-needle cannulations at the prescribed needle gauge and blood flow rate (Qb) between the 4 week and 90 day follow-up visits after initial AV fistula creation.

- *Assisted Maturation Rate*: Percent of access sites which achieved or maintained maturation following intervening manipulations (surgical or endovascular) designed to promote or reestablish maturation.

- *Unassisted Maturation Rate*: Percent of access sites that achieved and maintained maturation without any surgical or endovascular intervention designed to promote or reestablish maturation.

- *Assisted Patency Rate*: Percent of access sites which were patent after intervening manipulations (surgical or endovascular) intended to promote or reestablish patency.

- *Unassisted Patency Rate*: Percent of access sites that maintained patency without any surgical or endovascular intervention designed to maintain or reestablish blood flow in the access site.

- *Intervention Rate*: Percent of subjects who had one or more surgical or endovascular interventions to maintain or reestablish blood flow in the access site

- *Transposition Rate*: Percent of subjects who required one or more surgical transpositions performed to facilitate needle access.

Other Outcome Measures: Other outcome measures included the following:

- *Time to First Cannulation:* Elapsed time to first use of access site.
- *Ultrasound Flow:* Flow rate of blood through outflow vein(s).
- *Time to Access Site Abandonment:* Elapsed time to abandonment of the access site.
- *Catheter Utilization:* Total number of days a catheter was used before access site maturation per subject.
- *6 Month Patency and Flow:* Patency and flow at 6 months following AVF creation.
- *1 Year (12 Month) Patency and Flow:* Patency and flow at 12 months following AVF creation.

In addition to the secondary endpoints and other outcome measures, additional analyses that were not pre-specified in the clinical protocol were performed and are discussed in the results section below.

Eligibility Criteria Summary: The study population consisted of male and female patients from the United States, at least 18 years of age and no more than 80 years of age.

Key inclusion criteria included the following:

- Diagnosed with end-stage renal disease (ESRD) or chronic kidney disease requiring dialysis or anticipated start of dialysis within 6 months of enrollment.
- Patients deemed medically eligible for upper extremity autogenous AV fistula creation, per institutional guidelines and/or clinical judgment.
- Arterial lumen diameter of ≥ 2.0mm and adjacent vein diameter of ≥ 2.0mm at the target anastomosis site.
- Radial artery-adjacent vein proximity ≤ 1.5 mm measured lumen edge-to-lumen edge as determined by pre-procedural ultrasound and confirmed pre-procedure.
- Adequate collateral arterial perfusion and vein quality based on pre-operative assessment, without evidence of subclavian artery stenosis on the ipsilateral side.
- Negative Allen's Test for ulnar artery insufficiency.

Key exclusion criteria included the following:

- Patient required creation of an arteriovenous fistula distal to the wrist.
- Documented or suspected central venous stenosis including upper extremity arterial stenosis (≥ 50%).
- Prior vascular surgery at or proximal (central) to the AVF target site.
- Prior axillary dissection or mastectomy on the ipsilateral side as intended AV fistula site.
- Evidence of vascular disease at the radial artery/adjacent vein site on the ipsilateral side.
- History of steal syndrome from a previous hemodialysis vascular access on the ipsilateral side which required intervention or abandonment.

Accountability: Figure 6 below shows the disposition of all subjects through the end of the study. In the figure, long term follow-up (LTFU) refers to the 6- and 12-month study visits.

Note: Study subjects were not consented for LTFU until after a large percentage of the study subjects had completed their 90-day study visit and some had already passed the window for their 6-month visit. As a result, 6 subjects declined to re-consent to rejoin the study for LTFU and 34 subjects completed the 12-month study visit but not the 6-month study visit.

Patients were not included in the ITT population for the following reasons:

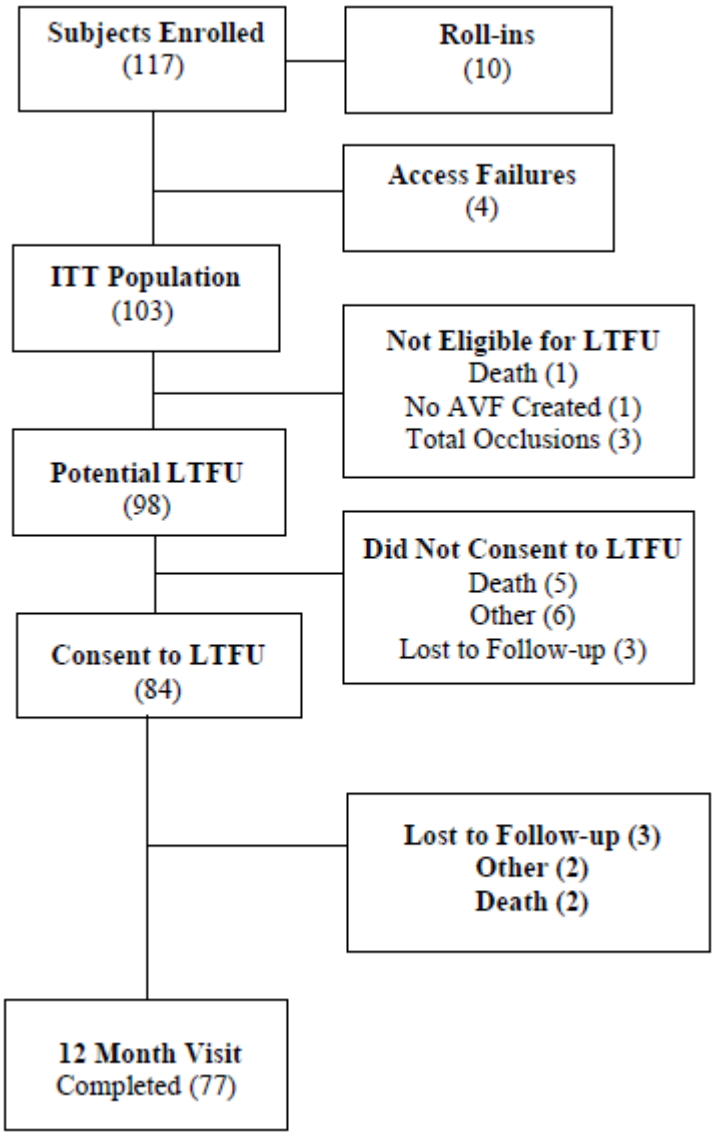
- Roll-ins – the first two patients at each clinical site who were included to facilitate *in vivo* training on the device and the specific vascular anatomy.
- Access failures – the device could not be introduced into the vessel or vessel spasm precluded continuation of the procedure.

Patients in the ITT population exited the study for the following reasons:

- No AVF created – an AVF was attempted during the index procedure but could not be successfully created.
- Total occlusions – three subjects whose access sites were abandoned within the first 30 days due to total occlusion of the anastomosis which could not be re-opened.

- Death – one death was reported at the 90-day visit, two deaths were reported at the 6-month visit, and five deaths were reported at the 12-month visit. Among the seven deaths that occurred after 90 days, five subjects had not consented to LTFU while two subjects had consented for LTFU.
- Lost to follow-up – the patient failed to return for follow-up visits, and documented attempts to locate and contact the subject were unsuccessful. A patient who missed a study visit but attended a subsequent visit was no longer considered lost to follow-up. A missed visit was considered a protocol deviation and the deviation was documented and reported.
- Other – subjects who terminated the study early for various other reasons such as declining to re-join the study after completing the 90-day visit, subjects who were using other means of vascular access, or experienced an SAE unrelated to the study device or procedure.

Figure 6: Subject Disposition Through End of Study



Demographics: The total Intent-to-Treat (ITT) population consisted of 103 patients. Information on the patient demographics is provided in Table 5 below.

Table 5: Demographic Characteristics of ITT Patients

Attribute		ITT Patients (N=103)
Age (mean, yrs)		56.6
BMI (mean, kg/m^2)		31.2
Sex (%)	**Male**	73.8
	Female	26.2
Race (%)	**White**	74.8
	Black	20.4
	Asian	1.9
	Other	2.9
Ethnicity (%)	**Hispanic/Latino**	35.9
	Not Hispanic or Latino	63.1
Diabetes (%)	**Type I**	4.9
	Type II	61.2
Hypertension (%)		98.1
Vascular Disease other than Target Site (%)		34.0
Relevant Previous Surgical Procedures (%)	**Prior Failed Surgical AVF on Contralateral Side**	6.8
	Prior Nephrectomy	4.9
	Other Relevant Surgical Procedure	21.4
Catheter Present for Hemodialysis at Screening (%)		62.1

Table 6 below presents the pre-procedure vessel mapping results by ultrasound in the ITT population, and Table 7 shows the vessel locations used in the study. Table 8 presents the patients' dialysis status at screening and end of study.

Table 6: Pre-Procedure Ultrasound Vessel Characteristics, ITT Population

Attribute	# of ITT Patients (N=103)
Proximal Radial Artery Diameter (mean ± SD, mm)	3.08 ± 0.62
Perforating Vein Diameter (mean ± SD, mm)	3.48 ± 0.88
Artery-Vein Proximity (mean ± SD, mm)	0.65 ± 0.48

Table 7: Target Vessel Locations, Completed Cases Population

Target Vessel	# of CC Patients (N=90)
Cephalic Vein	68 (75.6%)
Basilic Vein	20 (22.2%)

Brachial Vein 1	1 (1.1%)
Brachial Vein 2	1 (1.1%)

Table 8: Dialysis Status at Screening and End of Study

Time Period (Analysis Population)	**Dialysis Status**	
	Pre-Dialysis N (%)	**On Dialysis N (%)**
Screening (ITT Population, N=103)	39 (37.9)	64 (62.1)
Screening (Long Term Visit Population, N=81)	28 (34.6)	53 (65.4)
12 Months (Long Term Visit Population, N=81)	14 (17.3)	67 (82.7)

Results: The principal safety and effectiveness results from patients in the study are provided below. The primary endpoints were evaluated for the Intent-to-Treat (ITT) population.

Primary Safety Endpoint: The primary safety endpoint of the study was met as none of the subjects experienced one or more of the following device-related SAEs: vessel perforation, vessel dissection, electrical shock during index, and significant embolization in a previously uninvolved arterial territory within 90 days of the procedure. A hypothesis test was not used for the primary safety endpoint.

Table 9: Primary Safety Endpoint Results – 90-Day Device Related SAE Rate

Safety Endpoint	**# of Subjects**	**% of Subjects**	**95% Confidence Interval**
Vessel perforation during index procedure	0	0.0%	0.0%, 3.5%
Vessel dissection during index procedure	0	0.0%	0.0%, 3.5%
Electrical shock during index procedure	0	0.0%	0.0%, 3.5%
Embolization in previously uninvolved arterial territory	0	0.0%	0.0%, 3.5%
Composite Safety Endpoint	0	0.0%	0.0%, 3.5%

Primary Effectiveness Endpoint: The primary effectiveness endpoint was the maturation success rate at the 90 day follow-up visit, with maturation defined as an access site intended for dialysis needle cannulation with venous diameter $\geq$ 4 mm and blood flow $\geq$ 500 ml/min, as measured by duplex ultrasound.

The primary effectiveness endpoint was tested for the ITT population using a one-sample hypothesis comparing the Ellipsys Vascular Access System (Test) to a Performance Goal of 49%. The point estimate for the historical performance goal was derived from a meta-analysis of eight previous studies of open surgical AVF procedures. The null and alternative statistical hypotheses were:

$$H_0: P_{Test} \leq 49\% \text{ vs. } H_A: P_{Test} > 49\%,$$

where P_{Test} was the maturation success rate in the Test group. This hypothesis was tested with a one-sided binomial test. The null hypothesis was tested using a one-sided significance level of 0.025. A supportive analysis of the primary endpoint was calculated as the lower one-sided 97.5% exact binomial confidence limit based on Clopper-Pearson methods for the ITT population. Additionally, supportive analyses for the primary effectiveness endpoint were done using the same methodology for the As Treated (AT) and Completed Cases (CC) populations.

The primary endpoint was met with a 90-day maturation success rate of 89.3%.

The statistical analysis populations used in the study were defined as follows:

- Intent-to-Treat (ITT): The ITT population included all subjects enrolled following the roll-in stage in whom the procedure had been attempted and the study device deployed, whether successful or not.

- As-Treated (AT): The AT population included all subjects in the ITT population where the study device was successfully deployed in the target vasculature and an AVF was created.

- Completed Cases (CC): The CC population included all subjects in the ITT population with a patent AVF completing the 90-day evaluation.

Table 10: Primary Effectiveness Endpoint Results – 90-Day Maturation Success Rate

Analysis Population	Successes (N)	Total (N)	Percent (%)	Lower 97.5% Confidence Interval	p-value
ITT	92	103	89.3%	81.7%	<0.0001
AT	92	102	90.2%	82.7%	<0.0001
CC	86	90	95.6%	89.0%	<0.0001

Secondary Endpoints: A summary of the secondary endpoint analyses are provided below. All analyses presented below are based on the ITT population.

Table 11: Secondary Safety Endpoint Results – SAEs Through 12 Month Follow-Up

Adverse Events Relatedness	SAEs Through 90 Days			SAEs Through 12 Months		
	# of Events (N)	# of Subjects (N)	Percent (N=103) (%)	# of Events (N)	# of Subjects (N)	Percent (N=103) (%)
Related to Device Only	0	0	0.0%	0	0	0.0%
Related to Procedure Only	1	1	1.0%	2[1]	2	1.9%
Related to Both Device and Procedure	0	0	0.0%	0	0	0.0%
Not Related to Device or Procedure	18	17	16.5%	76	40	38.8%

1. The two SAEs adjudicated as related or possibly related to the procedure included a reaction to pre-procedure medication and a dialysis catheter infection.

Table 12: Secondary Effectiveness Endpoint Results – 90 Day Follow-Up

Secondary Endpoint	Successes (N)	Total (N)	Percent (%)	95% Confidence Interval
Device Success	102	103	99.0%	[94.7, 100.0]
Technical Success	98	103	95.1%	[89.0, 98.4]
Intervention Rate	98	103	95.1%	[89.0, 98.4]
Transposition Rate	19	103	18.4%	[11.5, 27.3]
Rapid Maturation Rate	29	103	28.2%	[19.7, 37.9]
Assisted Maturation Rate	85	103	82.5%	[73.8, 89.3]
Unassisted Maturation Rate	1	103	1.0%	[0.0, 5.3]
Assisted Patency Rate	89	103	86.4%	[78.2, 92.4]
Unassisted Patency Rate	1	103	1.0%	[0.0, 5.3]

Adverse Events: The adverse events (AEs) presented in Table 13 were observed in the study through 90 days and 12 months. The data represent all AEs that were observed during the study, regardless of seriousness or relation to the device and/or procedure. All events were adjudicated by an independent Medical Monitor.

A total of 25 occlusion events were observed in 19 subjects (17.5%) throughout the study. For 15 of the 19 subjects (78.9%), the occlusion event occurred within 24 hours of the study procedure. There was no propagation of thrombus to adjacent vessels. In all cases, this was not a life-threatening or serious event that required hospitalization, and there was no incapacity or disability. In all but two of the acute thrombosis cases, flow was restored quickly the same day or the next day using standard percutaneous techniques and overall 20/25 (80%) of the occlusion events were successfully resolved. Though 5/25 (20%) of the AVFs that remained occluded after treatment had minor associated thrombosis, the primary mechanism for occlusion was attributed to vessel spasm.

One death was reported at the 90-day visit, two deaths were reported at the 6-month visit, and five deaths were reported at the 12-month visit.

Table 13: Adverse Events Summary (ITT Population, N=103)

	Cumulative Through 90 Days		Cumulative Through 12 Months	
Event Type	**Total Events**	**# of Subjects w/ Event**	**Total Events**	**# of Subjects w/ Event**
Occlusion of anastomosis[1]	18	18 (17.5%)	25	19 (18.4%)
Total occlusion	12	12 (11.7%)	15	13 (12.6%)
Partial occlusion	6	6 (5.8%)	10	8 (7.8%)
Stenosis at the AV anastomosis	8	7 (6.8%)	9	8 (7.8%)
Death[2]	1	1 (0.9%)	8	8 (7.8%)
Hematoma	6	6 (5.8%)	8	8 (7.8%)
Infection of vascular access	2	2 (1.9%)	8	5 (4.9%)
Infection unrelated to vascular access site[3]	2	2 (1.9%)	8	6 (5.8%)
Infiltration	3	2 (1.9%)	7	6 (5.8%)
Volume overload	0	0 (0.0%)	7	5 (4.9%)
Venous stenosis	5	4 (3.9%)	7	5 (4.9%)
Coronary artery disease	0	0 (0.0%)	5	3 (2.9%)
Anemia	0	0 (0.0%)	5	5 (4.9%)
Bleeding unrelated to access site	3	3 (2.9%)	4	4 (3.9%)
Bleeding at access site	3	2 (1.9%)	3	2 (1.9%)
End-stage kidney disease	2	2 (1.9%)	3	3 (2.9%)
Myocardial infarction	0	0 (0.0%)	2	2 (1.9%)
Congestive heart failure	1	1 (0.9%)	2	2 (1.9%)
Pulmonary embolism	1	1 (0.9%)	2	2 (1.9%)
Stroke	0	0 (0.0%)	1	1 (0.9%)
Steal syndrome[4]	0	0 (0.0%)	1	1 (0.9%)
Embolization coil migration[5]	1	1 (0.9%)	1	1 (0.9%)
Arterial extravasation	1	1 (0.9%)	1	1 (0.9%)

Deep vein pseudo-aneurysm	1	1 (0.9%)	1	1 (0.9%)
Failure to create an AVF	1	1 (0.9%)	1	1 (0.9%)
Seroma	0	0 (0.0%)	1	1 (0.9%)
Mild paresthesia	1	1 (0.9%)	1	1 (0.9%)
Other[6]	19	12 (11.7%)	66	32 (31.1%)

1. 15/18 (83.3%) of occlusions at 90 days were successfully resolved. 20/25 (80.0%) of occlusions at 12 months were successfully resolved. Two subjects experienced a partial occlusion and a total occlusion, and are counted in the number of subjects for both types.
2. No deaths were adjudicated as related to the study device or procedure.
3. Infections unrelated to the access site included a toe infection (1), ischemic infection (1), AICD lead infection (1), hernia repair infection (1), infection of surgical wound (1), infected peritoneal dialysis catheter (1), and unspecified infections (2).
4. Steal syndrome related to surgical transposition error was successfully resolved.
5. Coil migrated to lungs during a maturation assistance procedure 28 days post-index procedure. AE was resolved and was asymptomatic.
6. Types and numbers of Other adverse events included: osteomyelitis (6), cellulitis (6), hyperkalemia (5), fall resulting in fracture/hematoma (4), hypoglycemia (3), pain (3), atrial flutter (2), COPD/asthma (2), clostridium difficile (2), incident hypertension, atrial thrombus, atrial fibrillation, cardiac A/V block, hypotension, cancer, aortic dissection, respiratory failure, pneumonia, bacteremia, tooth abscess, discitis, necrotic cholecystitis, peritonitis, gallstone pancreatitis, DIC, allergic reaction to contrast, hematoma at lower extremity, neurological reaction to under-dialysis, epistaxis, musculoskeletal injury, cephalic vein occlusion, hypotension hypoperfusion, DKA, PAD ischemia, apnea, intubation complications, elevated INR, diarrhea, herpes, low back pain, and nausea/vomiting.

Other Outcome Measures: Other selected outcome measures are reported below.

Study AVF Utilization

Table 14 below presents the total number of subjects who received 2-needle cannulation of their study AVF, the time to first 2-needle cannulation for hemodialysis, and estimated duration of AVF use in ITT subjects who were eligible for hemodialysis. Results are also stratified by dialysis status at the time of study enrollment (i.e. pre-dialysis or already on dialysis). Subjects were considered eligible for hemodialysis if they were recorded as being on hemodialysis, regardless of access site. Three (3) subjects who were on peritoneal dialysis but not on hemodialysis at the 6- and 12-month visits were not considered eligible for hemodialysis.

There were 71 subjects who achieved 2-needle cannulation out of a total 81 ITT subjects (87.7%) eligible for hemodialysis at any time during the study.

AVF time used was estimated using the first recorded 2-needle cannulation date and last recorded dialysis date using the study AVF for each subject at their final visit. AVF time used was not estimated for eight (8) ITT subjects who had undergone 2-needle cannulation because six (6) subjects did not attend any long-term (6- or 12-month) visits, and two (2) subjects reverted to central venous catheter (CVC) dialysis.

Of the 102 subjects who had an AVF created during the study, seven (7) access sites (6.9%) were abandoned after a mean of 101 days. The main reasons for abandonment were total occlusion of

the anastomosis or a target vessel that could not be reopened or central stenosis impeding the venous outflow.

Table 14: Study AVF Utilization for Hemodialysis – 12 Months

Parameter	Dialysis Status at Study Enrollment	# of Subjects Evaluated (N)	Mean (days)	Standard Deviation (days)	Median (days)	Min-Max (days)
Time to First 2-Needle Cannulation for Hemodialysis	Pre-Dialysis	16	162.9	86.6	140.5	53-345
	On Dialysis	55	100.2	51.9	82.0	34-224
	All Evaluable Subjects	**71**	**114.3**	**66.2**	**88.0**	**34-345**
Estimated # of Study Days AVF Used for Hemodialysis	Pre-Dialysis	15	184.5	99.6	203.0	10-319
	On Dialysis	48	242.0	64.4	247.5	84-471
	All Evaluable Subjects	**63**	**228.3**	**77.4**	**242.0**	**10-471**
Time to Access Site Abandonment[1]	N/A	7	101.4	125.5	56.0	1-355

1. Time to abandonment only calculated from the seven subjects whose access sites were abandoned.

Table 15 below shows CVC usage during the study. Of the 62 subjects who were on hemodialysis using the study AVF at the end of the study, nine subjects (14.5%) had no history of CVC use and went directly to hemodialysis using the Ellipsys AVF. A total of 48 subjects (77.4%) on hemodialysis with the study AVF at the end of the study had been on dialysis using a CVC at screening with a mean usage of 134 days before removal. Five subjects (8.1%) on hemodialysis with the study AVF at the end of the study required a CVC to start hemodialysis during the study, and all were initiated prior to 90 days and prior to maturation of the study AVF, with a mean CVC usage of 93.4 days.

Table 15: Central Venous Catheter (CVC) Usage During Study[1]

Hemodialysis Status at 12 Months	Parameter	# of Subjects Who Had CVC Present at Screening	# of Subjects Who Had CVC Initiated During Study	No CVC Use During Study
Subjects on hemodialysis using study AVF (N=62)	# of Subjects	48 (77.4%)	5 (8.1%)	9 (14.5%)
	Mean (Median) (study days used)[2]	134.4 (117.0)	93.4 (110.0)	N/A
	SD (study days used)	65.1	36.3	N/A
	Min – Max (study days used)	40-310	29-114	N/A
Subjects on hemodialysis with CVC (N=5)	# of Subjects	5 (100%)	0	0
	Mean (Median) (study days used)[2]	248.4 (184.0)	N/A	N/A
	SD (study days used)	157.2	N/A	N/A

	Min – Max (study days used)	100-467	N/A	N/A

1. Based on the number of subjects on hemodialysis at 12 months, regardless of access site (N=67).
2. "Study days used" was determined based on the first day of CVC usage in the study through the date of catheter removal or end of the study, whichever came first.

Study AVF Functionality

For the purposes of the study, a "functional" AVF was defined as an AVF being used for hemodialysis or an AVF that had venous patency and brachial artery inflow ≥ 350 mL/min. At the end of the 12-month study period, at least 61/103 ITT subjects (59.2%) had a functional AVF that was being used for hemodialysis. An additional 14/103 ITT subjects (13.6%) had a functional AVF that was not being used for hemodialysis. Of those 14 subjects, 13 (12.6%) were still pre-dialysis and one (1) subject (0.9%) was still dialyzing with a central venous catheter.

In total, at least 75/103 ITT subjects (72.8%) had an AVF that met the functional criteria at 12 months. An additional 11 subjects (10.7%) could not have their AVF functionality evaluated at 12 months because they exited the study after the 90 day primary endpoint evaluation and did not consent to 6- or 12-month follow-up, were lost to follow-up, or exited the study after 6 months. See Table 16 below for a summary of subjects' status at 12 months.

Table 16: Subject Status at 12 Months[1], ITT Population (N=103)

Status	End of Study n (%)
Subjects With Functional AVF at 12 Months:	
AVF functioning with no intervention	0
AVF functioning with intervention, no occlusion	56 (54.4)
AVF functioning with intervention after occlusion	5 (4.9)
Functional AVF not being used at 12 months[2]	14 (13.6)
Subjects Who Did Not Complete 12 Months or Had Non-Functional AVF at 12 Months:	
Primary Failure	6 (5.8)
Abandoned after initial function	2 (1.9)
Dead, functional AVF	2 (1.9)
Dead, non-functional AVF	0
Dead, AVF status unknown	1 (1.0)
Lost to follow-up, AVF status unknown	2 (1.9)
Exited study, functional AVF	0
Exited study, non-functional AVF	0
Exited study, AVF status unknown	1 (1.0)
Subjects Who Did Not Consent to Long-Term Follow-Up:	
Dead, functional AVF	1 (1.0)
Dead, non-functional AVF	0
Dead, AVF status unknown	4 (3.9)
Exited study, AVF status unknown	9 (8.7)

[1]Last known status of each subject.
[2]Includes subjects not yet on hemodialysis (9, including 1 subject who received a pre-emptive transplant), subjects who remained on PD (3) or CVC (1), and one subject who received a transplant and no longer requires dialysis.

Table 17 below summarizes the study subjects' functional access status through 12 months for all ITT subjects. Functional dialysis status at 12 months was determined by recording whether the subject was on dialysis, and if so, the primary access site was recorded (AVF, hemodialysis catheter, or other). In total, 61/103 (59.2%) of the ITT subjects were using the study AVF as their primary mode of dialysis access at 12 months.

When all subjects who were not yet on dialysis at 12 months but had a patent AVF were excluded, 61/89 (68.5%) subjects were on hemodialysis using the study AVF at 12 months. Note that this denominator includes all subjects who A) were not on hemodialysis at 12 months but their AVF was not patent, B) exited the study or were lost to follow-up before their 12 month visit, or C) died (regardless of AVF functionality at the time of death) as a conservative estimate.

Table 17: Status of AVF Access at 12 Months

Functional Access By Population	n (%)
ITT Population[1]	
First cannulation prior to 90-day visit	36/103 (35.0)
AVF used for hemodialysis 3 times prior to 90 day visit	31/103 (30.1)
Hemodialysis using AVF or revised AVF at 12 months	61/103 (59.2)
ITT Population, Excluding Subjects Not On Hemodialysis[2]	
First cannulation prior to 90-day visit	36/76 (47.4)
AVF used for hemodialysis 3 times prior to 90 day visit	31/76 (40.8)
Hemodialysis using AVF or revised AVF at 12 months	61/89 (68.5)

[1]Percentages calculated out of the full ITT population.
[2]Percentages calculated out of the ITT population, excluding subjects not on hemodialysis at the visit of interest, or not on hemodialysis at the time of death.

Ultrasound Blood Flow Evaluations

Clinical literature suggest that AVF blood flow values ≥ 2000 mL/min may be predictive of high-output cardiac failure.[1,2] Time-average mean-mean velocity (TAMMV) and time-average mean-peak velocity (TAMPV) ultrasound measurements of vessel blood flow were performed to evaluate any relationship between fistula blood flow rates and cardiac-related adverse events observed in the study. As shown in Table 18 below, TAMMV measurements appeared to level off at mean values < 1100 mL/min at 12 months. One (1) case of transient steal syndrome was observed after a surgical error during a transposition surgery and was successfully resolved.

Peak flow (TAMPV) values were analyzed to determine the relationship between any high-flow measurements and the onset of any cardiac-related adverse events. TAMPV values were analyzed instead of mean flow (TAMMV) values to provide a worst-case analysis and ensure all relevant study subjects were included. Overall, out of the 103 ITT subjects and 10 roll-in subjects, there were 15 subjects who experienced a TAMPV ultrasound flow rate > 2000 mL/min

[1] Basile C, Lomonte C, Vernaglione L et al. The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. Nephrol Dial Transplant 2008; 23: 282–287.
[2] Ye WL, Fang LG, Ma J et al. Long-term effects of arteriovenous fistula on cardiac structure and function in non-diabetic hemodialysis patients. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2013; 35: 95–101.

at one study visit (12 subjects) or more than one study visit (3 subjects). Of those 15 subjects, 11 (73.3%) did not experience steal syndrome or any adverse events that were determined to be cardiac-related by the Medical Monitor. Of the three subjects who experienced a cardiac-related adverse event (3/15 = 20%), the cardiac-related adverse events occurred before the high flow values were observed and/or the subjects had significant histories of cardiovascular disease. For one of the subjects with a cardiac-related adverse event, the event occurred between two study visits where flow rates of 1540 mL/min and 1149 mL/min were observed. As discussed above, the one (1/15 = 6.7%) observed case of steal syndrome was related to a transposition surgery and was successfully resolved.

Table 18: TAMMV Ultrasound Measurements of Vessel Flow (mL/min)[1]

Vessel		90 Days (N=103)	6 Months (N=49)	12 Months (N=77)
Brachial Artery Flow (mL/min)	ITT Subjects Evaluable (N)	99	49	77
	Mean (Median)	919.3 (849.9)	989.0 (983.8)	1089.7 (1077.3)
	SD	388.5	433.1	446.7
	Min-Max	41.6-2281.4	60-2277	79-2657
Cephalic Vein Flow (mL/min)	ITT Subjects Evaluable (N)	70	39	56
	Mean (Median)	631.9 (578.0)	746.6 (607.1)	815.1 (920.8)
	SD	314.0	417.4	410.5
	Min-Max	37.6-1805.2	343-2435	0-2277
Basilic Vein Flow (mL/min)	ITT Subjects Evaluable (N)	23	7	20
	Mean (Median)	860.8 (699.4)	1096.6 (994.1)	1084.8 (920.8)
	SD	586.8	258.9	899.8
	Min-Max	366.5-3058.6	792-1509	70-4343
Brachial Vein Flow (mL/min)	ITT Subjects Evaluable (N)	2	1	1
	Mean (Median)	1273.4 (1273.4)	706.8 (706.8)	421.8 (421.8)
	SD	79.0	N/A	N/A
	Min-Max	1217.5-1329.2	706.8-706.8	421.8-421.8

1. Mean flow (TAMMV) was estimated as follows: TAMMV = time average mean-peak velocity (TAMPV) * (0.57) as described in Rajan DK, Ebner A, Desai SB, et al. Percutaneous creation of an arteriovenous fistula for hemodialysis access. J Vasc Interv Radiol. 2015; 26:484-490.

Summary of Maturation Assistance and Maintenance Procedures (MAPs)

As noted in Table 12 above, the 90-day assisted maturation rate in the study was 82.5% and the 90-day unassisted maturation rate was 1.0%. Since the Ellipsys AVF may create multiple potential access vessels, a staged approach was taken where maturation assistance and maintenance procedures (MAPs) were performed to assist AVF maturation and maintain patency.

The three main situations that required MAPs included:

1) Salvage of low flow or occluded fistulae;
2) Second stage procedures to modulate and direct blood flow or transpose the vessel; and
3) Maintenance or restoration of AVF patency after target vessel maturation.

Many of the MAPs performed to direct blood flow included the implantation of embolization coils. In the ITT population, 97 embolization coils were placed in 66 subjects, equating to an average of 0.94 coils per ITT subject or 1.47 coils per subject receiving at least one coil. A total of 107 embolization coils were placed in a total of 71 subjects among the ITT population and 10 roll-in subjects (N=113 total subjects). All embolization coil placements were intended to direct flow from competing veins to promote maturation of the study AVF. Of the 107 coils, 49 were placed in the deep brachial veins to direct flow to the superficial outflow and 53 were branch ligations placed in more superficial veins. The remaining 5 coils were placed in the median basilic vein (3), perforating vein, and cephalic vein.

Definitions for MAP Analysis

- Surgical MAPs: vessel branch ligations or interventions such as elevation, transposition, or superficialization of the target vessel to facilitate placement of cannulation needles which occurs only after the vessel has matured.

- Percutaneous MAPs: endovascular interventions intended to A) redirect blood flow by increasing the flow in the target vessel by percutaneous transluminal angioplasty (PTA), stenting, or valvuolotomy or B) decrease the flow in non-target vessels by coil embolization, banding, or branch ligation. The most commonly performed MAP was PTA of the study anastomosis and/or outflow vessels.

- Maturation Procedures:
    - Subjects requiring hemodialysis: MAPs performed to increase or direct blood flow sufficiently to mature the target vessel in subjects requiring hemodialysis, prior to the first 2-needle cannulation.
    - Subjects who were not yet on hemodialysis: MAPs that occurred before the primary endpoint definition for maturation of the target vessel was met.

- Maintenance Procedures:
    - Subjects requiring hemodialysis: MAPs performed on or after the day of the first 2-needle cannulation for hemodialysis, intended to treat the effects of cannulation on the access vein.
    - Subjects not yet on hemodialysis: MAPs performed after the subject met the primary endpoint definition for maturation of the target vessel.

Tables 19 and 20 below shows the mean number of MAPs that were required during the first 90 days and cumulatively during the study. In the ITT population, 99/103 subjects (96.1%) had MAPs to mature and maintain the AVF throughout the study. The remaining four subjects

included three total occlusions within 24 hours of the index procedure leading to AVF abandonment and one subject in whom a fistula was not created.

Most of the MAPs occurred during the first 90 days, as 98/103 subjects (95.1%) required an average of 2.2 MAPs during the first 90 days. Among the ITT population, 7/103 subjects (6.7%) required a total of 7 MAPs (one MAP per subject) at the same time as the index procedure. A total of 18/103 subjects (17.5%) required a total of 18 MAPs (one MAP per subject) within 24 hours of the index procedure.

Table 19: MAPs During First 90 Days, ITT Population

Type of MAP	# of Subjects (%)	Mean (Median) # of MAPs	SD # of MAPs	Min-Max # of MAPs
Percutaneous MAPs	96 (93.2%)[2]	1.9 (2.0)	1.0	1-5
Percutaneous and/or Surgical MAPs[1]	98 (95.1%)[2]	2.2 (2.0)	1.0	1-5
All ITT Subjects	103	2.0 (2.0)	1.1	0-5

1. Surgical MAPs in the first 90 days consisted of transpositions of mature access vessels.
2. One subject (0.9%) with a patent AVF did not require any MAPs during the first 90 days. An additional four subjects (3.9%) did not require any MAPs because they either did not have an AVF created successfully or their AVF occluded completely during the first 24 hours after the procedure.

Table 20: Cumulative MAPs Through Last Study Visit, ITT Population

Type of MAP	Parameter	Maturation MAPs	Maintenance MAPs	Total MAPs
Percutaneous MAPs	# of Subjects (%)	96 (93.2%)	24 (23.3%)	96 (93.2%)
	Mean (Median) # of MAPs	2.0 (2.0)	1.8 (1.0)	2.4 (2.0)
	SD # of MAPs	1.0	1.4	1.6
	Min-Max # of MAPs	1-6	1-7	1-9
Surgical MAPs	# of Subjects (%)	31 (30.1%)	7 (6.8%)	38 (36.9%)
	Mean (Median) # of MAPs	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)
	SD # of MAPs	0.2	0.0	0.2
	Min-Max # of MAPs	1-2	1-1	1-2
Percutaneous and/or Surgical	# of Subjects (%)	98 (95.1%)	29 (28.2%)	99 (96.1%)

MAPs	Mean (Median) # of MAPs	2.3 (2.0)	1.7 (1.0)	2.7 (2.0)
	SD # of MAPs	1.1	1.5	1.7
	Min-Max # of MAPs	1-6	1-8	1-10

Tables 21 and 22 below show the number of subjects stratified by the number and types of MAPs required to mature the access vein and to maintain a patent access site with adequate flow for cannulation during the study.

In general, most subjects (88/103 = 85.4%) required 1-3 MAPs to achieve maturation with 36.9% requiring two procedures. Most subjects (94/103 = 91.3%) required ≤ 1 MAP to maintain patency of a mature AVF, with 74/103 (71.8%) requiring none at all during the study.

Table 21: Number of Procedures per Subject Through Last Study Visit, ITT Population

Parameter	# of Subjects with Maturation MAPs (%)	# of Subjects with Maintenance MAPs
N/A – Not eligible for MAPs[1]	4 (3.9%)	0 (0.0%)
0 procedures	1 (1.0%)	74 (71.8%)
1 procedure	25 (24.3%)	20 (19.4%)
2 procedures	38 (36.9%)	5 (4.9%)
3 procedures	25 (24.3%)	2 (1.9%)
4 procedures	6 (5.8%)	0 (0.0%)
5 procedures	2 (1.9%)	1 (1.0%)
6 or more procedures	2 (1.9%)	1 (1.0%)

1. Four subjects from the ITT cohort did not have any MAPs because they either did not have an AVF successfully created or the AVF was abandoned within 24 hours of the index procedure due to total occlusion of the AVF.

Table 22: Types and Incidence of MAPs Through Last Study Visit, ITT Population

Type of MAPs	# of Subjects with Maturation MAPs (N=103)			# of Subjects with Maintenance MAPs (N=103)		
	# of MAPs	# of Subjects[1]	% of Subjects	# of MAPs	# of Subjects[1]	% of Subjects
Surgical MAPs	**32**	**31**	**30.1%**	7	7	**6.8%**
Transposition	18	18	17.5%	3	3	2.9%
Transposition – Surgical Revision	6	6	5.8%	1	1	1.0%
Surgical Revision	4	4	3.9%	2	2	1.9%
Flow Direction	3	3	2.9%	1	1	1.0%
Other[2]	1	1	1.0%	0	0	0.0%
Percutaneous MAPs	**190**	**96**	**93.2%**	**42**	**24**	**23.3%**
PTA	91	64	62.1%	31	20	19.4%
PTA – Flow Direction	63	54	52.4%	2	2	1.9%
Flow Direction	32	27	26.2%	2	2	1.9%
PTA – Stent	2	2	1.9%	5	4	3.9%
PTA – Stent – Flow Direction	2	2	1.9%	0	0	0.0%
Stent	0	0	0.0%	1	1	1.0%
Other[3]	0	0	0.0%	1	1	1.0%

1. Number of subjects with one or more procedures of a given type. Subjects may appear in more than one category.
2. One subject received a surgical PTA + stent.
3. One subject received a catheter embolectomy.

Analysis of Adverse Events Associated with MAPs

An analysis was performed to determine any association between MAPs performed to promote maturation or maintain patency of the AVF during the study and adverse events (AEs). The analysis covered all subjects' study participation from the completion of the study procedure through last follow-up visit for each subject. To determine this relationship, all AEs that occurred within one month of a MAP procedure were reviewed to determine if they were associated with that procedure, and a complete listing of all study AEs was then reviewed to determine if there were any outliers.

Table 23 below presents the MAPs that had associated AEs for the ITT population. Out of a total of 271 MAPs, 256 of them (94.5%) did not have any associated AEs and 15 MAPs (5.5%) had associated AEs. Of the 39 surgical MAPs performed, five of them (12.8%) had associated AEs. Of the 232 percutaneous procedures, 10 (4.3%) had associated AEs.

As discussed above, a total of 107 embolization coils were placed in a total of 71 subjects among the 113 total subjects from the ITT and roll-in populations. One AE was reported to be associated with a coil embolization procedure. In this AE, a coil did not deploy completely and migrated distally due to fistula blood flow. No clinical sequelae were reported and the AE was adjudicated as non-serious.

Table 23: MAPs and Associated AEs During Study, ITT Population

Parameter	# of MAPs Through Last Study Visit
Total # of MAPs	**271**
With No Associated AEs	256/271 (94.5%)
With Associated AEs	15/271 (5.5%)
Total Surgical MAPs	**39**
With No Associated AEs	34/39 (87.2%)
With Associated AEs	5/39 (12.8%)
Transposition	2
Transposition – Surgical Revision	2
Other[1]	1
Total Percutaneous MAPs	232
With No Associated AEs	222/232 (95.7%)
With Associated AEs	10/232 (4.3%)
Flow Direction	1
PTA	7
PTA – Flow Direction	1
Stent	1

1. One subject received a surgical PTA + stent.

Analysis of AVF Patency and Relationship with MAPs

Patency of the study AVF was evaluated among the ITT population. For the purposes of this patency analysis, the following definitions were used:

- Primary Patency: the interval from the time of access placement until any intervention designed to maintain or reestablish patency, access thrombosis, access abandonment, or the time of measurement of patency.
    - As discussed below, primary patency was analyzed two ways. In one analysis, embolization coils counted as interventions designed to maintain or reestablish patency. In the other analysis, embolization coils did not count as interventions designed to maintain or reestablish patency.

- Assisted Primary Patency: the interval from the time of access placement until access thrombosis, access abandonment, or the time of measurement of patency.

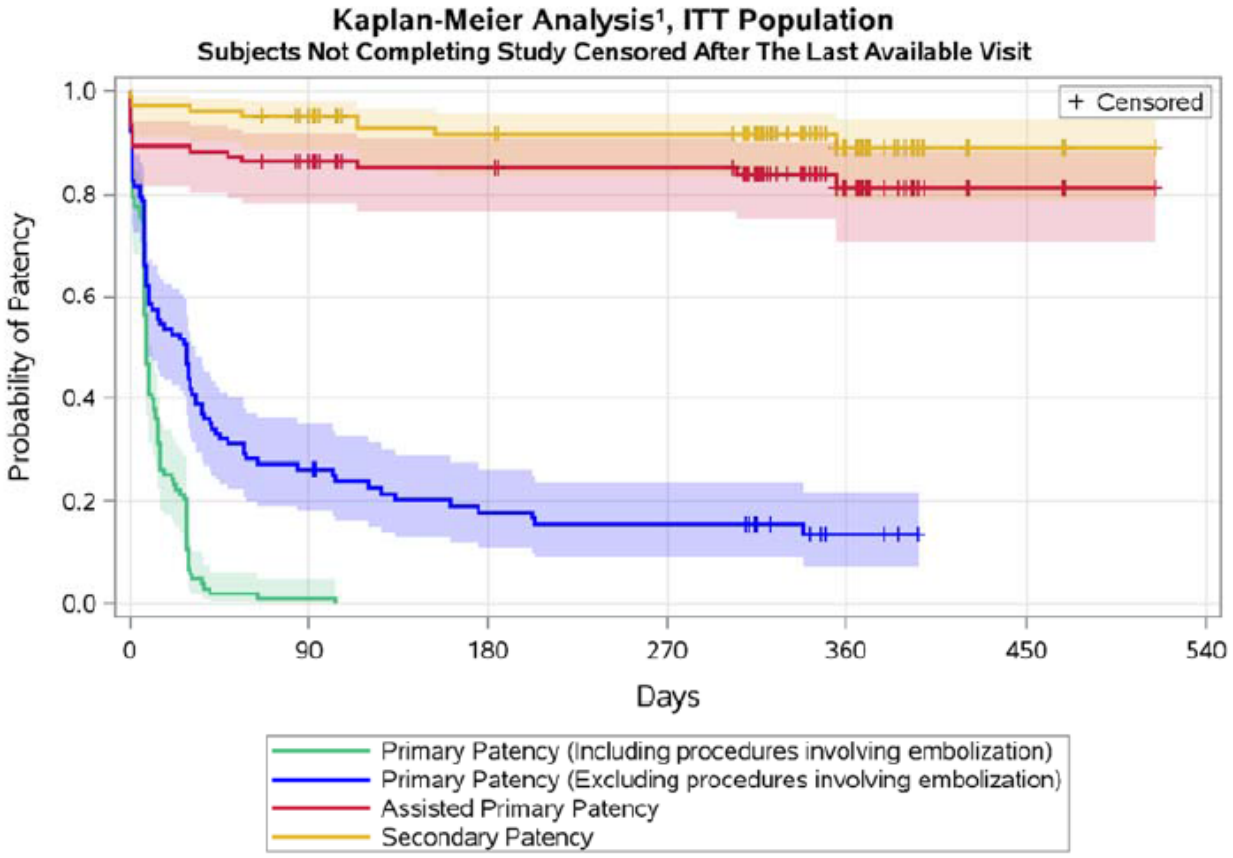
- Secondary Patency: The interval from the time of access placement until access abandonment, or the time of measurement of patency.

Primary patency was achieved in 1/103 subjects (1.0%) at 90 days. If procedures involving embolization coils to divert blood flow and assist maturation were excluded from the primary patency analysis, the primary patency rate was 26% at 90 days and 14% at 12 months. Assisted primary patency and secondary patency were 81% and 89% at 12 months, respectively.

Figure 7 and Table 24 below summarize the Kaplan-Meier analysis of patency rates for the ITT population, with 95% confidence intervals represented by shaded regions and subjects censored after the last available visit if they did not complete the study.

If subjects who did not complete the study were counted as patency failures after their last study visit, the primary patency (excluding procedures involving embolization coils), assisted primary patency, and secondary patency were 11%, 65%, and 72% at 12 months respectively.

Figure 7: Kaplan-Meier Analysis of Patency



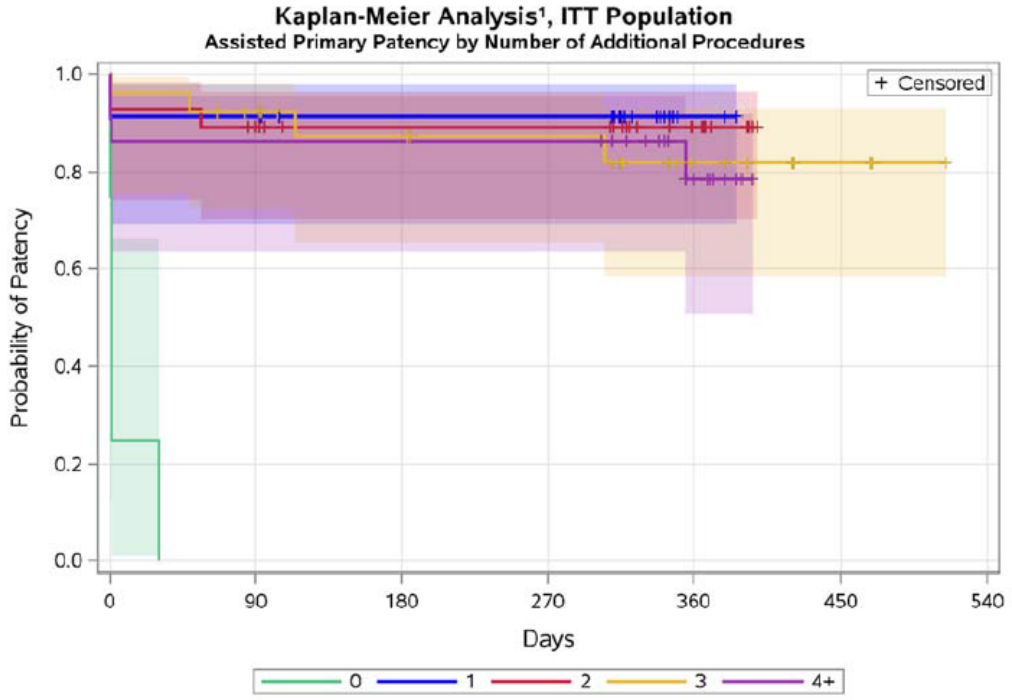
[1] *Pointwise confidence limits are displayed for the survival curves.*

Table 24: Life Table for Patency, ITT Population

		Days						
Patency Type		**0**	**90**	**180**	**270**	**360**	**450**	**540**
Primary Patency (Including procedures involving embolization)	No. at Risk	103	1	0				
	Prob. of Patency	0.92	0.01					
	Standard Error	0.03	0.01					
Primary Patency (Excluding procedures involving embolization)	No. at Risk	103	27	15	13	3	0	
	Prob. of Patency	0.92	0.26	0.18	0.15	0.14		
	Standard Error	0.03	0.04	0.04	0.04	0.04		
Assisted Primary Patency	No. at Risk	103	86	72	70	26	3	0
	Prob. of Patency	0.93	0.86	0.85	0.85	0.81	0.81	
	Standard Error	0.02	0.03	0.04	0.04	0.04	0.04	
Secondary Patency	No. at Risk	103	95	78	76	30	3	0
	Prob. of Patency	0.99	0.95	0.92	0.92	0.89	0.89	
	Standard Error	0.01	0.02	0.03	0.03	0.04	0.04	

The assisted primary patency rate at one year was 91% for subjects with one MAP, and the assisted primary patency rate decreased as the number of MAPs increased. For subjects with 4 or more MAPs, the assisted primary patency rate at one year was 79%. Secondary patency at one year ranged from 91% to 100% for subjects with one or more MAPs. Figure 8 and Table 25 below show the rates of assisted primary patency at one year stratified by the number of MAPs performed throughout the study, with shaded areas indicating the 95% confidence intervals. Subjects with zero MAPs throughout the study were primary failures; one subject who achieved primary patency at 90 days is not included in the "0 MAP" category because they received a MAP at a later timepoint.

Figure 8: Kaplan-Meier Analysis of Assisted Primary Patency, by # of MAPs Throughout Study



[1] *Pointwise confidence limits are displayed for the survival curves.*

Table 25: Life Table for Assisted Primary Patency, by # of MAPs

No. of Procedures		Days 0	90	180	270	360	450	540
0	No. at Risk	4	0					
	Prob. Of Patency	0.75						
	Standard Error	0.22						
1	No. at Risk	23	21	16	16	2	0	
	Prob. Of Patency	0.91	0.91	0.91	0.91	0.91		
	Standard Error	0.06	0.06	0.06	0.06	0.06		
2	No. at Risk	28	24	19	19	8	0	
	Prob. Of Patency	0.93	0.89	0.89	0.89	0.89		
	Standard Error	0.05	0.06	0.06	0.06	0.06		
3	No. at Risk	26	22	18	16	7	3	0
	Prob. Of Patency	1.00	0.92	0.87	0.87	0.82	0.82	
	Standard Error	0.00	0.05	0.07	0.07	0.08	0.08	
4+	No. at Risk	22	19	19	19	9	0	
	Prob. Of Patency	0.91	0.86	0.86	0.86	0.79		
	Standard Error	0.06	0.07	0.07	0.07	0.10		

Conclusions: The clinical study demonstrated that there is a reasonable assurance of safety and effectiveness that the Ellipsys System creates an arteriovenous fistula that can mature as a method of vascular access for hemodialysis. A fistula was successfully created in 99.0% of subjects and 89.3% of subjects met the primary endpoint success criteria for fistula maturation at 90 days. The rate of SAEs related to the device and/or procedure through 12 months was 1.9%, and the primary safety endpoint was met. The Ellipsys AVF was used for hemodialysis for an estimated average of 228.3 days out to 12 months, among study subjects who were on hemodialysis and evaluable at 12 months. At least 72.8% of subjects had a functional AVF at 12 months. Primary patency was only achieved in 1.0% of subjects at 90 days, as an average of 2.7 additional procedures (or MAPs) were required to assist fistula maturation or maintain mature AVFs. The majority of the MAPs included PTA of the anastomosis to improve blood flow and embolization coil implantation to direct blood flow to the target vein(s). However, 94.5% of the MAPs were not associated with any adverse safety events, and the assisted primary patency rate at 12 months was 81%.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

POSTMARKET EVALUATION

A postmarket evaluation will be required to collect data on the long-term safety and effectiveness of the Ellipsys System in U.S. patients who have chronic kidney disease, need hemodialysis, and are candidates for the creation of an arteriovenous fistula with the Ellipsys System.

LABELING

The Ellipsys System labeling consists of Instructions for Use, a user manual, and packaging labels. The Instructions for Use include the indications for use; a description of the device,

contraindications, warnings, precautions; a detailed summary of the clinical data collected in support of the device; a list of potential adverse events; a shelf life; the expertise needed for the safe use of the device; and instructions for the safe use of the device. The labeling satisfies the requirements of 21 CFR 801.109.

Please see the Limitations section above for important contraindications, warnings and precautions presented in the device labeling.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a percutaneous catheter for creation of an arteriovenous fistula for hemodialysis access and the measures necessary to mitigate these risks.

Table 26: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	**Mitigation Measures**
Unintended vascular or tissue injury	Non-clinical performance testing Animal testing Clinical performance testing Labeling
Adverse hemodynamic effects	Non-clinical performance testing Animal testing Clinical performance testing Labeling
Failure to create a durable fistula that is usable for hemodialysis	Animal testing Clinical performance testing
Use of the device adversely impacts future vascular access sites	Clinical performance testing Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Infection	Sterilization validation Shelf life testing Labeling
Electrical malfunction or interference leading to electrical shock, device failure, or inappropriate activation	Non-clinical performance testing Electrical safety testing Electromagnetic compatibility (EMC) testing
Software malfunction leading to device failure or inappropriate activation	Software verification, validation, and hazard analysis

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the percutaneous catheter for creation of an arteriovenous fistula for hemodialysis access is subject to the following special controls:

1. Clinical performance testing must evaluate:

a. The ability to safely deliver, deploy, and remove the device;
b. The ability of the device to create an arteriovenous fistula;
c. The ability of the arteriovenous fistula to attain a blood flow rate and diameter suitable for hemodialysis;
d. The ability of the fistula to be used for vascular access for hemodialysis;
e. The patency of the fistula; and
f. The rates and types of all adverse events.

2. Animal testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be assessed:
    a. Delivery, deployment, and retrieval of the device;
    b. Compatibility with other devices labeled for use with the device;
    c. Patency of the fistula;
    d. Characterization of blood flow at the time of the fistula creation procedure and at chronic follow-up; and
    e. Gross pathology and histopathology assessing vascular injury and downstream embolization.

3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    a. Simulated-use testing in a clinically relevant bench anatomic model to assess the delivery, deployment, activation, and retrieval of the device;
    b. Tensile strengths of joints and components;
    c. Accurate positioning and alignment of the device to achieve fistula creation; and
    d. Characterization and verification of all dimensions.

4. Electrical performance, electrical safety, and electromagnetic compatibility (EMC) testing must be performed for devices with electrical components.

5. Software verification, validation, and hazard analysis must be performed for devices that use software.

6. All patient-contacting components of the device must be demonstrated to be biocompatible.

7. Performance data must demonstrate the sterility of the device components intended to be provided sterile.

8. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

9. Labeling for the device must include:
    a. Instructions for use;
    b. Identification of system components and compatible devices;
    c. Expertise needed for the safe use of the device;

d. A detailed summary of the clinical testing conducted and the patient population studied; and
e. A shelf life and storage conditions.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in the clinical study described above. Types of harmful events include stenosis at the arteriovenous anastomosis, thrombus or occlusion at the anastomosis, steal syndrome, embolization coil migration, pulmonary embolism, arterial extravasation, deep vein pseudo-aneurysm, mild paresthesia, infection, venous stenosis, infiltration, hemorrhage, hematoma, and death. Through the 12-month duration of the clinical study, the rate of device-related harmful events was 0%, the rate of serious procedure-related harmful events was 2/103 (1.9%), and the rate of non-serious harmful events was 53/103 (51.5%). There were no deaths adjudicated as related to the device or procedure. A total of 25 occlusion events were observed in 19 subjects (17.5%); for 15 of these 19 subjects (78.9%) the occlusion event occurred within 24 hours of the study procedure, and 20/25 (80%) of the occlusions were successfully resolved.

The probable benefits of the device are also based on nonclinical laboratory and/or animal studies as well as data collected in the clinical study as described above. The 90-day maturation success rate, defined as the rate of access sites intended for dialysis needle cannulation with venous diameter ≥ 4 mm and blood flow ≥ 500 ml/min as measured by duplex ultrasound, was 92/103 (89.3%). Out of a total of 81 subjects eligible for hemodialysis at any time during the study, 71 subjects (87.7%) achieved 2-needle cannulation of the AVF. Among 63 subjects who were evaluable for AVF utilization, the AVF was used for an estimated 228.3 study days (at 12 months) on average. At least 75/103 subjects (72.8%) had a functional AVF at 12 months. Primary patency was only achieved in 1.0% of subjects at 90 days, as an average of 2.7 additional procedures were required to assist fistula maturation or maintain mature AVFs. The assisted primary patency rate at 12 months was 81%.

Additional factors to be considered in determining probable risks and benefits for the Ellipsys System include: The device requires a staged maturation approach with additional procedures such as PTA and embolization of non-target veins to assist maturation. Despite the high rate of additional procedures, 94.5% of them were not associated with any adverse events. Fistula flow rates at 12 months appeared to fall below 1200 mL/min on average, and cardiac-related adverse events appeared to be related to underlying cardiovascular disease rather than high blood flow. For subjects who were on dialysis with a central venous catheter (CVC) at the time of enrollment, the duration of CVC exposure after the index procedure was comparable to the duration of CVC exposure for surgical AVFs.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for the creation of an arteriovenous fistula in patients with chronic kidney disease who need hemodialysis, the probable benefits outweigh the probable risks for the Ellipsys System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Ellipsys Vascular Access System is granted and the device is classified under the following:

Product Code: PQK
Device Type: Percutaneous catheter for creation of an arteriovenous fistula for hemodialysis access
Class: II
Regulation: 21 CFR 870.1252