# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Stent Graft, Infrapopliteal, Venous Arterialization

Device Trade Name: LimFlow™ System

Device Product code: QWN

Applicant's Name and Address: LimFlow Inc.
3031 Tisch Way
110 Plaza West
San Jose, CA 95128

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P220025

Date of FDA Notice of Approval: 9/11/2023

Breakthrough Device: Granted breakthrough device status under the Expedited Access Pathway (EAP) on October 3, 2017 for treating critical limb ischemia by minimally invasively creating an arterio-venous bypass graft to produce the venous arterialization procedure in the below-the-knee vasculature.

## II. INDICATIONS FOR USE

The LimFlow System is indicated for patients who have chronic limb-threatening ischemia with no suitable endovascular or surgical revascularization options and are at risk of major amputation.

## III. CONTRAINDICATIONS

The LimFlow System is contraindicated in the following:

- Patients with deep venous thrombus in target vein.
- Patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LimFlow System labeling.

## V. DEVICE DESCRIPTION

The LimFlow System is comprised of self-expanding conical and cylindrical nitinol stents of varying lengths, covered with an electrospun PTFE covering (BioWeb™), four

radiopaque tantalum markers on the stent graft ends (Figure 1), and is loaded onto a delivery system for deployment (Figure 2 ). The device is introduced percutaneously through a commercially available sheath into the femoral artery.

The LimFlow System should be used with the following LimFlow devices when performing the Transcatheter Arterialization of the Deep Veins (TADV) procedure:

- LimFlow Venous Catheter (K222083)
- LimFlow Arterial Catheter (K221541)
- LimFlow Valvulotome (K221902)

The stent is offered in both cylindrical and conical shapes with varying stent lengths and diameters, which are listed in Table 1 where "X" indicates the available stent configuration.

**Table 1: Stent Size Matrix**

| Stent Design | Stent diameter (nominal) [mm] | Working length (nominal) [mm] | | | |
|---|---|---|---|---|---|
| | | 60 | 100 | 150 | 200 |
| Conical | 3.5-5.5 | X | | | |
| | 4.0-5.5 | X | | | |
| Cylindrical | 5.5 | X | X | X | X |

Conical stents are used to form the arteriovenous connection whereas cylindrical stents are used to extend the stent graft down to the ankle.

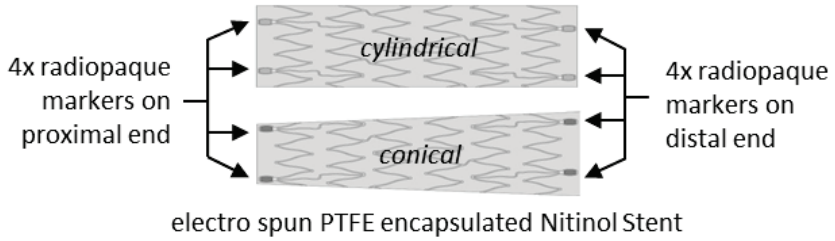



**Figure 1: LimFlow Stent Graft Cylindrical (above) and Conical (below)**

The stent graft is supplied pre-mounted between the inner catheter and the outer sheath on the distal end of the endovascular system. In this compressed configuration, the Nitinol stent struts lie close together and the radiopaque markers appear as a contiguous band at each end of the stent graft. The stent is deployed using a handle which features a knob that is activated by the user, as shown in Figure 2.

The features of the handle delivery system are as follows:

- Usable length of the delivery system: 120 cm.
- Crossing profile of delivery device: 7F.
- 0.018" guidewire compatible

- Radiopaque markers located at the device tip; proximal and distal stent pocket markers; and four markers on each end of stent graft.

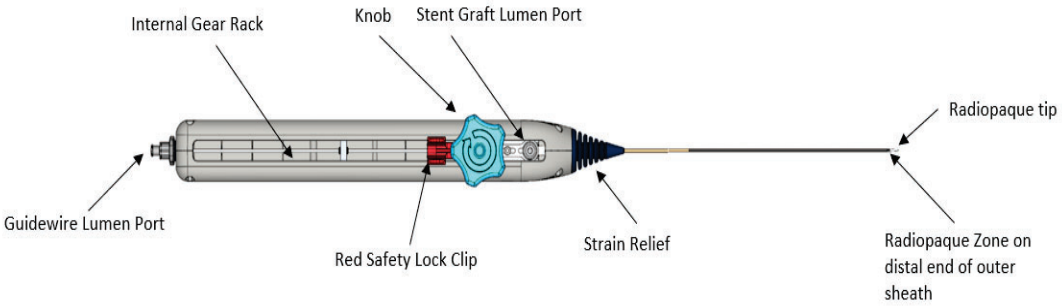



**Figure 2: LimFlow Handle Delivery System**

Handle mechanism (Figure 2): The proximal side of the Handle delivery system consists of a knob that translates rearward during deployment and retracts the outer sheath while the inner tubing is stationary. During delivery of the implant to the target site, unintended stent movement is restricted by the safety clip until the physician is prepared to deploy. During the deployment, forward (distal) motion of the sheath is prevented by means of a mechanism that only permits further rearward motion of the outer sheath once deployment has been initiated. The distal aspect consists of the outer tubing, containing the loaded stent graft, and the inner catheter which includes the guidewire lumen, distal and proximal radiopaque markers, and atraumatic distal tip. Coaxial to the guidewire lumen is the midlayer, which serves to permit stent deployment as the outer tubing is retracted. The two ports on the handle help facilitate flushing of the guidewire and stent graft lumens prior to the procedure.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

Patients indicated to receive the LimFlow System for treatment have no suitable endovascular or surgical revascularization options and are at risk of major amputation. These patients may have had repeated percutaneous procedures (e.g., atherectomy, angioplasty) to open the below the knee vessels and/or a failed surgical distal bypass. Unresolved ischemia (lack of blood circulation to the foot), can lead to tissue necrosis with concomitant risk of infection (including sepsis), requiring major amputation. Major amputation has its own advantages and disadvantages, including high mortality and morbidity. A patient should fully discuss these alternatives with his/her physician to select the method that may be most appropriate for them.

## VII. MARKETING HISTORY

At the time of this approval, The LimFlow system with the Handle Delivery system has not been marketed in the United States or any foreign country. The previous generation of the LimFlow System with the Pin & Pull delivery system has been commercially available outside the United States since October 2018 in the following countries: Austria, Czech Republic, Denmark, France, Germany, Ireland, Italy, Netherlands,

Switzerland, and the United Kingdom. The LimFlow System with the Pin & Pull delivery system has also been available via Special Access in Mexico, New Zealand, and Singapore. The LimFlow System with the Pin & Pull delivery system has not been withdrawn from commercial use for any reason related to its safety or effectiveness.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of the device are listed below.

- Allergic response
- Arterial / venous occlusion
- Arterial / venous thrombosis requiring further procedures
- Arteriovenous fistula (unplanned)
- Bleeding / oozing from puncture site requiring blood transfusion
- Bruising at wound site
- Compartment syndrome
- Congestive cardiac failure
- Contrast-induced nephropathy and renal failure
- Death
- Device failure / malfunction
- Edema
- Embolization (air, tissue, device)
- Hematoma
- Infection
- Inflammatory response
- Intimal tear / dissection
- Lower extremity ischemia
- Occlusion of the stent graft
- Perforation of vessel wall
- Peripheral nerve injury
- Pseudoaneurysm
- Requirement for major amputation of index limb
- Retroperitoneal bleeding
- Systemic infection, sepsis
- Vascular injury requiring repair
- Vasospasm
- Vasovagal response
- Wound dehiscence
- Wound site pain

For the specific adverse events that occurred in the clinical study, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Biocompatibility

Biocompatibility testing on the materials used in the LimFlow System was performed following the recommendations provided in International Organization for Standardization (ISO) 10993, *Biological Evaluation of Medical Devices*, FDA's Guidance, *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems,* and FDA's Guidance, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*, *September 10 2020*.

The components of the stent graft and delivery system were categorized per ISO 10993-1:2018, *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process* based on the intended duration and contact with or within the body. The stent grafts were categorized as an implant device with permanent exposure (> 30 days) to circulating blood, and the delivery systems were categorized as external communicating devices with limited contact (≤ 24 hours) with circulating blood.

Specific biocompatibility tests were performed based on the categorization of the stent graft and delivery system in accordance with ISO 10993-1, *Biological Evaluation of Medical Devices*. Tables 2 and 3 provide a listing of the tests performed for both the delivery system and implant, along with the corresponding results. All biocompatibility tests were conducted in accordance with the Good Laboratory Practices (GLP) per 21 CFR, Part 58.

**Table 2: Delivery System Biocompatibility Testing**

| Biological Endpoint | Test Method | Results |
|---|---|---|
| Cytotoxicity | Growth Inhibition Test in L929 Mouse Fibroblasts Using ISO elution method | Non-cytotoxic |
| Skin Sensitization | Maximization Sensitization test on Guinea Pigs | Non-sensitizing |
| Irritation | Intracutaneous Irritation test on Rabbits | Non-irritating |
| Acute Systemic Toxicity | Acute Systemic Toxicity on mouse | Non-systemically toxic |
| Material mediated Pyrogenicity | Pyrogen test on rabbits according to European Pharmacopeia and USP <151> | Non-pyrogenic |
| Hemocompatibility | ASTM Hemolysis, Direct and Indirect | Non-hemolytic |
| | Thrombogenicity: Thromboplastin Time (PTT) | No impact on the Unactivated Partial Thromboplastin Time |
| | Complement Activation Assay C3a | Not a complement activator |
| | Complement Activation Assay SC5b-9 | Not a complement activator |

**Table 3: LimFlow Stent Graft Biocompatibility Testing**

| Biological Endpoint | Test Method | Results |
|---|---|---|
| Cytotoxicity | Growth Inhibition Test in L929 Mouse Fibroblasts Using ISO elution method | Non-cytotoxic |
| | ISO MTS Cytotoxicity test | Non-cytotoxic |
| Skin Sensitization | Maximization Sensitization test on Guinea Pigs | Non-sensitizing |
| Irritation | Intracutaneous Irritation test on rabbits | Non-irritating |
| Acute Systemic Toxicity | Acute Systemic Toxicity on mouse | Non-systemically toxic |
| Material-Mediated Pyrogenicity | Pyrogen test on rabbits according to USP <151> | Non-pyrogenic |
| Hemocompatibility | ASTM Hemolysis, Direct and Indirect | Non-hemolytic |
| | Complement Activation Assay, C3a | Not a complement activator |
| | Complement Activation Assay, SC5b-9 | Not a complement activator |
| | Thrombogenicity: Thromboplastin Time (PTT) and Platelet Leukocyte Count (PLC) | No impact on the Unactivated Partial Thromboplastin Time and platelet / leukocyte counts similar to control |
| Subchronic / Chronic Systemic Toxicity | Subcutaneous Implantation study – 13 weeks | Non-systemically toxic |
| Implantation | Intra-muscular Implantation study – 13 weeks | Non-irritating |
| | Intra-muscular Implantation study – 4 weeks | Non-irritating |
| Genotoxicity | Bacterial Reverse Mutation Test | Non-mutagenic |
| Physicochemical characterization | Chemical characterization of volatile organic compounds, semi-volatile organic compounds, nonvolatile organic compounds and toxicological risk assessment | Extractable levels not expected to pose concerns for genotoxicity, systemic toxicity, or carcinogenicity |

For the delivery system, *in vivo* thrombogenicity was leveraged from the GLP safety study. For the implant, *in vivo* thrombogenicity was leveraged from the GLP safety study. Implantation, subchronic toxicity, and chronic toxicity were also leveraged from the GLP safety study. Genotoxicity and carcinogenicity were leveraged from the chemical characterization analysis and toxicological risk assessment.

## B. Bench Testing

*In vitro* bench testing was conducted as part of the design verification and validation to support the safety and effectiveness of the LimFlow System and is consistent with FDA *Non-Clinical Tests and Recommended Labeling of Intravascular Stents and Associated Delivery Systems, April 18, 2010* and its addendum, *Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, August 30, 2013*. The bench test results are summarized in Table 4.

**Table 4**: **Summary of *In Vitro* Bench Testing**

| Test | Purpose/Objective | Acceptance Criteria | Results |
|---|---|---|---|
| **Stent Engineering Testing** | | | |
| Material Composition | To verify the chemical composition of the stent graft components | Stent frame must comply to ASTM F2063-18 (Nitinol) and radiopaque markers to ASTM F560-17 (Tantalum). Electrospun PTFE encapsulation material must be identified and comply with LimFlow specifications | Pass |
| Shape Memory and Superelasticity | To ensure Austenite Finish Transition Temperature (Af) meets the required specification and mode of action | The Af temperature 20 ± 5°C for the nitinol implant, measured in accordance with ASTM F2082-15 | Pass |
| Stent Corrosion Resistance | To assess pitting corrosion resistance of the implant per ASTM F2129-17 pre-fatigue and evaluate the potential for fretting, pitting and crevice corrosion post fatigue for intended implant duration in overlapped configuration | Eb ≥ 300mV for pitting corrosion pre-fatigue<br><br>Characterization only - No evidence of corrosion, cracking, or other defects post fatigue with scanning electron microscopy (SEM) and light optical microscopy (LOM) | Pass |
| Mechanical Properties | To characterize the mechanical properties of nitinol stent material and generate a Fatigue Strain Limit diagram to support stress/strain and fatigue analysis | Characterization only - The tested nitinol stent material must exhibit a tensile stress at yield, elongation, and tensile stress at maximum load that is acceptable for the intended use | Mechanical properties were successfully characterized |
| Dimensional Verification - Implant | To verify that critical implant dimensions (outer diameter and length) are met post-deployment under simulated physiological conditions | Total length:<br>59.0 ± 1.0 mm for 60 mm stent grafts<br>201.5 ± 2.0 mm for 200 mm stent grafts<br><br>Outer diameter should be ± 0.5 mm of the nominal diameter for all configurations | Pass |
| Percent Surface Area | To characterize the implant's base stent percent free surface area (not including the covering) | Characterization only study | The percent surface area was determined |
| Foreshortening | To quantify the change in length of the implant from its crimped to deployed condition | Foreshortening must be ≤ 5% | Pass |
| Integrity (post-deployment) | To verify that the implant shows no defects that would render it unsuitable for the intended use post deployment | No through holes per the specification. No bent or broken struts | Pass |

| Test | Purpose/Objective | Acceptance Criteria | Results |
|---|---|---|---|
| Radial Resistive Force (RRF) and Chronic Outward Force (COF) | To determine RRF and COF generated by the stent at the clinically relevant diameter | Across all stent sizes and RVDs the radial force normalized over the stent length shall be:<br><br>Radial Resistive Force:<br>Min: 0.30 N/mm<br><br>Chronic Outward Force :<br>Max: 0.61 N/mm | Pass |
| Particulate evaluation | To evaluate and characterize the particulate counts of the LimFlow system | Characterization purposes only;<br>- particle size ≥ 10µm: ≤ 12 particle/mL<br>- particle size ≥ 25µm: ≤ 2 particle/mL | Pass |
| Strain and Fatigue Analysis/Finite Element Analysis (FEA) | To locate and determine the critical stresses and/or strains within the stent due to manufacture, deployment and worst case in vivo loading by means of a Finite Element Analysis. The calculation of Safety Factor (SF) and determination of worst case conditions for accelerated durability testing was also performed | The stent must demonstrate acceptable fatigue safety performance using a Constant Life fatigue analysis | Pass |
| Accelerated Durability / Radial Pulsatile Fatigue | To evaluate the durability (maintenance of structural integrity) of the implant under radial pulsatile fatigue conditions simulating 10 years of use in an overlapped condition | The implant must exhibit acceptable simulated 10-year durability.<br>No type 3 or 4 fractures. No signs of fretting corrosion and no cracks which could impact stent integrity. No type II holes, detached encapsulation material, or bent markers. | Pass |
| Accelerated Durability / Crush Fatigue | To characterize the behavior of the implant when subjected to worst-case cyclic crush fatigue conditions simulating 10 years of use | The implant must exhibit acceptable simulated 10-year durability.<br>No type 3 or 4 fractures. Radial Resistive Force and Chronic Outward Force post durability testing must remain within limits. | Pass |
| MRI Safety and Compatibility | To assess the safety and compatibility of the stent in the MRI environment | The stent shall be MR conditional to 1.5 and 3 Tesla. | The results show that the stent may be labelled as MR Conditional in accordance ASTM F2053 |

| Test | Purpose/Objective | Acceptance Criteria | Results |
|---|---|---|---|
| Radiopacity | To evaluate the radiopacity of the implant and catheter delivery system under fluoroscopy | The delivery system and stent must be visible under fluoroscopy | Pass |
| Crush Resistance | To evaluate the ability of the implant to resist permanent deformation for a load applied perpendicular to the longitudinal axis of the device in a flat-plate condition | Post-test diameter is within ±10% of diameter prior to test | Pass |
| Kink Resistance | To determine if the implant can withstand a worst-case bend radius for the stent graft | The implant must not kink when bent around a circular mandrel with the worst-case bend radius. The implant must recover its original size and shape after test | Pass |
| **Delivery System Engineering Testing** | | | |
| Dimensional Verification – Delivery System | To verify the effective length, shaft inner and outer diameter, and crossing profile of the delivery system | Usable catheter length = 1205 mm (± 5 mm)<br>Maximum crossing profile ≤ 2.60 mm<br>Tip length: 14.0 mm (± 0.5 mm) | Pass |
| Flexibility / Kink Resistance | To verify the catheter delivery system is able to reliably track through tortuous, clinically relevant anatomy without kinking | The system must not kink during delivery, deployment, or withdrawal to and from the target deployment site in a clinically relevant anatomical model.<br>The radius of the endovascular system must be characterized at the point at which the endovascular system starts to kink. | Pass |
| Delivery, Deployment and Retraction | To assess the delivery system in a simulated use environment with respect to compatibility of delivery system with accessory devices, ability to deliver the implant at the intended location, deploy the implant, deployment force and accuracy, stent graft conformability, retraction of the delivery system, and delivery system, device, and accessory integrity | The endovascular system must be advanced and retracted through a clinically relevant anatomical model, and implants must be deployed into a clinically relevant landing zone.<br><br>The deployment force must be ≤ 40 N during simulated use in a clinically relevant anatomical model.<br><br>Deployment accuracy within ±5 mm<br><br>System must also withdraw from model and pass visual inspection including stent apposition/conformability post deployment. | Pass |

| Test | Purpose/Objective | Acceptance Criteria | Results |
|---|---|---|---|
| | | Implants must be evaluated to various deployment configurations and compatible with accessory devices representative of those clinically used for the procedure. | |
| Torque Strength | To determine the rotations of the delivery system without failure of the tip, tubing, or other components when clamped at the distal tip | The delivery system shall be able to withstand a minimum of 2 rotations without failure of the tip, tubing, or other components when clamped at the distal tip | Pass |
| Bond Joint Strength | To determine the bond strength of the joints and/or fixed connections of the delivery system and verify that the strength of the bond joints are adequate for the intended use | The delivery system must have sufficient strength to maintain its function during access, deployment, and retraction per ISO 25539-1. | Pass |

## C. Animal Testing

Several studies were performed to evaluate the *in vivo* performance of the LimFlow System. Follow-up time-points were acute and at 28, 90, and 180 days. A marketed endovascular stent graft with approved indications in other anatomies was used as a comparator control to help determine a baseline understanding of the safety and performance. The animal model tolerated implantation of the devices with no attenuation of patency over time. Histological analysis revealed full endothelialization and integration of the stent struts by 180 days. Both stent grafts showed minimal neointimal response, absence of vessel wall injury and minimal to mild inflammatory response in the treated vascular tissues at chronic timepoints in the animal model demonstrating the safety and no long-term inflammation risk for the LimFlow System.

Table 5 summarizes the results of three studies conducted on finished, sterile devices. The results of the animal studies support the safety and performance of the device.

**Table 5**: **Summary of Animal Studies**

| Study Type | Number of Stent Grafts / Number of Animals / Location | Testing Summary |
|---|---|---|
| Acute device performance and safety, GLP compliant, in Yorkshire swine | 9 study devices / 6 pigs / external iliac artery | All devices met acceptance criteria for device performance for delivery and deployment (13 parameters in total).<br>The test articles received a thrombogenicity score of 0; no thrombus present.<br>PASS |
| Chronic study (30d, 90d), safety and performance, non GLP-compliant, in sheep | 16 study devices, 10 control articles / 18 sheep / carotid artery | Test articles and control devices remained patent at 90 days.<br>All target organs were macroscopically normal.<br>The local tissue tolerance (histopathology) of all stent grafts were within expected ranges.<br>No delamination or stent calcification were noted.<br>Advanced neointimal coverage of stent was observed for the LimFlow Stent Grafts.<br>PASS |
| Chronic study (28d, 90d, 180d), safety and performance, GLP-compliant, in sheep | 15 study devices, 15 control articles / 15 sheep / carotid artery | Test articles and control devices remained patent at 180 days.<br>The local tolerance of the test article was within expected ranges and comparable to the control article.<br>Endothelialization of the neointima was complete 180 days after implantation for the test article.<br>Non target organs contained no relevant microscopic findings.<br>Delivery, accuracy and deployment were scored acceptable.<br>PASS |

## D. Sterilization

The LimFlow System is a single-use device that is sterilized with ethylene oxide gas and distributed sterile to the end user. Sterilization and validation have been conducted in accordance with AAMI/ANSI/ISO *11135-1:2007 "Sterilization of Health Care Products – Ethylene Oxide – Part 1: Requirements for the Development, Validation, and Routine Control of Ethylene Oxide Sterilization Process for Medical Devices* to ensure a Sterility Assurance Level (SAL) of $10^{-6}$.

### E. Packaging and Shelf Life

The packaging qualification and device verification testing was performed for the LimFlow System at baseline and on product aged to 1 year. The packaging validation included a visual assessment, dye penetration testing, determination of pin-holes, and seal tensile strength testing to demonstrate that the packaging system was able to maintain a sterile barrier after exposure to temperature, distribution conditioning, and accelerated aging. A shelf life of 1 year has been established based on product and packaging shelf-life testing.

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (PROMISE II) to establish reasonable assurance of safety and effectiveness of the LimFlow System using the Transcatheter Arterialization of the Deep Veins (TADV) procedure for treating no-option patients with chronic limb-threatening ischemia (CLTI) by creating an arteriovenous connection in the below-the-knee vasculature in the United States under IDE #G160156. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

### A. Study Design

Patients were treated between December 2019 and March 2022. The database for this PMA reflected data collected through September 2022 and included 105 patients. There were 20 investigational sites.

The PROMISE II Study was a prospective, single-arm, multi-center pivotal study conducted in the United States designed to confirm the safety and effectiveness of the LimFlow System in a no-option CLTI population. The study was designed to consist of a minimum of 60 and up to 120 subjects. This study utilized a Bayesian Goldilocks adaptive design for sample size determination. Following a series of interim analyses, a total of 105 subjects were enrolled.

The subjects were reviewed by an independent committee of vascular surgeons to determine eligibility based on a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit. Wound photography was assessed by an independent wound core lab at all follow-up visits, and patency (via duplex ultrasound) was assessed by an independent imaging core lab at 1-month and 6-months. An independent Clinical Events Committee (CEC) reviewed and adjudicated any endpoint events such as amputations, renal sequelae, re-interventions, stent occlusions, and subject deaths. A Data Monitoring Committee (DMC) acted in an advisory capacity to the Sponsor in the monitoring of participant safety and evaluation of the progress of the study.

The primary safety and effectiveness endpoint was Amputation-Free Survival (AFS), which was defined as freedom from major (above ankle) amputation and death, at six months compared to a historical performance goal. This was evaluated using a Bayesian

method in which the six-month AFS rate was assigned a uniform prior distribution and mathematically updated after observing binary six-month outcomes; subjects with incomplete follow-up were included in the final analysis via Bayesian multiple imputation. By design, subjects without death or major amputation who had incomplete follow-up had their unknown final outcome repeatedly imputed with subject-specific probabilities of having an event dependent on the subject's amount of event-free follow-up time. The imputation model followed a Bayesian piecewise exponential survival model fitted to the full dataset for all subjects; results of the many "filled-in" or "completed" datasets were then combined into a single posterior probability of success.

The criterion of trial success was a posterior probability of at least 0.977 that the true six-month AFS exceeds an objective performance goal of 54.0%. The threshold of 0.977 was pre-specified to control the study's false positive rate at the level 0.025, as demonstrated in extensive pre-trial simulations. The primary endpoint was analyzed using the methods described above. All secondary endpoint analyses were conducted using frequentist methods and descriptive statistics.

1. Key Clinical Inclusion and Exclusion Criteria

Enrollment in the PROMISE II study was limited to patients who met the following key inclusion criteria:

- Clinical diagnosis of chronic limb-threatening ischemia, defined as any of the following clinical assessments: previous angiogram or hemodynamic evidence of severely diminished arterial inflow of the index limb (e.g., ABI ≤ 0.39, TP / TcPO2 < 30 mm Hg) and
    - Rutherford Classification 5, ischemic ulceration or
    - Rutherford Classification 6, ischemic gangrene
- Subject had been assessed by the Principal Investigator, reviewed by the Independent Review Committee (IRC), and it had been determined that no conventional distal bypass surgical or endovascular therapy for limb salvage was feasible due to either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could have been used for autogenous vein conduit.
- Subjects requiring dialysis were included, provided they met all the following requirements at time of screening:
    - On dialysis for > 6 months
    - Autologous arteriovenous fistula or peritoneal access used for hemodialysis
    - Serum albumin > 30 g/liter
    - BMI > 20

Patients were not permitted to enroll in the PROMISE II study if they met any of the key following exclusion criteria:

- Concomitant hepatic insufficiency, thrombophlebitis in the target limb, or non-treatable coagulation disorder within the 90 days prior to study index procedure
- Life expectancy less than 12 months.
- Severe heart failure (e.g., NYHA Class IV).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at the following timepoints post-procedure: 2-weeks, 1-month, 3-months, 6-months, 9-months, 12-months, 24-months, and 36-months. An additional visit for duplex ultrasound only was performed at 2-months post-procedure. Table 6 below lists the preoperative evaluations and post-operative parameters assessed for specific visits. Adverse events and complications were recorded at all visits.

## Table 6: Study Assessment Schedule

| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline and Screening (-6M to proc) | Treatment (Day 0) to Discharge | 2 Weeks (+/- 3 Days) | 1 Month (+/-1 week) | 2 Month (+/- 2 weeks) | 3 Month (+/- 2 weeks) | 6 Month (+/- 2 weeks) | 9 Month (+/- 2 weeks) | 1 Year (+/- 4 weeks) | 2 Year (+/- 4 weeks) | 3 Year (+/- 4 weeks) |
| Written Informed Consent | √ | | | | | | | | | | |
| Baseline imaging[1] that establishes pedal artery target | √ | | | | | | | | | | |
| Inclusion / Exclusion criteria, including IRC, assessment that subject is not a candidate for conventional surgical or endovascular limb salvage procedures | √ | | | | | | | | | | |
| Demographic data, medical history, medication review, physical exam, and pregnancy test (if applicable) | √ | | | | | | | | | | |
| Additional exams if required to confirm eligibility[2] | √ | | | | | | | | | | |
| Pedal vein assessment for case planning | √ | | | | | | | | | | |
| Review of medications / dual anti-platelet regimen[3] | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ |
| Rutherford Classification (RCC) | √ | | | √ | | √ | √ | √ | √ | √ | √ |
| WIfI Classification (ischemia measured via $TcPO_2$[4] or Toe Pressure) | √ | | √ | √ | | √ | √ | √ | √ | √ | √ |
| Wound healing assessment, and photographs[5] | √ | | √ | √ | | √ | √ | √ | √ | √ | √ |
| Wound culture, if suspected infection[6] | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ |
| Pulse evaluation via hand-held continuous wave Doppler distal to the stent graft[7] | | √[8] | √ | √ | | √ | √ | √ | √ | √ | √ |
| Serum Creatinine | √ | | | √ | | | √ | | | | |
| Numeric Pain Scale Rating (1-10) | √ | | | √ | | √ | √ | √ | √ | √ | √ |
| Procedural angiogram[8] and device performance data | | √ | | | | | | | | | |
| Procedure time, defined from sheath insertion to final catheter removal | | √ | | | | | | | | | |
| Fluoroscopy and Contrast for the index procedure | | √ | | | | | | | | | |
| Device- or procedure-related AE and SAEs[9,10] | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Assessment of amputation and/or re-intervention of the Stent Graft | | | √ | √ | | √ | √ | √ | √ | √ | √ |
| Duplex Ultrasound Exam to assess Stent Graft patency[11] | | | | √ | √ | √ | √ | √ | √ | √ | √ |
| All-cause mortality | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

[1] E.g., an angiogram without procedure or angiogram from a failed recanalization
[2] Including an MRI, if there is suspected osteomyelitis and bypass conduit vein mapping if there is a pedal artery target and the ipsilateral saphenous vein has not been previously harvested
[3] Dual antiplatelet therapy (DAPT) is recommended for 3 months post-procedure. At a minimum, all subjects are recommended to be started on DAPT at least one week before procedure or adequately pre-loaded with DAPT as per institution practice.
[4] $TcPO_2$ will be measured at 2 constant points on the dorsum of the midfoot through the 12-month follow-up at sites who perform $TcPO_2$.
[5] Prior to any re-intervention of the stent graft, an angiogram/image and wound photograph should be obtained for adjudication purposes.
[6] Optional; Sponsor will reimburse for culture any time there is a suspected infection.
[7] Hand-held continuous wave Doppler will be performed immediately post-procedure and again between 4 and 30 hours post-procedure to assess for acute thrombosis; any findings of acute thrombosis in this time frame must be reported to the Sponsor within 24 hours of the exam.
[8] Must include pre- and post-index arteriogram showing vasculature from hip to foot
[9] Review of any hospitalizations or procedures involving the index limb, and/or potentially related to the device or procedure; all SAEs through 6 months. For subjects out of area or who refuse to come in for a visit, a telephone assessment should be conducted to capture as much information as possible at the time point.
[10] If any LimFlow device is introduced but stent-graft implantation is either not attempted or unsuccessful, subjects will be followed for safety for 30 days with a minimum of phone calls to assess AFS.
[11] May be performed at any additional non-study visit as standard of care, as indicated by clinical symptoms.

3. Clinical Endpoints

The primary safety and effectiveness endpoint was Amputation-Free Survival (AFS) defined as freedom from major (above ankle) amputation and death at 6 months compared to a historical performance goal.

Subgroup analysis of the primary endpoint was included in the study with the following pre-specified sub-groups:

- Sex (Male/Female)
- Dialysis status (Yes/No)
- Age ($\leq 70$, $> 70$
- Diabetes (Type I/Type II, None)
- Race/Ethnicity
- Rutherford Classification

The secondary endpoints were:

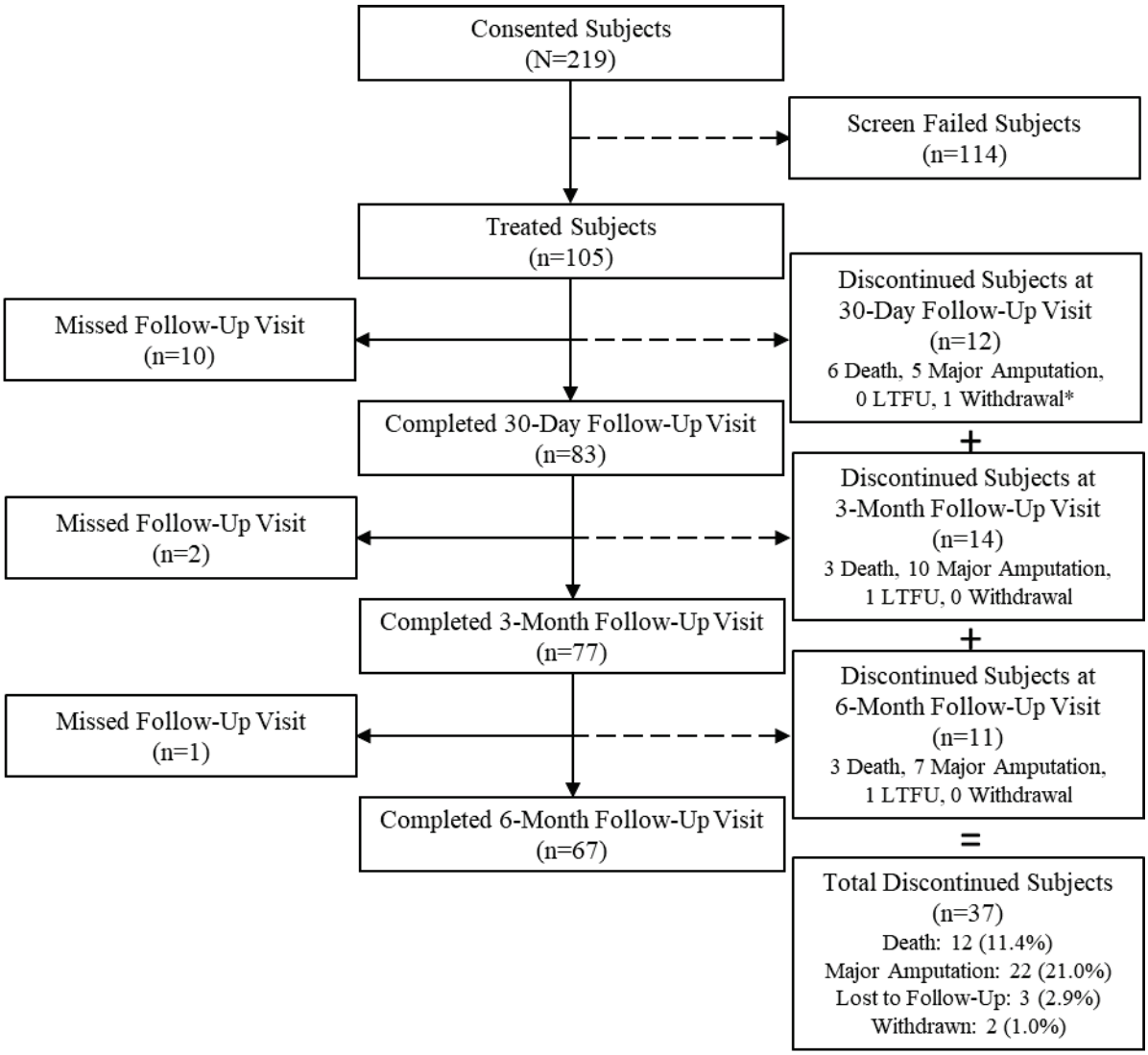
- Primary Patency: Defined as absence of occlusion of the endovascular intervention that is maintained without the need for additional or secondary surgical or endovascular procedures, at 30 days and 6 months. Analysis of patency endpoints was carried out with a review of duplex ultrasound imaging as well as adverse events.
- Primary Assisted Patency: Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred, at 30 days and 6 months.
- Secondary Patency: Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures after occlusion occurs, at 30 days and 6 months.
- Limb Salvage: Defined as percentage of subjects with freedom from above-ankle amputation of the index limb, evaluated at 30 days, 3 months, and 6 months.
- Change in Rutherford Classification: Defined as a change of one class or greater, as evaluated at 30 days, 3 months, and 6 months.
- Technical Success: Defined as the successful creation of an arteriovenous fistula in the desired limb location with immediate morphological success, based on angiographic outcomes.
- Procedural Success: Defined as the combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention of the stent graft at 30 days.
- Target Wound Healing: Defined as complete healing of the patient's target wound as evaluated at 30 days, 3, 6, 9 months, and 1 year . All wound analysis was performed by an independent wound core lab.

- All Wound Healing: Defined as complete healing of the patient's wounds as evaluated at 30 days, 3, 6, 9 months, and 1 year.
- All Wound Area Reduction: Defined as reduction in area of the patient's wounds as evaluated at 30 days, 3, 6, 9 months, and 1 year.
- Freedom from Contrast-Induced Nephropathy: Defined as subjects without acute (within 72 hours after intravenous contrast administration) impairment of renal function, measured as an absolute ≥ 0.5 mg/dL (44 μmol/L) increase compared to baseline serum creatinine value that results in a value above the upper limit of the normal range.
- Procedure Time: Defined as the time of the first puncture (venous or arterial) to when the last catheter is removed.
- Radiation Exposure: Defined as patient radiation exposure (in milligray) during the procedure.
- Contrast Volume: Defined as the total volume of contrast media (in milliliters) given during the procedure.

With regard to safety, adverse events (AE) were reported by sites for Seriousness and then processed by MedDRA coding with System Organ Class (SOC) and Preferred Term (PT) by a medical monitor. They were evaluated further for unanticipated adverse device effect (UADE) status by the medical monitor.

## B. Accountability of PMA Cohort

At the time of database lock, 105 patients were enrolled in the PMA study. One subject did not receive the device, and four subjects withdrew or were lost-to-follow-up before the 6-month post-operative visit. The patient disposition for the PROMISE II study is provided in Figure 3. The population included in determination of the PROMISE II Trial primary endpoint was all members of the Modified Intent-To-Treat Population (mITT) available for follow-up at the 6-month time point. The mITT population was defined as all subjects where a LimFlow device was introduced into the patient, regardless of technical or procedural success or major protocol deviation. Study subjects will remain in this study through 3-year follow-up unless they exit either (a) prematurely due to withdrawal of consent to continue or (b) at the point they reached the primary study endpoint of AFS (either major above-ankle amputation or death). It should be noted that post-primary analysis, a subject was found to have expired after study withdrawal by an investigator but prior to completion of 30-day follow-up.




*Post-primary analysis, subjects was found to have expired after being withdrawn from the study by the investigator
LTFU: lost to follow-up

**Figure 3: PROMISE II Subject Accountability**

## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed on CLTI patients. The study population's baseline key demographics and medical history are reported in Tables 7 and 8.

**Table 7: Key Subject Baseline Demographics**

| | N=105 |
|---|---|
| Age, years (SD) | 69.0 (10.4) |
| Sex, male | 68.6% 72/105 |
| Race | |
| Asian | 1.9% 2/105) |
| Black or African descent | 15.2% 16/105 |
| Caucasian | 61.0% 64/105 |
| Declined to state | 21.9% 23/105 |
| Ethnicity | |
| Hispanic or Latino | 27.6% 29/105 |
| Not Hispanic or Latino | 72.4% 76/105 |
| BMI (SD) | 26.2 (5. 32) (N=104[1]) |
| Smoking history (current or past smoker) | 41.9% 44/105 |
| Past smoker, not current | 36.2% 38/105 |
| Current smoker | 5.7% 6/105) |
| Never smoked | 58.1% 61/105 |

[1] BMI was not captured in one subject. Throughout the report data are presented with transparency to the denominator in cases where there are subjects in which the specific data point/assessment was not performed/available

**Table 8: Subject Medical History and Baseline CLTI Status**

| Characteristic | N=105 |
|---|---|
| Diabetes | 77.1% 81/105 |
| Type I | 13.6% 11/81) |
| Type II | 86.4% 70/81) |
| Chronic Kidney Disease (CKD) | 39.0% 41/105 |
| Dialysis | 18.1% 19/105 |
| Autologous arteriovenous fistula | 63.2% 12/19) |
| Peritoneal dialysis | 36.8% 7/19) |
| Hypertension | 91.4% 96/105 |
| Hyperlipidemia | 69.5% 73/105 |
| Prior MI | 22.9% 24/105 |
| Prior stroke | 8.6% 9/105) |
| Hepatic insufficiency | 3.8% 4/105) |
| Prior deep vein thrombosis | 3.8% 4/105) |
| Heart Failure | 20.0% (21/105) |
| Prior intervention to target limb | 74.3% 78/105 |
| Baseline Rutherford Class 6 | 35.2% 37/105 |
| Baseline Rutherford Class 5 | 64.8% 68/105 |

The participants in the PROMISE II trial represented the expected ratio of men to women. The median age of the study population was 70, which is consistent with available CLTI registry data typical of the patient population in the United States for this disease.[1,2,3,4] The proportion of Black, Hispanic, or Latino patients enrolled was slightly higher (42.8%) than the same racial and ethnic compositions reported in the general United States population. The proportion of Black, Hispanic, or Latino study participants is congruent with the distribution found in other CLTI-focused trials.[5] The PROMISE II study is representative of the United States patient population with CLTI.

## D. Safety and Effectiveness Results

### 1. Procedural Outcomes

Technical success, defined as successful creation of an arteriovenous fistula in the desired limb location with immediate morphological success was achieved in 104 cases resulting in a 99.0% technical success rate. There was one case of technical failure in 105 treated subjects, which occurred when venous arch wiring was not possible, therefore valvulotomy and stenting did not occur.

Procedural success was defined as a composite endpoint accounting for a combination of technical success as well as an absence of all-cause death, above-ankle amputation, or clinically-driven major reintervention of the stent graft through 30 days. As procedural success considers follow-up through 30 days, any subject who exited the study for non-endpoint purposes was excluded from the analysis. Procedural success was achieved in 76.9% of the 104 subjects available for follow-up or who reached the procedure failure endpoint prior to 30 days. The key procedural characteristics are provided in Table 9.

**Table 9: Key Performance and Procedure Data**

| Characteristic | N=105 |
|---|---|
| Technical Success[1] | 104/105 (99.0% |
| 30-day Procedural Success[2] | 80/104 (76.9% |
| Procedure time, mean (range)[3] | 217.1 minutes (84.0 – 576.0) |
| Total radiation exposure, mean (range) | 267.0 milligray (10.2 – 1615.0) |
| Contrast volume, mean (range) | 137.7 mL (5.0 – 490.0) |

[1] Technical Success was defined as: percentage of subjects with completion of the endovascular procedure and immediate morphological success.
[2] Procedural Success was defined as: percentage of subjects with combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention of the stent graft at 30 days.
[3] Defined as successful arterial or venous puncture (whichever was done first) to removal of last catheter

### 2. Safety Results

The analysis of safety was based on the mITT cohort of 105 patients available for the 6-month evaluation. The key safety outcomes for this study are presented in Table 10.

**Table 10: Key Safety Results**

| Characteristic[1] | |
|---|---|
| 30-day Mortality[2] | 6/99 (6.1%) |
| 6-month Mortality[2] | 12/80 (15.0%) |
| 30-day Major Amputation (Below-knee) | 5/98 (5.1%) |
| 3-month Major Amputation (Below-knee) | 15/94 (16.0%) |
| 6-month Major Amputation (Below-knee) | 23/91 (25.3%) |
| Freedom from contrast-induced nephropathy through 72 hours post-procedure | 103/105 (98.1% |

[1] All denominators represent the subjects available for follow-up to that time point plus any subject who experienced that event prior to a premature exit, where applicable.
[2] One additional subject was found to have expired after being withdrawn from the study by an investigator 5 days following the study procedure. The Post-Hoc analysis in Table 20 accounts for this patient death.

Events during the first 30-days post-procedure were considered procedure related, so the 6 deaths, 5  4.8%  major amputations, and 2 (1.9%) events of contrast-induced nephropathy were adjudicated to be procedure related.

There were 12 deaths within the 6-month time period in the PROMISE II study. Table 11 lists the deaths reported in the study and the reported cause of death. No deaths were adjudicated to be device-related per CEC.

**Table 11: Subject Deaths through 6 Months[1]**

| Days on Study | Cause of Death |
|---|---|
| 2 | Cardiac arrest |
| 3 | Cardiac arrhythmia |
| 5 | COVID-19 |
| 9 | Cardiac arrest |
| 21 | COVID-19 |
| 21 | Cardiopulmonary arrest, pneumonia |
| 47 | Sequelae of unspecified cerebrovascular disease |
| 83 | End-stage renal disease |
| 89 | Sepsis |
| 103 | Unknown |
| 148 | Congestive cardiac failure |
| 155 | COVID-19 with multiorgan system failure |

[1] One additional subject was found to have expired after being withdrawn from the study by an investigator 5 days following the study procedure.

**Adverse effects that occurred in the PMA clinical study:**

All study adverse events (AE) were reported by sites for Seriousness and then processed by MedDRA coding with System Organ Class (SOC) and Preferred Term (PT) by a medical monitor. They were evaluated further for unanticipated adverse device effect (UADE) status by the medical monitor.

Device- and procedure-relatedness was assessed by the study CEC for any events that required adjudication (study endpoint-qualifying events). All adverse events occurring within 30 days of the procedure were, by CEC charter definition, considered procedure-related during adjudication and are listed in Table 12. There were no events labelled by the independent medical monitor as unanticipated adverse device effects in the study. As CLTI patients typically have many comorbidities and unrelated adverse events, serious adverse events listed in the following two tables are focused on site-reported adverse events within 30 days post-procedure and serious adverse events through 6 months.

**Table 12: Site-reported Adverse Events through 30 days**

| Event Type | All events | |
|---|---|---|
| | During Procedure N=105 | Post-Procedure N=105 |
| Amputation of the index limb (major)[1] | 0/105 (0.0%) | 6/105 (5.7%) |
| Arterial or venous occlusion[2] | 0/105 (0.0%) | 2/105 (1.9%) |
| Arterial/Venous thrombus formation | 0/105 (0.0%) | 3/105 (2.9%) |
| Access site bleeding or hematoma requiring reintervention | 0/105 (0.0%) | 0/105 (0.0%) |
| Congestive cardiac failure | 0/105 (0.0%) | 1/105 (1.0%) |
| Contrast-induced nephropathy and renal failure | 0/105 (0.0%) | 2/105 (1.9%) |
| Death[3] | 0/105 (0.0%) | 6/105 (5.7%) |
| Infection (local) | 0/105 (0.0%) | 11/105 (10.5%) |
| Infection (systemic, sepsis)[4] | 0/105 (0.0%) | 3/105 (2.9%) |
| Lower extremity ischemia | 0/105 (0.0%) | 5/105 (4.8%) |
| Pseudoaneurysm | 0/105 (0.0%) | 1/105 (1.0%) |
| Target limb or wound pain requiring intervention | 0/105 (0.0%) | 17/105 (16.2% |
| Other[5] | 3/105 (2.9%) | 35/105 (33.3%) |

[1] Major amputation is defined as above-ankle amputation of the index limb.
[2] Complete absence of flow on color Doppler, or absence of sound and/or waveform by bedside doppler, and/or absence of flow on angiographic images (conventional or CT).
[3] Post-primary analysis, a subject was found to have expired after being withdrawn from the study by the investigator. Including this event changes the death rate to 7/105 6.7% .
[4] Post-primary analysis, an additional case of sepsis was documented. Including this event changes the sepsis rate to 4/105 (3.8% .
[5] Other refer to single events such as headache, anxiety, or vomiting.

There were no device-related events that occurred during the index procedure. CEC-adjudicated device-related adverse events over time are presented in Table 13 with data presented as cumulative incidence of events over time. Due to the nature of reinterventions occurring multiple times in one subject, the total count of events is also presented. All events were adjudicated conservatively as device-related if the device involvement could not be ruled-out. Any occlusion that extended to the area of stenting – regardless of the origin of occlusion – was automatically adjudicated as device-related. Similarly, any reintervention performed which touched a LimFlow stented area of vessel was also adjudicated as device-related.

**Table 13: Device and Procedure-Related Site-reported Adverse Events through 6-months**[1]

| **Device-Related Event** | **30 days** | **3 month** | **6 month** |
|---|---|---|---|
| Subjects through timepoint | 104 | 103 | 102 |
| Death (number / device related) | 6/0 | 9/0 | 12/0 |
| Major Amputation (rate)[2] | 3/104 (2.9%) | 7/103 (6.8% | 9/102 (8.8%) |
| Site-reported occlusion or reintervention (occlusive or non-occlusive) | | | |
| Count of events[4] | 21 | 46 | 63 |
| Patients with any event (rate) | 18/104 (17.3%) | 35/103 (34.0%) | 44/102 (43.1%) |
| Occlusion (no intervention) | | | |
| Count of events[4] | 1 | 3 | 6 |
| Patients with event (rate) | 1/104 (0.1% | 2/103 (1.9%) | 6/102 (5.9%) |
| Reintervention of the stent graft | | | |
| Count of occlusive events[4] | 14 | 29 | 39 |
| Count of non-occlusive events[4] | 6 | 14 | 18 |
| Patients with any reintervention (rate) | 18/104 (17.3%) | 33/103 (32.0%) | 41/102 (40.2%) |
| **Procedure-Related Event[3]** | | | |
| Death (number / procedure related) | 6/6 | -- | -- |
| Major Amputation (rate) | 5/104 (4.8%) | -- | -- |
| Contrast-Induced Nephropathy | 2/104 (1.9%) | -- | -- |

[1] Denominator includes all patients not lost to follow-up or withdrawn.
[2] Major amputation is defined as above-ankle amputation of the index limb.
[3] Per the Safety Charter, if events were deemed to be device-related, it superseded procedure-relatedness, and no further adjudication was completed for procedure-relatedness. If, however, the event was deemed as unrelated to the study device, procedure-relatedness was adjudicated. All adjudicated adverse events occurring within 30 days of the procedure were by default, procedure-related
[4] Note: Count of events includes all events, even if multiple events occurred in the same patient

The rates of adverse events seen in the study are in line with expectations for this high-risk population which has many comorbidities, and events align with the underlying baseline risk factors and medical history for this population. Investigators were allowed to report clinical experiences associated with standard wound care even if the protocol did not require reporting. Serious adverse events that occurred in >5% of patients are presented in Table 14**.**

**Table 14: Subjects with Serious Adverse Events through 6 months[1]**

| Serious Adverse Events | n/N (%) where N=105 |
|---|---|
| Death[2] | 12/105 (11.4%) |
| Gastrointestinal hemorrhage | 5/105 (4.8%) |
| Incision site impaired healing | 6/105 (5.7%) |
| Gangrene | 10/105 (9.5%) |
| Osteomyelitis | 7/105 (6.7%) |
| Sepsis[3] | 6/105 (5.7%) |
| Wound infection | 6/105 (5.7%) |
| Wound complication | 6/105 (5.7%) |
| Pain in extremity | 6/105 (5.7%) |
| Acute kidney injury | 5/105 (4.8%) |
| Debridement | 5/105 (4.8%) |
| Peripheral ischemia | 6/105 (5.7%) |

[1] The events listed in this table are site reported then coded using MedDRA version 21.0 and then stratified by System-Organ Class (SOC) and Preferred Term.

[2] Post-primary analysis, a subject was found to have expired after being withdrawn from the study by the investigator; including this event changes the death rate to 13/105 (12.4% .

[3] Post-primary analysis, an additional case of sepsis was documented; including this event changes the sepsis rate to 7/105 (6.7%).

Standard wound care for this patient population includes debridement, negative pressure therapy, and minor amputations. Table 15 provides an overview of all ipsilateral minor and major amputations observed through 6 months.

**Table 15: Subjects with Ipsilateral Amputations through 6 months**

| Ipsilateral Amputation | n/N |
|---|---|
| Any Ipsilateral Amputation[a] | 72/105 (68.6% |
| Toe amputation | 31/105 (29.5% |
| Foot amputation (below ankle, above toe) | 42/105 (40.0% |
| Major Amputation (below knee) | 23/105 (21.9% |

[a] Subjects who had more than one amputation (e.g., toe amputation followed by TMA) are represented in the individual types of amputation but are only counted once in the Any Ipsilateral Amputation rate.

A listing of all Adverse Events (inclusive of adverse events and serious adverse events) is provided in Table 16.

**Table 16: Subjects with Adverse Events through 6 months[1]**

| Event | Event rate (N=105) |
|---|---|
| Any Adverse Event | 375 |
| Sent for Adjudication | 130 |
| Any Subjects with at least one AE | 98 |
| **Blood and lymphatic system disorders** | **12 (11.4%)** |
| Anemia | 4 (3.8% |
| Anemia postoperative | 1 (1% |
| Blood loss anaemia | 5 (4.8% |

| Event | Event rate (N=105) |
|---|---|
| Leukocytosis | 1 (1% |
| Normocytic anemia | 1 (1% |
| **Cardiac disorders** | **25 (23.8%)** |
| Acute left ventricular failure | 1 (1% |
| Acute myocardial infarction | 3 (2.9% |
| Arrhythmia | 1 (1% |
| Atrial fibrillation | 1 (1% |
| Bradycardia | 1 (1% |
| Cardiac arrest | 2 (1.9% |
| Cardiac failure | 1 (1% |
| Cardiac failure acute | 1 (1% |
| Cardiac failure congestive | 3 (2.9% |
| Cardiomyopathy | 1 (1% |
| Cardio-respiratory arrest | 1 (1% |
| Cardiovascular disorder | 1 (1% |
| Dyspnea | 1 (1% |
| Fluid overload | 2 (1.9% |
| Myocardial infarction | 2 (1.9% |
| Pulmonary oedema | 1 (1% |
| Pulseless electrical activity | 1 (1% |
| Peripheral swelling | 1 (1% |
| **Endocrine disorders** | **1 (1%)** |
| Hyperglycemia | 1 (1% |
| **Gastrointestinal disorders** | **11 (10.5%)** |
| Diarrhea | 1 (1% |
| Gastrointestinal disorder | 1 (1% |
| Gastrointestinal hemorrhage | 5 (4.8% |
| Haematochezia | 1 (1% |
| Rectal hemorrhage | 1 (1% |
| Small intestinal obstruction | 1 (1% |
| Vomiting | 1 (1% |
| **General disorders and administration site conditions** | **40 (38.1%)** |
| Asthenia | 1 (1% |
| Death[2] | 12 (11.4% |
| Impaired healing | 7 (6.7% |
| Incision site impaired healing | 8 (7.6% |
| Incision site pain | 1 (1% |
| Pain | 2 (1.9% |
| Procedural pain | 1 (1% |
| Tissue discoloration | 1 (1% |
| Vascular access site pseudoaneurysm | 1 (1% |
| Vascular stent occlusion | 9 (8.6% |
| Vascular stent stenosis | 2 (1.9% |
| Wound necrosis | 2 (1.9% |
| Wound secretion | 1 (1% |
| Device related infection | 1 (1% |
| **Immune system disorders** | **1 (1%)** |
| Anaphylactic reaction | 1 1% |
| **Infections and infestations** | **65 (61.9%)** |
| Abscess limb | 1 (1% |
| Cellulitis | 4 (3.8% |
| Fungal peritonitis | 1 (1% |

| Event | Event rate (N=105) |
|---|---|
| Gangrene | 15 (14.3% |
| Gas gangrene | 1 (1% |
| Infection | 1 (1% |
| Localized infection | 5 (4.8% |
| Necrotising soft tissue infection | 1 (1% |
| Osteomyelitis | 11 (10.5% |
| Pneumonia | 3 (2.9% |
| Post procedural infection | 1 (1% |
| Sepsis[3] | 8 (7.6% |
| Septic shock | 1 (1% |
| Urinary tract infection | 1 (1% |
| Wound infection | 11 (10.5% |
| **Injury, poisoning and procedural complications** | **31 (29.5%)** |
| Arteriovenous fistula thrombosis | 1 (1% |
| Fall | 1 (1% |
| Limb injury | 3 (2.9% |
| Post procedural hematoma | 1 (1% |
| Postoperative wound complication | 4 (3.8% |
| Rib fracture | 1 (1% |
| Toxic encephalopathy | 1 (1% |
| Vascular pseudoaneurysm | 2 (1.9% |
| Vessel perforation | 1 (1% |
| Wound complication | 12 (11.4% |
| Wound dehiscence | 2 (1.9% |
| Wound hemorrhage | 2 (1.9% |
| **Investigations** | **8 (7.6%)** |
| Blood glucose decreased | 1 (1% |
| Diagnostic procedure | 1 (1% |
| Laboratory test abnormal | 1 1% |
| SARS-CoV-2 test positive | 2 (1.9% |
| Troponin increased | 2 (1.9% |
| Ultrasound scan abnormal | 1 (1% |
| **Metabolism and nutrition disorders** | **10 (9.5%)** |
| Decreased appetite | 1 (1% |
| Diabetic ketoacidosis | 1 (1% |
| Hyperkaliemia | 1 (1% |
| Hyponatremia | 1 (1% |
| Malnutrition | 1 (1% |
| Metabolic encephalopathy | 2 (1.9% |
| Respiratory failure | 1 (1% |
| Shock hemorrhagic | 1 (1% |
| Abnormal weight gain | 1 (1% |
| **Musculoskeletal and connective tissue disorders** | **12 (11.4%)** |
| Compartment syndrome | 1 (1% |
| Myositis | 1 (1% |
| Pain in extremity | 9 (8.6% |
| Soft tissue necrosis | 1 (1% |
| **Nervous system disorders** | **2 (1.9%)** |
| Cerebrovascular accident | 1 (1% |
| Status epilepticus | 1 (1% |
| **Psychiatric disorders** | **4 (3.8%)** |
| Anxiety | 1 (1% |

| Event | Event rate (N=105) |
|---|---|
| Delirium | 1 (1% |
| Mental disorder | 1 (1% |
| Mental status changes | 1 (1% |
| **Renal and urinary disorders** | **8 (7.6%)** |
| Acute kidney injury | 6 (5.7% |
| End stage renal disease | 1 (1% |
| Nephropathy toxic | 1 (1% |
| **Respiratory, thoracic and mediastinal disorders** | **16 (15.2%)** |
| COVID-19 | 5 (4.8% |
| COVID-19 pneumonia | 1 (1% |
| Epistaxis | 2 (1.9% |
| Hypoxia | 3 (2.9% |
| Pneumonia aspiration | 1 (1% |
| Pulmonary embolism | 1 (1% |
| Pulmonary oedema | 1 (1% |
| Pharyngeal hemorrhage | 1 (1% |
| Pneumonitis | 1 (1% |
| **Skin and subcutaneous tissue disorders** | **19 (18.1%)** |
| Decubitus ulcer | 1 (1% |
| Diabetic wound | 1 (1% |
| Dry gangrene | 5 (4.8% |
| Gangrene | 4 (3.8% |
| Ischaemic skin ulcer | 2 (1.9% |
| Rash | 2 (1.9% |
| Skin ulcer | 4 (3.8% |
| **Surgical and medical procedures** | **46 (43.8%)** |
| Amputation | 1 (1% |
| Angioplasty | 2 (1.9% |
| Debridement | 6 (5.7% |
| Foot amputation | 11 (10.5% |
| Leg amputation | 9 (8.6% |
| Peripheral revascularisation | 3 (2.9% |
| Therapeutic embolization | 4 (3.8% |
| Toe amputation | 9 (8.6% |
| Thrombolysis | 1 (1% |
| **Vascular disorders** | **64 (61%)** |
| Arterial occlusive disease | 2 (1.9% |
| Arterial stenosis | 1 (1% |
| Arteriosclerosis | 1 (1% |
| Deep vein thrombosis | 1 (1% |
| Hematoma | 3 (2.9% |
| Hemorrhage | 1 (1% |
| Hypertension | 1 (1% |
| Hypotension | 1 (1% |
| Internal hemorrhage | 1 (1% |
| Ischemic limb pain | 3 (2.9% |
| Peripheral arterial occlusive disease | 2 (1.9% |
| Peripheral artery stenosis | 4 (3.8% |
| Peripheral ischemia | 6 (5.7% |
| Peripheral vein stenosis | 3 (2.9% |
| Peripheral venous disease | 1 (1% |
| Steal syndrome | 2 (1.9% |

| Event | Event rate (N=105) |
|---|---|
| Vascular access site pseudoaneurysm | 1 (1% |
| Vascular stenosis | 3 (2.9% |
| Vascular stent occlusion[4] | 21 (20% |
| Vascular stent stenosis | 4 (3.8% |
| Vascular stent thrombosis | 2 (1.9% |

[1] The events listed in this table are site reported then coded using MedDRA version 21.0 and then stratified by System-Organ Class (SOC) and Preferred Term.

[2] Post-primary analysis, a subject was found to have expired after withdrawn from the study by the investigator; including this event changes the death rate to 13/105 12.4% .

[3] Post-primary analysis, an additional case of sepsis was documented; including this event changes the sepsis rate to 9/105 (8.6%).

[4] Vascular stent occlusions are those that were associated with a site-reported adverse event. A complete analysis of all patency-related events that indicates that the 6-month loss of primary patency rate is 74.1% may be found in Figure 8 and Table 22.

3. Effectiveness Results

The primary analysis of safety and effectiveness was based on the mITT cohort of 105 patients available for the 6-month evaluation as a Bayesian analysis of the 6-month amputation-free survival rate. Multiple imputations were performed to address missing data at the 6-month time point. Kaplan-Meier analyses were also conducted for key effectiveness outcomes of amputation free survival (AFS) and the components (limb salvage and survival) as presented in Figures 4-6 and Tables 17-19. Follow-up beyond 6-months (180 days) is ongoing.

Of the 105 mITT subjects in this analysis, 35 subjects had AFS events and 67 were event-free at 180 days. Three (3) subjects had incomplete follow-up (5 days, 72 days, 100 days) without events; these subjects were censored at these times for the Bayesian piecewise exponential survival model used for multiple imputation.

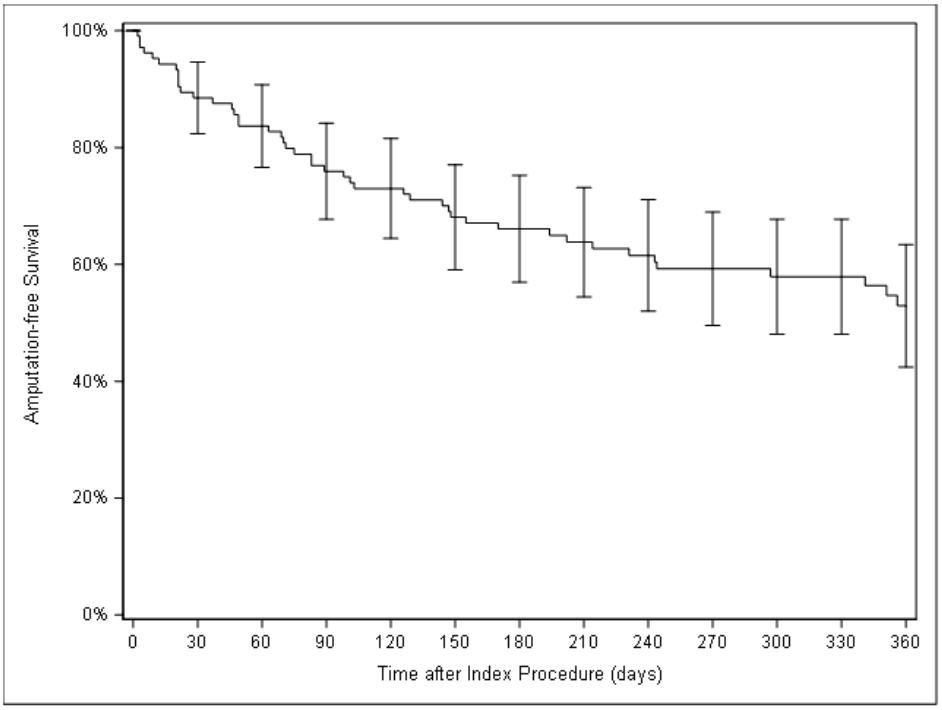



**Figure 4. Kaplan Meier Analysis of Amputation-Free Survival (AFS)**

**Table 17: Analysis of Amputation Free Survival Status over Time**

| **From day X To day Y LimFlow System (N= 105 Subjects)** | **0 0** | **1 30** | **31 60** | **61 90** | **91 120** | **121 150** | **151 180** |
|---|---|---|---|---|---|---|---|
| # Subjects at Risk | 105 | 105 | 92 | 87 | 78 | 74 | 69 |
| # Censored Subjects (Withdrawn or LTFU) | 0 | 1 | 0 | 1 | 1 | 0 | 0 |
| # Subjects with Event (Deaths or Major Amputations) | 0 | 12 | 5 | 8 | 3 | 5 | 2 |
| Event-free Rate [%] | 100.0% | 88.5% | 83.7% | 75.7% | 72.5% | 67.6% | 63.7% |
| 95% Confidence Interval [%] | N/A | 80.6% - 93.3% | 75.1% - 89.5% | 66.5% - 83.1% | 63.3% - 80.5% | 58.1% - 76.1% | 56.1% - 74.3% |

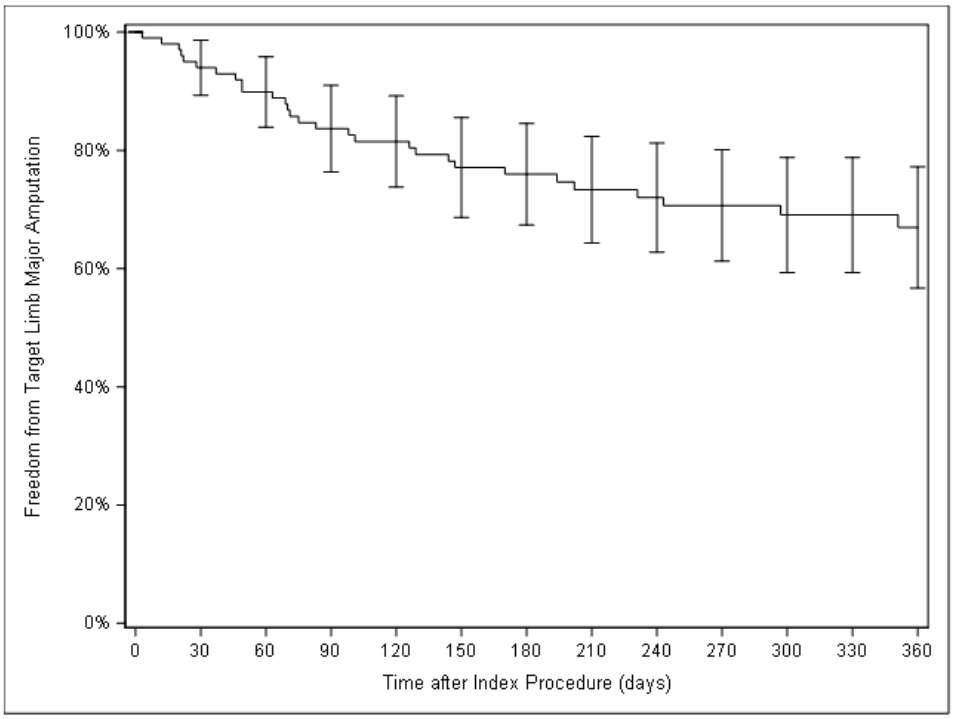



**Figure 5. Kaplan Meier Analysis of Limb Salvage**

**Table 18: Analysis of Limb Salvage over Time**

| From day X To day Y LimFlow System (N= 105 Subjects) | 0 0 | 1 30 | 31 60 | 61 90 | 91 120 | 121 150 | 151 180 |
|---|---|---|---|---|---|---|---|
| # Subjects at Risk | 105 | 105 | 92 | 87 | 78 | 74 | 69 |
| # Censored | 0 | 7 | 1 | 3 | 2 | 1 | 1 |
| # Events (Major Amputations) | 0 | 6 | 4 | 6 | 2 | 4 | 1 |
| Event-free [%] | 100.0% | 94.0% | 89.9% | 83.7% | 81.5% | 77.1% | 76.0% |
| 95% Confidence Interval [%] | N/A | 87.1% - 97.3% | 82.0% - 94.4% | 74.7% - 89.7% | 72.2% - 87.9% | 67.3% - 84.3% | 66.0% - 83.3% |

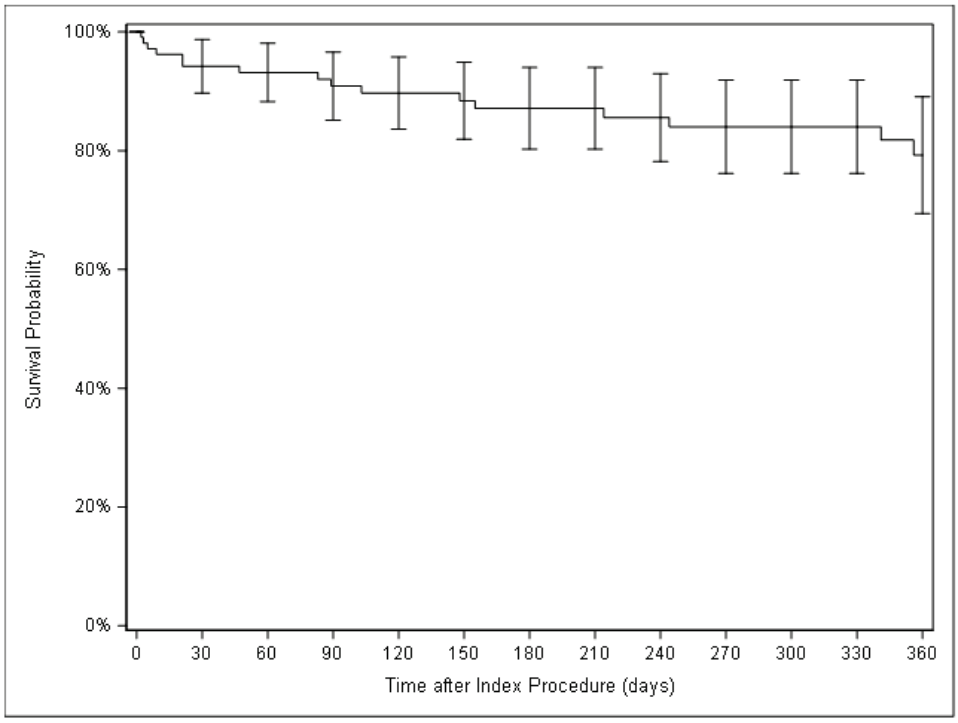



**Figure 6. Kaplan Meier Analysis of Survival**

**Table 19: Analysis of Survival over Time**

| From day X To day Y<br>LimFlow System<br>(N= 105 Subjects) | 0<br>0 | 1<br>30 | 31<br>60 | 61<br>90 | 91<br>120 | 121<br>150 | 151<br>180 |
|---|---|---|---|---|---|---|---|
| # Subjects at Risk | 105 | 105 | 92 | 87 | 79 | 75 | 69 |
| # Censored | 0 | 7 | 4 | 6 | 3 | 5 | 1 |
| # Events (Deaths) | 0 | 6 | 1 | 2 | 1 | 1 | 1 |
| Event-free [%] | 100.0% | 94.2% | 93.2% | 90.9% | 89.7% | 88.4% | 87.1% |
| 95% Confidence Interval [%] | N/A | 87.6%<br>-<br>97.4% | 86.2%<br>-<br>96.7% | 83.1%<br>-<br>95.2% | 81.6%<br>-<br>94.3% | 79.9%<br>-<br>93.4% | 78.3%<br>-<br>92.5% |

Bayesian analysis of the Amputation-Free-Survival (AFS) primary endpoint was performed as specified in the study design using the multiple imputation model described in Section X.A. The null and alternative hypotheses for the primary endpoint are:

$$H_0: \phi \leq 0.54$$
$$H_A: \phi > 0.54$$

where $\phi$ ("phi") is the probability of a subject being alive and free of major amputation at 180 days, and the value 0.54 is a pre-specified performance goal. The performance goal was derived from a literature review conducted by the Yale Cardiovascular Research Group where observed event rates were extracted from each

of the relevant studies and combined via a meta-analytic approach to arrive at an estimated historical AFS event rate for patients with no-option CLTI. From the posterior mean, the estimated AFS rate at 180 days is 65.8%, with a 95% BCI ranging from 56.5% to 74.5%. The posterior probability that ϕ exceeds the pre-specified performance goal of 0.54 is 0.9931; because this value exceeds the pre-specified threshold of 0.977, the objective is "passed," and the LimFlow System has met its performance goal.

**Table 20: Summary of Primary Endpoint Analysis – AFS at 180 days, mITT**

| Analysis | N | Posterior Mean | 95% BCI | | Posterior Probability that ϕ > 0.54 |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| Primary | 105 | 65.8% | 56.5% | 74.5% | 0.9931 |
| Post-Hoc* | 105 | 65.1% | 55.9% | 73.9% | 0.9903 |

* An analysis that includes a subject found to have expired after being withdrawn from the study by an investigator 5 days following the study procedure.

*Tipping Point Analysis*. Two tipping point analyses were performed. In the first analysis 3 subjects with incomplete follow-up and no event were included as either events or non-events, in all combinations. The second analysis was conducted, in which all 5 subjects who died of COVID-19 were removed from the analysis. In all analyses, the posterior probability exceeds the critical threshold of 0.977, and all scenarios result in the LimFlow System meeting its performance goal.

4. Primary Endpoint Subgroup Analysis

Bayesian subgroup analysis of the primary endpoint was performed as specified in the study design using the multiple imputation model described in Section X.A. The primary endpoint was analyzed in these subgroups in the same manner as it was in the full cohort. Numerical summaries of the 180-day AFS for pre-specified subgroups are shown in Table 21**.** The AFS rate is consistent across all subgroups, with the exception of subjects on dialysis. There were also small numerical differences based on gender, race, baseline Rutherford category, and presence of diabetes, but the confidence intervals overlap and the sample size is small. These differences are not unexpected in this patient population.

**Table 21: Primary Endpoint Analyses by Subgroup**

| Subgroup | N | AFS[1] | 95% BCI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age ≤ 70 | 55 | 65.7% | 52.8% | 77.5% |
| Age > 70 | 50 | 65.2% | 51.9% | 77.5% |
| Female | 33 | 59.4% | 42.8% | 75.0% |
| Male | 72 | 68.4% | 57.3% | 78.5% |
| Black or African Descent | 16 | 61.1% | 38.3% | 81.6% |
| Caucasian | 64 | 67.6% | 55.8% | 78.3% |
| Unknown/Declined | 23 | 59.2% | 39.5% | 77.4% |
| Hispanic or Latino | 29 | 62.9% | 45.0% | 79.0% |
| Not Hispanic or Latino | 76 | 66.5% | 55.7% | 76.5% |

| Subgroup | N | AFS[1] | 95% BCI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Diabetes Type I/II | 81 | 61.8% | 51.1% | 72.0% |
| Diabetes None | 24 | 76.9% | 59.3% | 90.6% |
| Rutherford 5 | 68 | 69.2% | 57.8% | 79.5% |
| Rutherford 6 | 37 | 59.0% | 43.4% | 73.7% |
| Dialysis Yes | 19 | 38.1% | 19.1% | 59.2% |
| Dialysis No | 86 | 72.2% | 62.3% | 81.1% |
| [1]Mean of posterior distribution | | | | |

5. Secondary Endpoints

Secondary endpoint measures included LimFlow vessel patency, change in Rutherford Class, wound healing, and quality of life.

*Vessel patency.* Vessel patency status was reviewed via duplex ultrasound at 30 days and 6 months for study subjects. These data, as analyzed by the study imaging core lab, was the foundation of study patency analysis and were combined with CEC-adjudication review of any incidence of occlusion or reintervention without occlusion found outside of protocol-required follow-up visits. The patency endpoint definitions used for the analysis were:

- Primary Patency (P): Defined as absence of occlusion of the endovascular intervention that is maintained without the need for additional or secondary surgical or endovascular procedures, at 30 days and 6 months.

- Primary Assisted Patency (PA): Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred, at 30 days and 6 months.

- Secondary Patency (S): Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures after occlusion occurs, at 30 days and 6 months.

At 6 months, the percentages of primary patency, primary-assisted patency, and secondary patency were 25.9%, 45.4%, and 64.2%, respectively. Repeat interventions to address native arterial disease and flow optimization within the transcatheter arterialization circuit occurred in 39 patients (37.5%). Additionally, 28 patients lost primary patency due to occlusion without reintervention.

Patency was analyzed as a Kaplan Meier analysis as is presented in Figure 8. Rates of event-free survival (subjects remaining patent) are presented in Table 22 below.

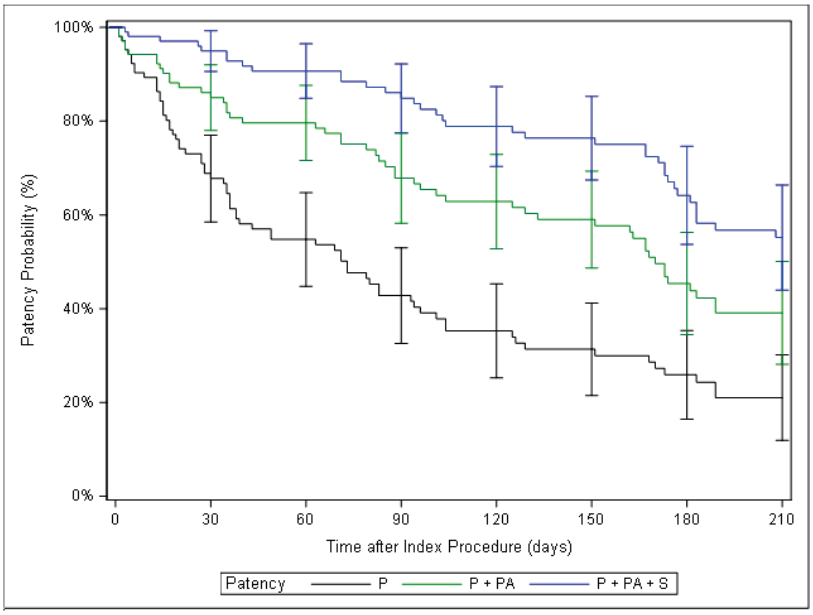



**Figure 7. Kaplan Meier Analysis of Patency**

**Table 22: Analysis of Patency over Time**

| From day X To day Y LimFlow System (N= 105 Subjects) | 0 0 | 1 30 | 31 60 | 61 90 | 91 120 | 121 150 | 151 180 |
|---|---|---|---|---|---|---|---|
| **Primary Patency (P)** | | | | | | | |
| # Event Free | 105 | 105 | 63 | 48 | 35 | 27 | 23 |
| # Not Evaluable | 0 | 10 | 3 | 3 | 2 | 1 | 3 |
| # Loss of Patency | 0 | 32 | 12 | 10 | 6 | 3 | 4 |
| Event-free [%] | 100.0% | 67.7% | 54.8% | 42.8% | 35.2% | 31.3% | 25.9% |
| **Primary + Primary-Assisted Patency (P+PA)** | | | | | | | |
| # Event free | 105 | 105 | 79 | 71 | 56 | 49 | 44 |
| # Not Evaluable | 0 | 11 | 3 | 5 | 3 | 2 | 5 |
| # Loss of Patency | 0 | 15 | 5 | 10 | 4 | 3 | 10 |
| Event-free [%] | 100.0% | 85.0% | 79.6% | 67.8% | 62.9% | 59.0% | 45.4% |
| **Primary + Primary-Assisted + Secondary Patency (P+PA+S)** | | | | | | | |
| # Event free | 105 | 105 | 89 | 82 | 72 | 64 | 59 |
| # Not Evaluable | 0 | 11 | 3 | 5 | 3 | 3 | 7 |
| # Loss of Patency | 0 | 5 | 4 | 5 | 5 | 2 | 9 |
| Event-free [%] | 100.0% | 94.9% | 90.7% | 84.9% | 78.9% | 76.4% | 64.2% |

*Rutherford category.* Rutherford category was captured at each timepoint and the change from baseline was evaluated at 30 days, 3 months, and 6 months, as described in Table 23. Table 24 shows the percentage of evaluable subjects with improvement of more than 1 category.

**Table 23: Rutherford Category**

| Rutherford category | Baseline | 30 days | 3 months | 6 months |
|---|---|---|---|---|
| # subjects evaluated | 105 | 77 | 74 | 64 |
| 0 | 0/105 (0.0%) | 1/77 (1.3%) | 7/74 (9.5%) | 9/64 (14.1%) |
| 1 | 0/105 (0.0%) | 0/77 (0.0%) | 0/74 (0.0%) | 3/64 (4.7%) |
| 2 | 0/105 (0.0%) | 1/77 (1.3%) | 1/74 (1.4%) | 1/64 (1.6%) |
| 3 | 0/105 (0.0%) | 0/77 (0.0%) | 1/74 (1.4%) | 0/64 (0.0%) |
| 4 | 0/105 (0.0%) | 3/77 (3.9%) | 2/74 (2.7%) | 5/64 (7.8%) |
| 5 | 68/105 (64.8% | 50/77 (64.9%) | 48/74 (64.9%) | 36/64 (56.3%) |
| 6 | 37/105 (35.2% | 22/77 (28.6%) | 15/74 (20.3%) | 10/64 (15.6%) |

**Table 24: Improvement in Rutherford Category in Evaluable subjects**

| Characteristic | |
|---|---|
| 30-day improvement in Rutherford $\geq$ 1 class | 18.2% 14/77) |
| 3-month improvement in Rutherford $\geq$ 1 class | 32.4% 24/74) |
| 6-month improvement in Rutherford $\geq$ 1 class | 42.2% (27/64) |

*Wound healing.* Wound healing was analyzed by an independent wound core lab, where wound photos were captured and evaluable. All wound images with sufficient resolution were evaluated. Collection of wound area measurements was challenging due to their susceptibility to lighting, background, plane, distance, angle, circumferential wounds, and the need for the wound to have a healthy tissue border. In addition, wound area data was missing at a high rate for similar reasons and is not included in this summary. The primary wound was determined at baseline, while the qualitative status of healing on all wounds was also analyzed by the core laboratory. During the COVID-19 public health emergency, elective procedures and follow-up were paused or challenging to complete. The protocol was updated to allow images to be taken at home. However, some of these images were not measurable or missing, as detailed in Table 25.

**Table 25: Primary Wound Image Status at Each Timepoint**

| | Baseline | 30 days | 3 months | 6 months |
|---|---|---|---|---|
| Subjects available for wound follow-up* | 105 | 93 | 79 | 68 |
| Evaluable | 105 | 76 | 72 | 63 |
| Unevaluable | 0 | 0 | 0 | 1 |
| Missing | 0 | 17 | 7 | 4 |

* The number of subjects available for wound follow-up were those that did not fail the primary endpoint (i.e., due to death or major amputation).

Wound healing was determined by an independent wound core lab based on the following criteria:

- Healed: All surfaces of the wound are fully epithelialized; in some cases, may have residual scab at the edge of epithelialization: this is distinct from a wound eschar but there is no exposed surface of unepithelialized tissue. Wound size is 0.
- Healing: Evidence of granulation tissue formation; epithelialization of wound edges is apparent; contraction of wound edges may be evident; in early stages of healing the granulation tissue may be less apparent or less robust (pink as compared to red) but the wound base is generally clean with no exudate or evidence of purulence; this term was also used for minor amputation sites that have characteristics of healthy wound tissue. Wound area is decreased in size or stable.
- Stable: No evidence of increasing granulation tissue formation, wound contraction, or increased epithelialization, but also with no evidence of worsening necrosis, exudate, or purulence/infection. Wound area not appreciably changed in size.
- Worsening: Increasing evidence of necrosis, exudate, or purulence; evidence of eschar development or increasing ischemic changes of surrounding skin and soft tissues; this term was used for minor amputations with non-healing wound bases. Wound area is unchanged or increased in size.

The results for wound healing for the primary wound in evaluable subjects are provided in Table 26. In subjects with evaluable wounds, over half were worsening at 30 days. At 6 months, 25% of evaluable wounds were healed.

**Table 26: Primary Wound Healing in Evaluable Subjects**

| **Status** | 30 days | 3 months | 6 months |
|---|---|---|---|
| # Evaluable | 76 | 72 | 63 |
| Healed | 3 | 6 | 16 |
| Healing | 9 | 28 | 32 |
| Stable | 24 | 16 | 7 |
| Worsening | 40 | 22 | 7 |

6. Quality of Life Pain Results

Study subjects reported pain at each follow-up visit on a scale of 1-10. At baseline, 57/92 subjects had a pain score of 5 or greater, while at 6-months, the majority of subjects (45/65, 69.0%) had a pain score 4 or less.

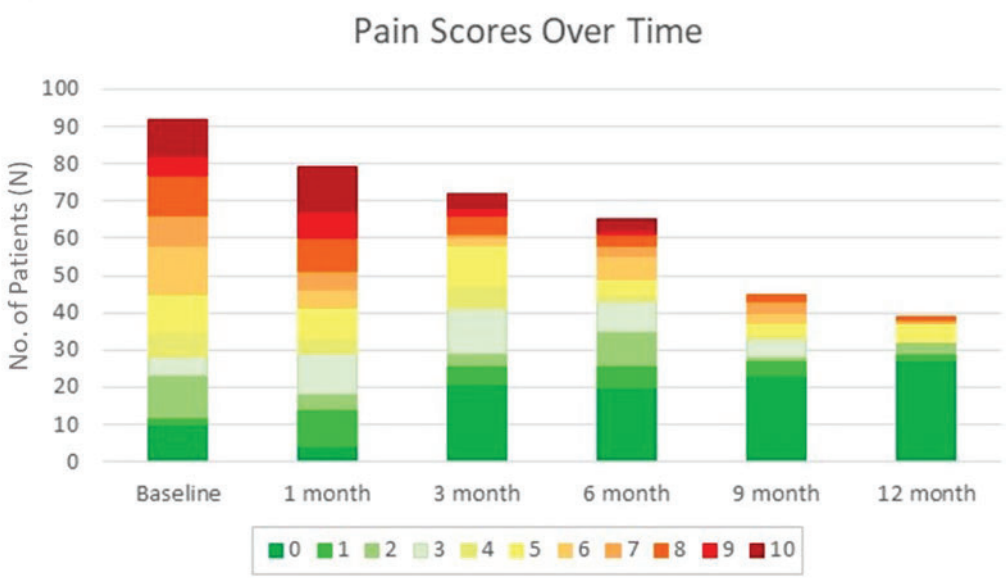



**Figure 8. Pain Scores Over Time**

7. Device Malfunctions

The definition of device malfunction in the PROMISE II study is any occurrence of equipment not functioning or operating as intended. There were 14 cases of device malfunction reported in the study with the LimFlow stent as detailed in Table 27. None of the device malfunctions resulted in an adverse event.

**Table 27: Device Malfunctions in PROMISE II**

| Malfunction Type | Incidents | Total units used in study |
|---|---|---|
| Stent deployment malfunction | 9 | 333 |
| Stent delivery system malfunction | 5 | |

In addition to the device malfunctions noted during the LimFlow procedure, there were two incidents of stent fracture observed during follow-up in patients where the LimFlow stent was placed more distal than is recommended. In both cases, the study subjects were asymptomatic with evidence of adequate blood-flow/perfusion through the vasculature beyond the area of fracture and no clinical sequelae were observed in the study subjects.

8. Protocol Deviations

With the exception of four eligibility deviations and one consent deviation discussed, the remaining protocol deviations were minor and were mainly limited to assessments not being done for clinical reasons/justification or visits being done outside of window. The vast majority of clinical assessment deviations involved sites not capturing wound images and transcutaneous oximetry (TCP02), which proved to be an assessment not feasible at the vast majority of sites. The trial was also impacted by the COVID-19 public health emergency, leading to missed follow-up and challenges

collecting evaluable wound images. These deviations are not unexpected in this challenging patient population and during the time of a pandemic.

The four eligibility deviations in the PROMISE II study include two subjects being enrolled despite having peritoneal arteriovenous fistula access used for dialysis, one with a significant concurrent medical, psychological, or social condition which interfered with the subject's study participation, and one subject with chronic kidney disease and was on dialysis with baseline serum albumin <30g/L.

9. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

### E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 31 investigators. None of the clinical investigators had disclosable financial interests/ arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The PROMISE I trial (NCT03124875) was the early feasibility study performed on the first generation of the LimFlow System which comprised of arterial and venous crossing catheters, an ultrasound system utilized in the establishment of the arteriovenous crossing, valvulotome, and the first and second generation of the LimFlow self-expanding conical and cylindrical stent grafts. The PROMISE I Study was a prospective, single-arm, multi-center feasibility study of the LimFlow System that enrolled 32 subjects in the United States under IDE# G160156. The objective of the PROMISE I trial was to evaluate the feasibility, safety, and effectiveness of the LimFlow System in creating a below-the-knee arteriovenous fistula for venous arterialization in subjects with chronic limb-threatening ischemia.

The study primary endpoint was amputation-free survival (AFS) at 30 days, defined as the percentage of subjects who survived with limb salvage. Limb Salvage was defined as freedom from above-ankle amputation of the index limb, and survival was defined as freedom from all-cause mortality. Descriptive statistics are provided as no hypothesis testing was performed due to the small sample size.

The study's secondary safety endpoint was Amputation-Free Survival at 6-months with the same definitions for AFS and Limb Salvage as the primary safety endpoint.

There were multiple secondary effectiveness endpoints that were evaluated in the study:

Primary Patency at 30 days: Defined as the absence of total occlusion of the stent graft without prior clinically driven major re-intervention of the stent graft at 30 days.

Primary Patency at 6 months: Defined as the absence of total occlusion of the stent graft without prior clinically driven major re-intervention of the stent graft at 6 months.

Secondary Patency at 6 months: Defined as the absence of total occlusion of the stent graft with or without prior clinically driven major re-intervention of the stent graft at 6 months.

Deterioration in Renal Function at 6 months: Defined as a 25% increase in serum creatinine after using iodine contrast agent without another clear cause for kidney injury.

Limb Salvage: Defined as percentage of subjects with freedom from above-ankle amputation of the index limb.

Technical Success: Defined as percentage of subjects with completion of the endovascular procedure and immediate morphological success with successful placement of the arterial and venous catheters in the desired location in the limb, and ability to place the stent graft.

Procedural Success: Defined as percentage of subjects with combination of technical success, and absence of all-cause mortality, above-ankle amputation or clinically driven major re-intervention of the stent graft through 30 days.

Wound Healing: This was initially defined as percentage of subjects with completed index wound healing at these timepoints, however additional analysis was completed to also characterize the cohort of subjects who showed healing progress (albeit complete wound healing) at each time point.

The study was successful in demonstrating feasibility with positive outcomes on all endpoints. A brief overview of the PROMISE I results are provided below in Table 28.

**Table 28: PROMISE I Results**

| KEY PERFORMANCE DATA | Kaplan Meier Estimates | Rate n/N (%) |
|---|---|---|
| Technical Success[1] | -- | 31/32 (96.9%) |
| Procedural Success[2] | -- | 24/31 (77.4%) |
| **PRIMARY & SECONDARY SAFETY ENDPOINTS** | | |
| 30-day Amputation-Free Survival (AFS) [95% CI] | 90.6% [73.7% - 96.9%] | 28/31 (90.3%) |
| 30-day Survival | 100.0% | 28/28 (100.0% |
| 30-day Limb Salvage | 90.6% | 28/31 (90.3%) |
| 6-month Amputation-Free Survival (AFS) [95% CI] | 73.8% [54.4% - 86.0%] | 22/30 (73.3%) |
| 6-month Survival | 96.3% | 22/23 (95.7%) |
| 6-month Limb Salvage | 76.7% | 22/29 (75.9%) |

| KEY PERFORMANCE DATA | Kaplan Meier Estimates | Rate n/N (%) |
|---|---|---|
| **SECONDARY ENDPOINTS (SAFETY)** | | |
| 12-month AFS | 69.5% | 20/29 (69.0%) |
| 12-month Survival | 91.6% | 20/22 (90.9%) |
| 12-month Limb Salvage | 75.9% | 22/27 (75.9%) |
| 24-month AFS | 58.7% | 16/28 (57.1%) |
| 24-month Survival | 77.3% | 16/21 (76.2%) |
| 6-month Renal Deterioration due to Contrast-Induced Nephropathy | -- | 3/32 (9.4%) |
| **SECONDARY ENDPOINTS (PERFORMANCE)** | | |
| 30-day Primary Patency | 73.2% | 22/30 (73.3%) |
| 6-month Complete Wound Healing | 19.0% | 5/20 (25% |
| 12-month Complete Wound Healing | 58.7% | 9/16 (56% |

[1]Technical Success was defined as: percentage of subjects with completion of the endovascular procedure and immediate morphological success with successful placement of the arterial and venous catheters in the desired location in the limb, and ability to place the stent graft.
[2]Procedural Success was defined as: percentage of subjects with combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention of the stent graft at 30 days.

Technical success was achieved in 31 cases resulting in a 96.9% technical success rate. There was one case of technical failure in 32 treated subjects. Arterial and venous catheters were successfully placed and initial arterio-venous crossing and wire placement were successful. Work in tortuous venous anatomy led to crossing wire being removed completely from the circuit and attempts to regain arterio-venous crossing were unsuccessful. The remaining LimFlow procedure was aborted prior to the use of valvulotomy and placement of stents.

Procedural success was achieved in 24 subjects (77.4%), out of 31 subjects available for follow-up or who failed the procedural success endpoint prior to 30 days.

The study primary endpoint of amputation-free-survival (AFS) at 30 days was 90.6%, and secondary endpoint of AFS at 6-months was 73.8%. This was well-maintained over the longer-duration with AFS at 12 and 24-months 69.5% and 58.7%, respectively. Limb salvage was 90.6% and 76.7% at 30 days and 3-months, respectively, with no incidents of above-ankle amputation throughout the rest of the 24 months of follow-up. All AFS events after 3-months were exclusively deaths mostly due to pre-existing medical conditions unrelated to CLTI.

An independent wound core lab reviewed wound images from baseline and all follow-up time-points, as available, to determine the healing status. Complete wound healing was 58.7% at 12-months.

The PROMISE I trial was successful in its objective to establish feasibility and demonstrate initial safety and effectiveness of the LimFlow System in creating a below-the-knee arteriovenous fistula for venous arterialization in subjects with chronic limb-threatening ischemia.

## XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The nonclinical and preclinical testing conducted on the stent grafts, delivery system, and accessories demonstrated that the performance characteristics of the device met the product specifications and are acceptable for clinical use. The shelf-life testing has established acceptable performance for a labeled shelf life of one year.

The prospective single-arm, multi-center study (PROMISE II) was designed to evaluate the transcatheter arterialization of the deep veins (TADV) via the LimFlow System in subjects with no-option CLTI. No-option CLTI was defined as either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit. The study demonstrated technical success in 104/105 (99.0%) subjects. The primary safety and effectiveness endpoint was amputation-free survival at 6 months. At 6 months, 67 subjects remaining in the study were event free. The 6-month amputation-free survival rate estimated by the mean of the posterior distribution is 65.8%, with 95% Bayesian credible interval (BCI of (0.565-0.745). The posterior probability that this rate exceeds the performance goal of 0.54 is 0.993, exceeding the study's pre-defined success criterion of 0.977. As estimated by Kaplan-Meier method, 6-month amputation-free survival is 66.1%. For minor amputations, 29.5% had toe amputations and 40% had amputations above the toe and below the ankle. Primary patency was 25.9% at 6 months, and secondary patency was 64.2%. Patients generally experienced improvements in Rutherford category, wound improvement, and reduced pain as compared to typical expectations for no-option CLTI patients.

The PROMISE II trial enrolled subjects that were representative of real-world patients, including those with dialysis-dependence and Rutherford class 5 or 6 wounds, who are routinely excluded from vascular device studies. Beyond routine co-morbidities including diabetes, 74.3% of the subjects had a history of prior unsuccessful revascularization of the index limb, indicating a complex cohort of patients at risk of major amputation.

### B. Safety Conclusions

The biocompatibility and *in vivo* animal testing demonstrated that the acute and chronic *in vivo* performance characteristics of the LimFlow System provide reasonable assurance of safety and acceptability for the intended clinical use. The risks of

the device are based on nonclinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval, as described above.

Adverse event rates were consistent with expectations for this high-risk population, which has many comorbidities, and events align with the underlying baseline risk factors and medical history for this population. Freedom from contrast-induced nephropathy was reported in 98.1% of subjects and 6-month limb-salvage was 76.0%. Overall, the clinical study results are adequate to provide a reasonable assurance of the safety of the LimFlow System in treating no-option CLTI by creating an arteriovenous connection in the below-the-knee vasculature.

## C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval, as described above. Probable benefits include improved blood flow to the foot, but not necessarily eliminating the need for amputation. The potential benefit of improved blood flow and wound improvement outweighs the standard endovascular/surgical risks associated with the index procedure in this no-option patient population who will likely have a major amputation if the TADV procedure with the LimFlow System is not attempted. There were no unanticipated adverse device effects reported.

Even with the current opportunities for treatment, the therapeutic options in CLTI patients are limited. Blood flow to the lower extremities and wound healing are severely inhibited in most CLTI patients who have reduced blood flow in the lower limb; therefore, even with aggressive local wound care, patients with severe limb ischemia and chronic ulceration who do not, or cannot, undergo revascularization often progress to amputation.

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the LimFlow System the probable benefits outweigh the probable risks.

## D. Overall Conclusions

In this prospective study of subjects with no-option CLTI, TADV was successfully performed in 99% of patients, was associated with 66.1% amputation-free survival and 76.0% limb salvage at 6 months. In conclusion, the LimFlow System is safe and effective and can achieve a high procedural success rate in patients with CLTI and no conventional surgical or endovascular revascularization options to promote wound healing and prevent major amputation.

## XIV. CDRH DECISION

CDRH issued an approval order on 9/11/2023. The final clinical conditions of approval cited in the approval order are described below.

1. PROMISE II Continued Follow-up Study. This study should be conducted per protocol LF-CA-PR-3, Revision 2, (dated February 3, 2021). This study is a single-arm, prospective, multi-center follow-up of the pivotal PROMISE II trial (G160156) that treated 105 subjects from 20 investigational sites. It will evaluate the long-term safety and effectiveness of the LimFlow System. All 102 remaining subjects, active at the end of the 6-month evaluation, will continue to be followed at 9, 12, 24 and 36 months.

   Follow-up at the timepoints will include the following assessments: Rutherford Classification, Wound, Ischemia, and foot Infection (WIfI) grade, wound assessment, amputation and/or reintervention of the stent graft, device or procedure related adverse events and serious adverse events, review of concomitant medications (antiplatelets/anticoagulants), all-cause mortality and Duplex ultrasound examination to assess stent graft patency.

2. The PROMISE III Post-Approval Study is a prospective, single-arm, multicenter study designed to collect additional information on the LimFlow System for creating an arteriovenous (AV) connection in the below the knee (BTK) vascular system using an endovascular, minimally invasive approach to arterialize the pedal veins for the treatment of chronic limb-threatening ischemia in subjects ineligible for conventional endovascular or surgical limb salvage procedures. A maximum of 100 patients will be enrolled at up to 25 sites in the United States.

   Patients will be followed at 14 (± 3) days, 30 (± 7) days, 3, and 6 (±2 weeks) months, 1, 2, and 3 (±4 weeks) years post index procedure.

   The primary endpoint is amputation free Survival (AFS) defined as freedom from major amputation (defined as above-ankle amputation of the index limb) and all-cause mortality at 6 months post index procedure.

   Key secondary endpoints to be evaluated are primary patency, primary assisted patency, secondary patency, limb salvage, change in Rutherford classification, target wound healing, all wound healing, and all wound area reduction.

   Follow-up assessment will include duplex ultrasound, pulse evaluation via hand-held continuous wave Doppler to the stent graft, pain questionnaire, wound ischemia, foot infection (WIfI) classification, and device- or procedure-related adverse events and serious adverse events.

   The study endpoint analyses will be summarized with descriptive statistics. The primary endpoint of amputation free survival will be analyzed with survival analysis (Kaplan Meier analysis).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES


1. Kim TI, Aboian E, Fischer U, Zhang Y, Guzman RJ, Ochoa Chaar CI. Lower Extremity Revascularization for Chronic Limb-Threatening Ischemia among Patients at the Extremes of Age. Ann Vasc Surg. 2021 Apr;72:517-528
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3. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med. 2007 Apr;32(4):328-33
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5. Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, et al. Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia. New England Journal of Medicine. 2022.