
RX Herculink Elite® Renal and Biliary Stent System

Instructions for Use

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RX Herculink Elite Renal Stent System

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

1.0 DEVICE DESCRIPTION

The **RX Herculink Elite Renal Stent System** includes:

- A balloon expandable L605 cobalt chromium alloy stent pre-mounted on the balloon of a rapid exchange (RX) stent delivery system
- Two radiopaque markers located underneath the balloon which identify the stent position and fluoroscopically mark the working length of the balloon
- Proximal shaft markers to aid with delivery catheter position, relative to a renal guiding catheter tip
- A third marker located approximately 30 cm from the center of the balloon that aids in locating the guide wire exit lumen and facilitating catheter removal and exchange

The delivery system can be utilized to optimize the stent wall apposition post stent deployment.

Table 1. *In Vitro Device Specifications**

Expanded Stent Diameter (mm)	Stent Lengths (mm)	<i>In Vitro</i> * Stent Deployment Pressure (atm)	Rated Burst Pressure RBP (atm)	Recommended Minimum Guiding Catheter ID (F) / (inches) / (mm)	Recommended Minimum Sheath / Introducer** (F) / (inches) / (mm)
4.0	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
4.5	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
5.0	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
5.5	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
6.0	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
6.5	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
7.0	15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80

* All data provided is based on *in vitro* testing. Assure full deployment of the stent (see *Clinician Use Information section 8.8 Stent Deployment Procedure*). Deployment pressures should be based on lesion characteristics.

** See individual manufacturer specifications for (F) equivalent

2.0 HOW SUPPLIED

Sterile. This device is sterilized with electron beam radiation. Non-pyrogenic. Do not use if the package is open or damaged.

Storage. Store in a dry, dark, cool place.

Contents. One (1) **RX Herculink Elite Renal Stent System**, one (1) Protective / Regrooming sheath, one (1) flush tool

3.0 INDICATIONS

The **RX Herculink Elite Renal Stent System** is indicated for use in patients with atherosclerotic disease of the renal arteries following sub-optimal percutaneous transluminal renal angioplasty (PTRA) of a *de novo* or restenotic atherosclerotic lesion (≤ 15 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 – 7.0 mm. Suboptimal PTRA is defined as $\geq 50\%$ residual stenosis, ≥ 20 mmHg peak systolic or ≥ 10 mmHg mean translesional pressure gradient, flow-limiting dissection, or TIMI [Thrombolysis In Myocardial Infarction] flow < 3 .

4.0 CONTRAINDICATIONS

The **RX Herculink Elite Renal Stent System** is contraindicated for use in:

- Patients with a contraindication for antiplatelet / anticoagulant therapy
- Patients who have a lesion that cannot be crossed with a wire or a balloon angioplasty catheter
- Patients with bleeding disorders
- Patients with a known hypersensitivity to cobalt or chrome
- Target lesions that are resistant to complete balloon inflation
- Stenting of an arterial vessel where leakage from the artery could be exacerbated by placement of a stent
- Patients with a target lesion with a large amount of adjacent acute or subacute thrombus

5.0 WARNINGS

The long term safety and effectiveness of this device for use in the renal arterial system have not been established.

Should **unusual resistance** be felt **at any time** during lesion access or Delivery System removal, the introducer sheath / guiding catheter and stent system should be removed **as a single unit**. Applying excessive force to the Stent Delivery System can potentially result in loss or damage to the Stent and Delivery System components. (See *Stent / System Removal – Precautions*.)

Since the use of this device carries the associated risk of subacute thrombosis, vascular complications and / or bleeding events, judicious selection of patients is necessary.

Stenting across a major bifurcation may hinder or prevent future diagnostic or therapeutic procedures.

Once fully deployed, the stent cannot be repositioned.

Persons allergic to L605 cobalt chromium alloy may suffer an allergic reaction to this implant.

Only physicians familiar with the complications, side effects and hazards commonly associated with renal stent placement should use this device.

The RX Herculink Elite Renal Stent System is intended to perform as a system. The stent should not be removed for use in conjunction with other dilatation catheters, nor should the RX Herculink Elite Renal Stent System be used in conjunction with other stents.

The safety and effectiveness of multiple overlapping stents have not been established. However, when multiple stents are required, stent materials should be of similar composition.

6.0 PRECAUTIONS

6.1 Stent Delivery System Handling – Precautions

- **For single use only.** Do not resterilize or reuse. Note product "Use By" date.
- **Do not remove stent from its delivery balloon as removal may damage the stent and / or lead to stent embolization.**
- Carefully inspect the RX Herculink Elite Renal Stent System prior to use to verify that the stent has not been damaged in shipment and that the device dimensions are suitable for the specific procedure. Take care to avoid unnecessary handling.
- Refer to the instructions for use supplied with any interventional devices to be used in conjunction with the RX Herculink Elite Renal Stent System, for their intended uses, contraindications, and potential complications.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important during stent system removal from the packaging, placement over a guide wire and advancement through a guiding catheter or introducer sheath.
- Do not "roll" the mounted stent with your fingers as this action may loosen the stent from the delivery balloon.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

6.2 Stent Placement – Precautions

- **Do not prepare or pre-inflate balloon prior to stent deployment** other than as directed. Use balloon purging technique described in the *Clinician Use Information* section.
- The inflated balloon diameter of the system used to deploy the stent should approximate the diameter of the vessel. Oversizing of the stent can result in a ruptured vessel. To ensure full expansion of the stent, the balloon should be inflated to a minimum of nominal pressure.
- Implanting a stent may lead to dissection of the vessel distal and / or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (surgical intervention, further dilatation, placement of additional stents, or other).
- Do not expand the stent if it is not properly positioned in the vessel. (See *Stent / System Removal – Precautions*.)
- Stenting across a major bifurcation may hinder or prevent future side branch access.
- Balloon pressures should be monitored during inflation. **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** Use of pressures higher than specified on product label may result in a ruptured balloon with possible vessel damage or perforation.

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- Stent retrieval methods (use of additional wires, snares and / or forceps) may result in additional trauma to the vasculature and / or the vascular access site. Complications may include bleeding, hematoma or pseudoaneurysm.
 - The RX Herculink Elite Renal Stent System is intended for deployment and post-deployment dilatation of the stent only and should not be used to dilate other lesions.
 - **Do not attempt to pull an unexpanded stent back through the introducer sheath / guiding catheter; dislodgment of the stent from the balloon may occur.**

6.3 Stent / System Removal – Precautions

Should **unusual resistance** be felt **at any time** during either lesion access or removal of the Delivery System post-stent implantation, the entire system should be removed **as a single unit**.

When removing the Delivery System as a single unit:

- DO NOT retract the Delivery System into the introducer sheath / guiding catheter.
- Position the proximal balloon marker just distal to the tip of the introducer sheath / guiding catheter.
- Advance the guide wire in the anatomy as far distally as safely possible.
- Secure the Delivery System to the introducer sheath / guiding catheter; then remove the introducer sheath / guiding catheter, guide wire and Delivery System as a **single unit**.

Failure to follow these steps and / or applying excessive force to the Delivery System can potentially result in loss or damage to the stent and / or Delivery System components.

If it is necessary to retain guide wire position for subsequent vessel access, leave the guide wire in place and remove all other system components.

6.4 Post Implant – Precautions

Great care must be exercised when **crossing a newly deployed stent** with a guide wire or balloon catheter to avoid disrupting the stent geometry.

Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the Herculink Elite stent, in single and in overlapped configurations up to 33 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for any duration of MRI scan that would otherwise be safe for the patient without implant.

MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the Herculink Elite stent.

The Herculink Elite stent should not migrate in this MRI environment. Magnetic force on the Herculink Elite stent was tested according to ASTM F2052-06e. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating.

Stent heating was derived by using the measured non-clinical, *in vitro* temperature rise according to ASTM F2182-09 in a GE Signa HDx 3 Tesla scanner and in a GE 1.5 Tesla coil in combination with the local specific absorption rates (SARs) in a digitized human heart model. The temperature rise was derived by a validated calculation. At overlapped lengths up to 33 mm, the Herculink Elite stent produced a non-clinical maximum local temperature rise of less than 3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for an MRI sequence of 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 33 mm in length or stents with fractured struts are unknown.

Image artifact may be present when scanning the Herculink Elite stent as demonstrated in non-clinical testing performed according to ASTM F2119-07 in a GE Signa HDx 3 Tesla scanner. The image artifact (both inside and outside the device lumen) extends approximately 7 mm from the device using the spin echo sequence (TR = 500 ms; TE = 20 ms; flip angle = 90°) and 13 mm from the device using the gradient echo sequence (TR = 100 ms; TE = 15 ms; flip angle = 30°). MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the Herculink Elite stent. Therefore, it may be necessary to optimize the MR imaging parameters in the presence of Herculink Elite stents.

7.0 POTENTIAL ADVERSE EVENTS

Potential complications associated with percutaneous renal artery treatment including the use of a renal stent may include, but are not limited to, the following:

- Abscess
- Allergic reaction to Cobalt Chromium or contrast agents
- Arrhythmias (ventricular fibrillation, ventricular tachycardia, other)
- Arteriovenous fistula
- Bowel infarct
- Death
- Dialysis
- Dissection
- Drug reaction to antiplatelet agents
- Drug reaction, allergic reaction to contrast media
- Emboli (air, tissue, or thrombotic emboli) resulting in tissue ischemia/infarction
- Emergency surgery to correct vascular complications
- Emergent renal artery bypass surgery
- Extremity ischemia/amputation
- Fever
- Gastrointestinal symptoms from anticoagulation/antiplatelet medication
- Hematoma at vascular access site
- Hemorrhage requiring transfusion
- Hypersensitivity reactions
- Hypertension / hypotension
- Infection and pain at vascular access site
- Intimal tear
- Kidney infarct
- Myocardial infarction
- Myocardial ischemia
- Nephrectomy
- Peripheral neuropathy
- Pseudoaneurysm at vascular access site
- Pseudoaneurysm formation
- Renal artery thrombosis, aneurysm, rupture, perforation, occlusion, spasm, or restenosis
- Renal insufficiency or failure
- Stent migration or embolization
- Stent misplacement
- Stroke/cerebral vascular accident
- Tissue necrosis or ulceration

8.0 CLINICIAN USE INFORMATION

8.1 Clinical Studies

Results from a multi-center clinical study (IDE G060067, also known as the HERCULES study) demonstrate the safety and effectiveness of the RX Herculink Elite Renal Stent System. Specifically, the 9-month binary restenosis rate was 10.5%, meeting the performance goal of 28.6%. In addition, use of the RX Herculink Elite Renal Stent System was associated with a low rate of major adverse events (MAEs), high technical and procedural success rates, improvement in hypertension, and maintenance of renal function. An overview of the HERCULES study is presented in **Table 2**.

Table 2. Overview of the HERCULES study

Device	RX Herculink Elite Renal Stent System
Study Design	Non-randomized, prospective, single-arm, multi-center clinical study
Patients Enrolled	202 (76 male and 126 female)
Number of Sites	37 investigational sites
Study Objective	This study is designed to evaluate the safety and effectiveness of the RX Herculink Elite Renal Stent System in the treatment of <i>de novo</i> or restenotic renal artery stenoses with suboptimal Percutaneous Transluminal Renal Angioplasty (PTRA) results in patients with uncontrolled hypertension.
Primary Endpoint	Binary restenosis rate at 9 months, defined as $\geq 60\%$ diameter stenosis, measured by duplex ultrasound (or quantitative angiography, if necessary) by an independent core laboratory. Analysis was done on a per-lesion basis.
Secondary Endpoints	<u>MAEs</u>: A composite safety endpoint of the following indices: death for any reason at 30 days; ipsilateral nephrectomy at 30 days; embolic events resulting in kidney damage at 30 days; and clinically indicated target lesion revascularization (TLR) up to 9 months (270 days). <u>Clinically Indicated Target Lesion Revascularization</u>: Defined as diameter stenosis $\geq 60\%$, as determined by the angiographic or ultrasound core laboratory, and any revascularization (including but not limited to atherectomy, embolectomy, endarterectomy, bypass surgery, repeat angioplasty, or stent implantation) to the target lesion. Freedom from clinically indicated TLR was evaluated at 9 months and is presented as time to first event on a per-lesion basis. <u>Acute Device Success</u>: The achievement of successful delivery and deployment of the assigned device(s) and successful removal of the delivery system as intended to the designated location. It was reported as a percentage of devices that were attempted to be implanted.

	<u>Acute Clinical Success</u>: Procedure success without major adverse events (MAE) or access site events requiring surgical or percutaneous intervention prior to hospital discharge. It is presented on a per subject basis. <u>Acute Procedural Success</u>: The attainment of a final result of < 30% residual stenosis as determined by the angiographic core laboratory, reported as a percentage of treated lesions. <u>Change in blood pressure</u>: Systolic and diastolic blood pressures were measured at baseline, post-procedure, 1, 6 and 9 months and the group average at each time point reported. The change at 9 months from baseline, for systolic and diastolic pressure, was calculated for each enrolled patient. Confidence intervals (95%) for the average changes were reported. In addition, systolic blood pressure was reported using categories of < 140 mmHg, ≥ 140 mmHg and < 160 mmHg, ≥ 160 mmHg and < 180 mmHg, and ≥ 180 mmHg. <u>Change in Antihypertensive Medications</u>: Number and type of antihypertensive medications at baseline, 1, 6, and 9 months were collected. The group average number of antihypertensive medications at each time point was reported. In addition, data was reported as a percentage of patients on 1, 2, 3, or 4 or more medications at baseline, 1, 6, and 9 months. <u>Change in Renal Function</u>: Defined as change in serum creatinine (sCr), it was measured at baseline, post-procedure, 1, 6 and 9 months, with the group average reported at each time point. The change at 9 months from baseline was calculated for each enrolled patient. <u>Primary Patency</u>: Defined as < 60% stenosis without prior re-intervention, as determined by duplex ultrasound or angiogram. <u>Secondary Patency</u>: Defined as rate of < 60% stenosis of the target lesion, at 9 months, as determined by duplex ultrasound or angiography regardless of PTA, stenting, or bypass since index procedure.
Study Hypothesis	Renal arteries treated with the RX Herculink Elite Stent will have a binary restenosis rate at 9 months that meets a performance goal of 28.6%.
Additional Analyses (Through 36 months)	Major Adverse Events: (death, nephrectomy, embolic events resulting in kidney damage) Target lesion revascularization (TLR) Blood pressure Anti-hypertensive medication intake Renal function

Patient Follow-up	<u>1-month clinic visit:</u> Blood pressure measurement, antihypertensive medication review, laboratory (sCr, BNP assay), duplex ultrasound, laboratory, adverse events. <u>6-month clinic visit:</u> Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr). <u>9-month clinic visit with ultrasound:</u> Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound, angiogram (only if duplex ultrasound done at nine-month follow up visit is determined to be “not evaluable”, or at the discretion of the Investigator). <u>12-month clinic visit:</u> Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr). <u>24-month clinic visit:</u> Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound. <u>36-month clinic visit:</u> Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound.
Data Source	New data collection

Study Design

The primary objective of the clinical study was to assess the binary restenosis rate at 9 months after stenting, with binary restenosis determined by duplex ultrasound or angiogram. The lesion was considered restenotic if the lesion was $\geq 60\%$ diameter prior to the 9-month primary endpoint evaluation. Specifically, the primary hypothesis was that the binary restenosis rate at 9 months on a lesion basis meets the performance goal of 28.6% (i.e., $< 28.6\%$). Secondary analyses included MAEs (defined as death for any reason at 30 days, ipsilateral nephrectomy at 30 days, clinically-indicated target lesion revascularization up to 9 months, and embolic events resulting in kidney damage at 30 days), acute device success, acute procedural success, acute clinical success; blood pressures, antihypertensive medication in-take, and renal function outcomes (measured by serum creatinine).

The HERCULES study was a prospective, non-randomized, multi-center, single-arm clinical study to demonstrate efficacy and safety of the RX Herculink Elite Renal Stent System (Herculink Elite) in the treatment of suboptimal post-procedural percutaneous transluminal renal angioplasty (PTRA) of atherosclerotic *de novo* or restenotic renal artery stenoses in patients with uncontrolled hypertension. Subjects were eligible to enroll in the study if they had a suboptimal angioplasty (defined as $\geq 50\%$ residual stenosis, ≥ 20 mmHg systolic or ≥ 10 mmHg mean translesional pressure gradient, flow-limiting dissection or TIMI [Thrombolysis In Myocardial Infarction] flow < 3) for *de novo* or restenotic renal artery lesions (≤ 15 mm length) due to atherosclerosis originating within 10 mm of the renal ostium, a reference vessel diameter ≥ 4 mm and ≤ 7 mm, and uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥ 140 mmHg or diastolic blood pressure [DBP] ≥ 90 mmHg on at least two antihypertensive medications). Treatment of two lesions, one per side, was allowed per patient. Patients were excluded from the study if they met any of the following conditions: only one functioning kidney,

kidney transplant, had a Q-wave myocardial infarction (MI) within 30-days of the index procedure, or serum creatinine ≥ 2.5 mg/dl. Angiography was performed post stent implantation. Follow-up included ultrasound imaging at 1 month, and ultrasound (angiogram, if ultrasound was not interpretable) at 9 months, 24 months and 36 months. Clinical assessments (e.g., blood chemistry, blood pressure, assessment of antihypertensive medications) were scheduled for 1, 6, 9, 12, 24, and 36 months.

Independent core laboratories analyzed angiographic and ultrasonic imaging. The study was overseen by an independent data safety monitoring board (DSMB) comprised of physicians and a biostatistician. The committee was set up and convened at the pre-specified interim time points of the trial to evaluate the safety of the trial. A Clinical Endpoint Adjudication Committee (CEAC) adjudicated the suspected cases of peri-procedural death, ipsilateral nephrectomy and embolic events that result in kidney damage.

The principal effectiveness of the Herculink Elite was evaluated to determine if the binary restenosis rate at 9 months was less than the performance goal (PG) of 28.6% that was derived from the contemporary literature of PTRAs and stenting for the atherosclerotic lesions in the aortorenal ostium. The sample size and power calculation were based on the primary endpoint of binary restenosis rate at 9 months. The PG for the binary restenosis rate at 9 months was determined to be 28.6%, based on pre-market studies of other renal artery stents used in a similar manner and which are now PMA-approved.

The primary and secondary endpoints measuring the safety and effectiveness of the device and procedure are described below.

Null Hypothesis: the 9-month binary restenosis rate, γ , is greater than or equal to 28.6%. (Interpretation: the binary restenosis rate does not meet a performance goal of 28.6%.)

$H_0: \gamma \geq 28.6\%$

Alternative Hypothesis: the 9-month binary restenosis rate, γ , is less than 28.6%. (Interpretation: the binary restenosis rate meets a performance goal of 28.6%.)

$H_a: \gamma < 28.6\%$.

The null hypothesis was tested using one-sided exact binomial test at significance level of 0.05.

For binary and categorical variables, event counts, rates and their confidence intervals were analyzed. Continuous variables were analyzed using the mean, standard deviation, and 95% confidence intervals (CI). Kaplan-Meier methodology was used to estimate the distributions of time-to-event variables.

Clinical Inclusion and Exclusion Criteria

The inclusion criteria for the HERCULES study were as follows:

- Subject is ≥ 18 years of age.
- Subject and subject's physician agree to have the subject return for all required contact following study enrollment.
- Subject has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site.
- Subject is a candidate for renal artery stenting.

- Subject has uncontrolled systolic hypertension (systolic BP $\geq$ 140 mmHg), or uncontrolled diastolic hypertension (diastolic BP $\geq$ 90 mmHg), or a combination of both in the presence of at least two (2) or more antihypertensive medications.
- Baseline sCr of $\leq$ 2.5 mg/dl.
- Subject has unilateral or bilateral *de novo* or restenotic after PTA (in-stent restenosis excluded) atherosclerotic lesion(s). If bilateral lesions are to be treated, the most severe lesion must be successfully treated without complications before progressing to treat the second lesion. Treatment of bilateral lesions is to occur in the same procedural event.
- Renal stenosis must be visually estimated to be $\geq$ 60% by angiography.
- Subject has a suboptimal PTA result, defined as one of the following:
 - $\geq$ 50% residual stenosis,
 - 10 mm Hg mean gradient or 20 mm Hg peak systolic gradient across the target lesion, or
 - A flow-limiting dissection (NHLBI grade D) or TIMI flow $<$ 3.
- Renal stenosis must be visually estimated to be within 10 mm of the aortic renal border by angiography.
- Target vessel reference diameter must be visually estimated to be $\geq$ 4 mm and $\leq$ 7 mm by angiography.
- Target lesion length must be visually estimated to be $\leq$ 15 mm (including dissection) by angiography.
- Expected ability to deliver the stent to the lesion (absence of excessive tortuosity or calcification).
- Expected ability to fully expand the stent.

The exclusion criteria for the HERCULES study were as follows:

- Known hypersensitivity or contraindication to cobalt chromium or standard intraprocedure anticoagulant(s); sensitivity to contrast which cannot be adequately pre-treated with medication.
- Known allergy or contraindication to clopidogrel (Plavix[®]) or aspirin.
- Bleeding disorder or hypercoagulable disorder, or will refuse blood transfusions.
- Gastrointestinal (GI) bleeding within 30 days before the index procedure that would interfere with antiplatelet therapy.
- Renal insufficiency, defined as serum Creatinine $>$ 2.5 mg/dl.
- Any immunosuppressive disorder, access site infection, or acute systemic infection due to any cause.
- Medical illnesses (e.g., cancer, end-stage congestive heart failure) that may cause the subject to be non-compliant with protocol requirements, confound the data interpretation, or is associated with a life expectancy of less than three years.
- Medical illnesses that would make them unlikely to respond to treatment (e.g., sickle cell nephropathy / sickle cell disease, scleroderma, arteriolar nephrosclerosis, hemolytic-uremic syndrome and vasculitis).
- Q-wave MI within 30 days before index procedure.
- Stroke or transient ischemic attack (TIA) within 30 days before index procedure.
- History of congestive heart failure and has a previously documented left ventricular ejection fraction (LVEF) $<$ 25%.

- Subject is normotensive or has adequate control of hypertension (SBP < 140 mm Hg and DBP < 90 mm Hg) utilizing diet control and / or medication regimen involving only one antihypertensive medication.
- Acute thrombophlebitis or deep vein thrombosis.
- Actively participation in another drug or device trial and did not complete the required protocol follow-up period. Subject may be enrolled only once in this study and may not participate in any other clinical trial during the follow-up period.
- Unable to understand and cooperate with study procedures or provide informed consent.
- Unable to return for follow-up visits.
- Subject is pregnant.
- Subject has undergone vascular surgery, such as coronary artery bypass grafting, abdominal aortic aneurysm repair, or aorto-femoral bypass, and has not fully recovered from the effects of surgery (< 3 months).
- Subject has planned staged treatment of bilateral renal artery stenosis.
- Subject has had prior surgical intervention to the target artery, or has undergone previous stent placement in the target lesion.
- Target lesion is located in a transplanted kidney.
- Kidney to be treated is < 8 cm as determined by duplex ultrasound report, computed tomography angiography (CTA) report, or magnetic resonance angiography (MRA) report within 180 days before procedure. If kidney size is documented by more than one method, e.g., CTA and ultrasound, and one of the methods is duplex ultrasound, the kidney size as documented by duplex ultrasound shall be used to determine study eligibility.
- Subject has planned additional ancillary procedure(s) during renal stenting procedure.

Angiographic Exclusion Criteria:

- Subject has a lesion segment, including dissection, > 15 mm in length.
- Requirement for more than 1 stent to treat full length of lesion and dissection.
- Target lesion has a total (100%) occlusion.
- Evidence of thrombus or mobile filling defect in the target lesion or vessel.
- Co-existing aneurysmal or occlusive disease of the abdominal aorta requiring surgical reconstruction during the follow-up period.
- Fibromuscular dysplasia.
- Subject artery has patent bifurcation within 10 mm of ostium that might be covered by placement of a stent.
- The target lesion is within the artery of a solitary functioning kidney or, the subject has a contralateral totally occluded renal artery.
- For planned treatment of bilateral lesions: the more critical lesion, i.e., lesion with the greater stenosis (which should be treated first), is either treated unsuccessfully or requires a bailout procedure. (NOTE: Less critical lesion is excluded at this point)

Follow-up Schedule

Clinical assessments occurred at baseline, operative / discharge and postoperative intervals at 1, 6, 9 months and 1, 2, and 3 years, as seen in **Table 3**.

Table 3. Availability of Clinical and Imaging Follow-up Data

Follow-up Period	Clinical Evaluations
1-month clinic visit	Blood pressure measurement, antihypertensive medication review, laboratory (sCr, BNP assay), duplex ultrasound, laboratory, adverse events.
6-month clinic visit	Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr).
9-month clinic visit with ultrasound	Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound, angiogram (only if duplex ultrasound done at nine-month follow up visit is determined to be "not evaluable", or at the discretion of the Investigator).
12-month clinic visit	Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr)
24-month clinic visit	Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound.
36-month clinic visit	Blood pressure measurement, antihypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound.

Clinical Endpoints

With regards to safety, there were no hypothesis-driven primary or secondary safety endpoints.

With regards to effectiveness, the primary effectiveness endpoint was evaluated according to the hypothesis that renal arteries treated with the RX Herculink Elite Renal Stent will have a binary restenosis rate at 9 months on a lesion basis that meets a performance goal of 28.6%. The formulation of the hypothesis can be found in the study design section. The study was considered a success if the primary effectiveness hypothesis was met.

Patient Accountability

Patient availability for study follow-up through 36 months is summarized in **Table 4**. The first subject was enrolled into the HERCULES study on August 31, 2007 and the last subject was enrolled on October 2, 2009. Over this period, 202 male and female subjects, who met the eligibility criteria and agreed to participate in the study and signed an informed consent, were enrolled at 37 study sites in the United States (US). Thirty-nine (39) subjects had bilateral lesions treated. Therefore, the intention-to-treat (ITT) population consists of 202 subjects and 241 lesions.

The last 36-month follow-up visit was completed on October 1, 2012. Eighteen patients expired, 21 withdrew and 4 were lost to follow-up. Three subjects had a study stent attempted without success, and a non-study stent implanted; they completed the study at the 30 day follow-up time point. Therefore, there were a total of 156 subjects eligible for the 36 month follow-up visit. Of the 156 eligible, 148 completed 36 month follow-up.

Table 4. Patient Accountability

	1-month visit	6-month visit	9-month visit	12-month visit	24-month visit	36-month visit
Death ¹	0	4	5	5	13	18
Withdrawn ¹	0	0	4	7	12	21
Lost to follow-up ¹	0	1	1	2	3	4
30-day follow-up complete for non-study stent ¹	0	3	3	3	3	3
Eligible	202	194	189	185	171	156
Missed visit ²	1	11	5	8	12	8
Follow-up complete	201	183	184	177	159	148

¹Cumulative counts.

²Missed visits for each follow-up timepoint.

Study Population Demographics and Baseline Parameters

Patient demographics (**Table 5**), medical history (**Table 6**), baseline blood pressure and medications (**Table 7**) and baseline lesion characteristics (**Table 8**) and baseline angiographic data (**Table 9**) were consistent with patient populations described in published literature of renal stent intervention. The mean age of the study populations was 72.1 ± 9.4 , with 62.4% female gender. The key risk factors include diabetes mellitus 45.0%, hypercholesterolemia 86.1%, coronary artery disease 67.3% and current or former tobacco use 56.9%. The baseline mean creatinine was 1.2 ± 0.4 mg/dl and 61.5% of subjects had an estimated baseline glomerular filtration rate (eGFR) of < 60 ml/min per 1.73 m^2 (**Table 6**).

Table 5. Patient Demographics

Demographic	Value (N = 202 patients)
Sex	
Male	37.6% (76/202)
Female	62.4% (126/202)
Age (years, mean $\pm$ SD (range))	72.1 ± 9.4 (44 - 89)
Ethnicity	
Caucasian or White	83.7% (169/202)
Black or African American	7.9% (16/202)
Hispanic or Latino	7.4% (15/202)
Other	1.0% (2/202)
Native Hawaiian or other Pacific Islander	0.5% (1/202)
Asian	0.5% (1/202)

Table 6. Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Diabetes	
Total	45.0% (91/202)
Type I	3.5% (7/202)
Type II	41.6% (84/202)
Hypercholesterolemia	
Total	86.1% (174/202)
Requiring medication	82.2% (166/202)
Not Requiring medication	4.0% (8/202)
Coronary Artery Disease	67.3% (136/202)
Brain Natriuretic Peptide (BNP) Level (pg/ml)	181.2 ± 297.0 (192)
Renal Function	
Serum Creatinine (mg/dl)	1.2 ± 0.4 (202)
eGFR < 60 ml/min per 1.73 m ²	61.5% (123/200)
Former Smoker	44.1% (89/202)
Current Smoker	12.9% (26/202)

Table 7. Baseline Blood Pressure and Medications

Past or Current Medical Condition	Percent Patients (number/total number)
Blood Pressure	
Mean Systolic	162.3 ± 18.5 (202)
Mean Diastolic	77.7 ± 11.5 (202)
Antihypertensive Medications	
1 Medication	0.5% (1/202)
2 Medications	28.2% (57/202)
3 Medications	31.7% (64/202)
≥ 4 Medications	39.6% (80/202)

Table 8. Baseline Lesion Characteristics

Characteristic	Percent Lesions (number/total number)
Lesion Location	
Right Renal Artery	52.3% (126/241)
Left Renal Artery	47.7% (115/241)
Type of Lesion	
Restenotic	0% (0/115)
<i>de novo</i>	100% (241/241)
Target Lesion Location	
Ostial	67.6% (163/241)
Within 10 mm of Ostium	32.4% (78/241)
Renal Arteries Treated	
Unilateral	67.6% (163/241)
Bilateral	32.4% (78/241)
Suboptimal PTA Outcome	
Residual Stenosis $\geq$ 50%	90.7% (214/236)
10 mmHg mean gradient or 20 mmHg peak systolic gradient	25.0% (59/236)
Flow-limiting dissection (NHLBI grade D) or TIMI flow < 3	4.7% (11/236)
Target Lesion Stenosis	81.3 $\pm$ 10.0 (241)

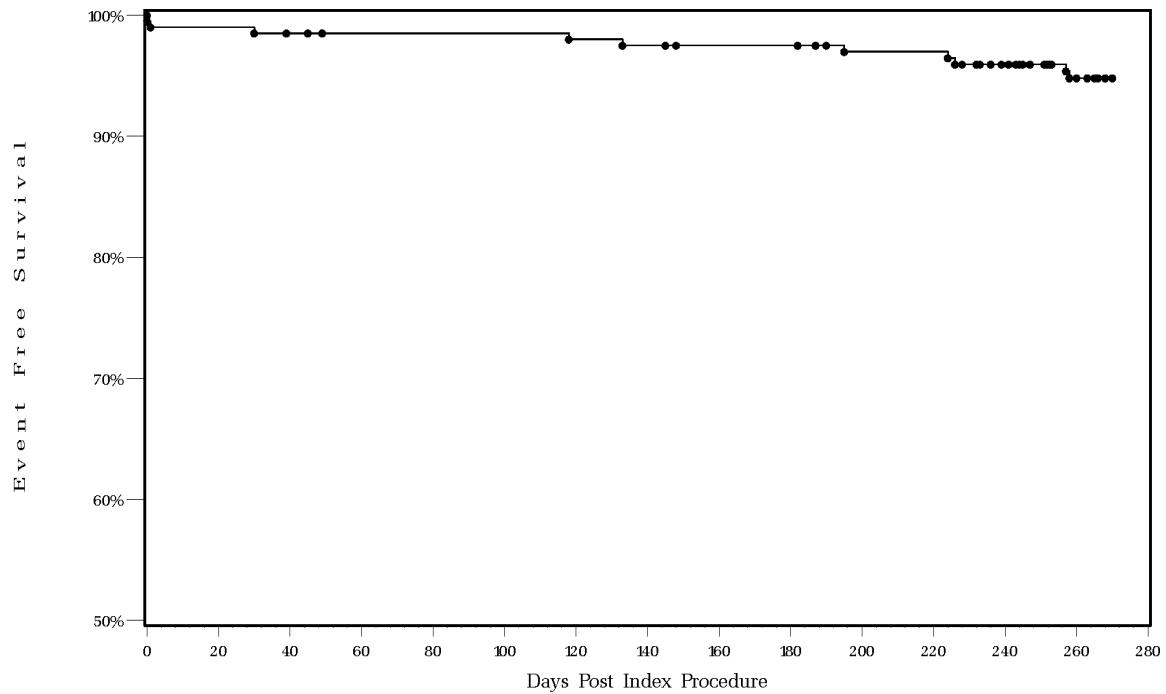
Table 9. Baseline Angiographic Data (core lab reported)

Measure	Mean $\pm$ SD (range, total lesions)
Lesion Length (mm)	8.5 $\pm$ 3.1 (1.8 – 22.1, n = 241)
Pre-procedure	
RVD (mm)	5.4 $\pm$ 1.1 (2.9 – 7.9, n = 241)
MLD (mm)	1.8 $\pm$ 0.7 (0.3 – 3.8, n = 241)
Percent Diameter Stenosis (%)	65.9 $\pm$ 11.4 (37.8 – 92.9, n = 241)

Safety and Effectiveness Results**Safety Results**

The safety endpoint for the HERCULES study is the composite rate of freedom from major adverse events (MAEs), including all cause death, ipsilateral nephrectomy, and embolic events resulting in kidney damage, all through 30 days, and clinically indicated target lesion revascularization (TLR) up to 270 days. Through the first 30 days, there was 1 death and 2 embolic events resulting in kidney damage. The freedom from MAEs and clinically indicated TLRs at 9 months was 94.8%, as shown in the Kaplan-Meier analysis (**Figure 1**). A listing of adverse effects that occurred in the clinical study through 36 months (1151 days) is shown in **Table 10**.

Figure 1. Kaplan-Meier Freedom from Death, Ipsilateral Nephrectomy and Embolic Events Resulting in Kidney Damage through 30 Days and Clinically Indicated Target Lesion Revascularization through 270 Days (Intent-to-Treat Population)



Days Post Index Procedure	0	(0, 30]	(30, 180]	(180, 270]
Subjects at Risk	202	201	198	191
Subjects Censored	0	1	5	186
Number of Events	1	2	2	5
Event Free (%)	99.5%	98.5%	97.5%	94.8%
Standard Error (%)	0.5%	0.9%	1.1%	1.6%

Table 10. Protocol Defined Major Adverse Events through 36 Months (1151 days)

MAEs Through 30-Days	(N = 202 Subjects) (N = 241 Lesions)	[95% CI]¹
All-cause death	0.5%	[0.0%, 2.7%]
Device-related death	0.0%	[0.0%, 1.8%]
Embolic events resulting in kidney damage	1.0%	[0.1%, 3.5%]
Nephrectomy	0.0%	[0.0%, 1.8%]
Clinically indicated TLR	0.0%	[0.0%, 1.8%]
Stent thrombosis	0.0%	[0.0%, 1.8%]
Retroperitoneal bleed	0.5%	[0.0%, 2.7%]
Myocardial Infarction	0.0%	[0.0%, 1.8%]
Stroke	0.0%	[0.0%, 1.8%]
Events Through 9 Months (312 Days)	(N = 202 Subjects) (N = 241 Lesions)	[95% CI]¹
Renal Failure	1.0%	[0.1%, 3.5%]
Renal Insufficiency	2.0%	[0.5%, 5.0%]
Events Through 9 Months (312 Days)²	(N = 202 Subjects) (N = 241 Lesions)	[95% CI]
All TLR	6.7%	[3.4%, 10.0%]
Clinically Indicated TLR	5.3%	[2.4%, 8.2%]
Death	2.5%	[0.3%, 4.7%]
Events Through 24 Months (786 Days)	(N = 202 Subjects) (N = 241 Lesions)	[95% CI]
All TLR ²	9.1%	[5.4%, 12.8%]
Clinically Indicated TLR ²	7.1%	[3.6%, 10.6%]
Death ²	7.1%	[3.4%, 10.8%]
Events Through 24 Months (786 Days)	(N = 202 Subjects) (N = 241 Lesions)	[95% CI]¹
Renal Failure	3.5%	[1.4%, 7.0%]
Renal Insufficiency	2.5%	[0.8%, 5.7%]
Events Through 36 Months (1151 Days)	(N = 202 Subjects) (N = 241 Lesions)	[95% CI]
All TLR	12.4%	[6.9%, 17.9%]
Clinically Indicated TLR	8.2%	[3.9%, 12.5%]
Death	9.9%	[5.6%, 14.2%]

Events Through 36 Months (1151 Days)	(N = 202 Subjects) (N = 241 Lesions)	[95% CI] ¹
Renal Failure	4.0%	[1.7%, 7.7%]
Renal Insufficiency	2.5%	[0.8%, 5.7%]

¹By Clopper Pearson exact confidence interval

²Based on Kaplan Meier estimate

Effectiveness Results

Two hundred forty-two (242) RX Herculink stents were placed to treat 241 renal artery lesions. By core lab assessment, the mean post-procedure percent diameter stenosis was 3.4% (**Table 11**). Therefore, the RX Herculink Elite Renal Stent System was effective in establishing patency at the conclusion of the procedure.

Table 11. Post-Procedure Angiographic Data (core lab reported)

Measure	Mean ± SD (range, total lesions)
Post-procedure	
MLD (mm)	5.1 ± 0.8 (3.4 – 7.3, n = 240)
Percent Diameter Stenosis (%)	3.4 ± 12.5 (-43.1 – 29.8, n = 240)

Primary Endpoint

The 9-month binary restenosis rate met the performance goal (**Table 12**). The 9-month binary restenosis rate was 10.5% and the upper limit of the 95% one-sided confidence interval was 14.7%, which is below the pre-specified performance goal of 28.6% ($p < 0.0001$). These results demonstrate the effectiveness of the RX Herculink Elite Renal Stent System in treating atherosclerotic lesions of the renal arteries following suboptimal angioplasty.

Table 12. Primary Endpoint Analysis – Binary Restenosis Rate (ITT Population)

Measure	Mean ± SD (range, total lesions)
9-Month In-Stent Binary Restenosis (≥ 60%) Rate	10.5% (22/209)
[One-Sided 95% Conf. Interval] ¹	[-, 14.7%]
One-Sided Exact Binomial Test p -value ²	< 0.0001

¹ By Clopper-Pearson exact confidence interval

² One-sided p -value is computed using the exact binomial test with the performance goal (PG) of 28.6%

Secondary Analyses

Device-related success measures ranged from 96.0% to 99.2%. Device success (successful delivery and deployment of a RX Herculink Elite stent), acute procedural success (< 30% residual stenosis post-procedure by core lab analysis), and acute clinical success (procedure success without MAE or access site event requiring surgical or percutaneous intervention prior to hospital discharge) outcomes are summarized in **Table 13**. These results support the safety and effectiveness of the RX Herculink Elite Renal Stent System in establishing renal artery patency.

Table 13. Device-related Acute Success Measures

Effectiveness	(N = 202 Subjects) (M = 241 Lesions)	[95% CI] ¹
Study Device Success	96.0% (237/247)	[92.7%, 98.0%]
Procedural Success	99.2% (238/240)	[97.0%, 99.9%]
Clinical Success	98.0% (197/201)	[95.0%, 99.5%]

¹By Clopper-Pearson exact confidence interval

Blood pressure-related outcomes demonstrated decreased systolic blood pressure from pre-procedure to 36-month follow-up. The baseline mean systolic and diastolic blood pressures were 162.3 ± 18.5 mmHg and 77.7 ± 11.5 mmHg, respectively. At 36 months mean systolic and diastolic blood pressures were 145.7 ± 20.7 mmHg and 75.4 ± 11.0 mmHg, respectively. When compared to baseline, the mean SBP was reduced at all time points (**Table 14** and **Figure 2**). The blood pressure data indicate that over 40% of subjects achieved the SBP < 140 mmHg at 36 months after renal stenting. The proportion of patients with SBP < 160 mmHg was increased to 74.8% at 36 months from the 56.4% at baseline. The proportion of patients with SBP $\geq$ 180 was decreased to 6.5% at 36 months from 19.3% at baseline (**Table 15** and **Figure 3**). These data demonstrate the clinical utility of the RX Herculink Elite Renal Stent System and suggest that revascularization with the RX Herculink Elite Renal Stent System does not adversely affect blood pressure outcomes.

Table 14. Blood Pressure Results

Blood Pressure	Mean $\pm$ SD (95% CI) ¹	
	Systolic (mmHg)	Diastolic (mmHg)
Pre-procedure	162.3 ± 18.5 (202) [159.8, 164.9]	77.7 ± 11.5 (202) [76.1, 79.3]
Post-Procedure	141.3 ± 20.8 (197) [138.3, 144.2]	67.8 ± 11.4 (197) [66.2, 69.4]
1 Month	144.9 ± 20.6 (183) [141.9, 147.9]	75.5 ± 11.2 (183) [73.9, 77.2]
6 Months	146.7 ± 23.1 (158) [143.1, 150.4]	74.8 ± 11.2 (158) [73.1, 76.6]
9 Months	145.3 ± 21.3 (173) [142.1, 148.5]	75.4 ± 11.5 (173) [73.6, 77.1]
12 Months	141.5 ± 20.5 (165) [138.4, 144.7]	74.4 ± 11.5 (165) [72.6, 76.1]
24 Months	143.6 ± 22.5 (150) [140.0, 147.3]	73.8 ± 12.2 (150) [71.8, 75.7]
36 Months	145.7 ± 20.7 (139) [142.2, 149.1]	75.4 ± 11.0 (139) [73.5, 77.2]

¹ By normal approximation

Figure 2. Summary of Systolic Blood Pressure Measurements Per Subject Analysis (Intent-to-Treat Population)

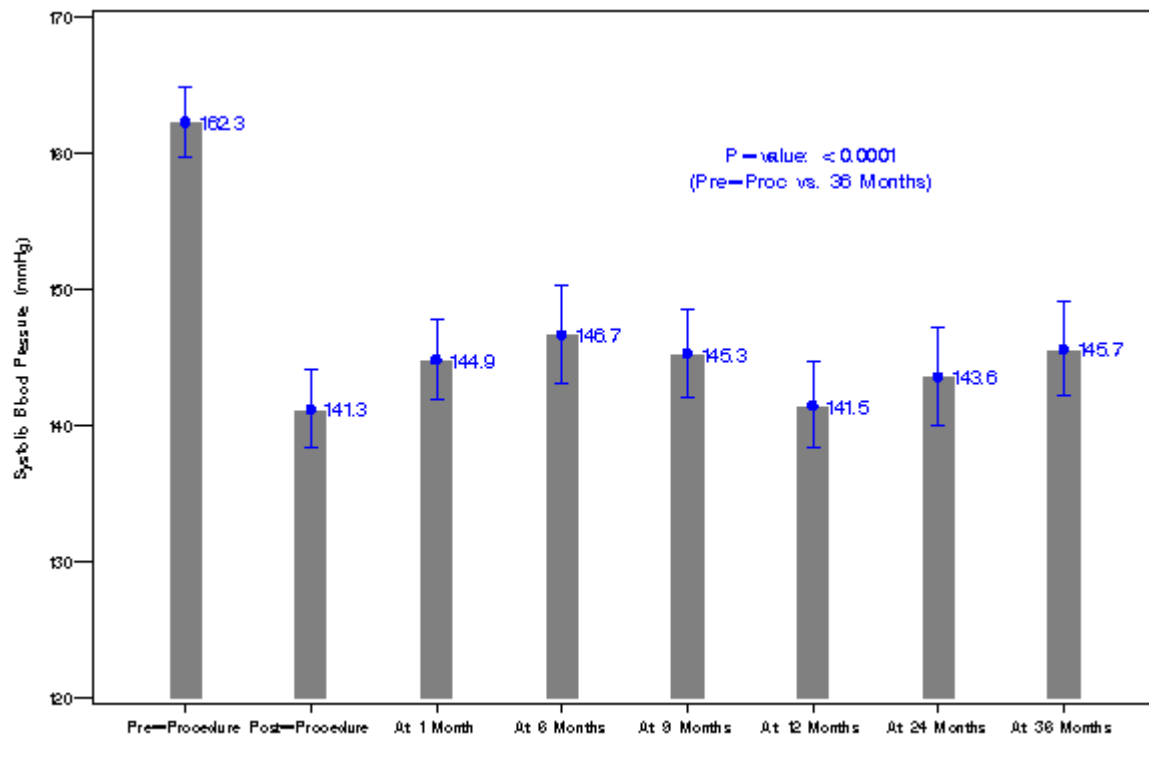
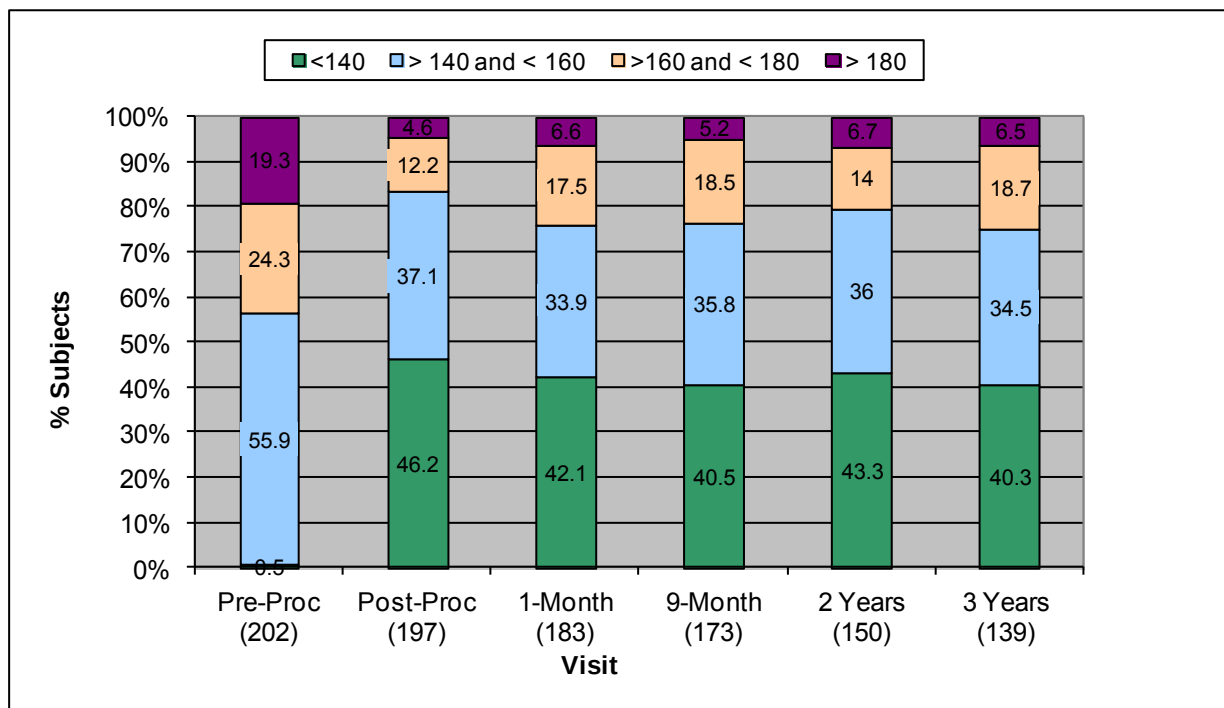


Table 15. Systolic Blood Pressure Goal Analyses

Time Period	Subjects (%) (N)	95% CI [†]
Pre-Procedure		
< 140 (mmHg)	0.5% (1/202)	[0.0%, 2.7%]
≥ 140 and < 160 (mmHg)	55.9% (113/202)	[48.8%, 62.9%]
≥ 160 and < 180 (mmHg)	24.3% (49/202)	[18.5%, 30.8%]
≥ 180 (mmHg)	19.3% (39/202)	[14.1%, 25.4%]
Post-Procedure		
< 140 (mmHg)	46.2% (91/197)	[39.1%, 53.4%]
≥ 140 and < 160 (mmHg)	37.1% (73/197)	[30.3%, 44.2%]
≥ 160 and < 180 (mmHg)	12.2% (24/197)	[8.0%, 17.6%]
≥ 180 (mmHg)	4.6% (9/197)	[2.1%, 8.5%]
30-Day		
< 140 (mmHg)	42.1% (77/183)	[34.8%, 49.6%]
≥ 140 and < 160 (mmHg)	33.9% (62/183)	[27.1%, 41.2%]
≥ 160 and < 180 (mmHg)	17.5% (32/183)	[12.3%, 23.8%]
≥ 180 (mmHg)	6.6% (12/183)	[3.4%, 11.2%]
6-Month		
< 140 (mmHg)	41.8% (66/158)	[34.0%, 49.9%]
≥ 140 and < 160 (mmHg)	33.5% (53/158)	[26.2%, 41.5%]
≥ 160 and < 180 (mmHg)	15.2% (24/158)	[10.0%, 21.8%]
≥ 180 (mmHg)	9.5% (15/158)	[5.4%, 15.2%]
9-Month		
< 140 (mmHg)	40.5% (70/173)	[33.1%, 48.2%]
≥ 140 and < 160 (mmHg)	35.8% (62/173)	[28.7%, 43.5%]
≥ 160 and < 180 (mmHg)	18.5% (32/173)	[13.0%, 25.1%]
≥ 180 (mmHg)	5.2% (9/173)	[2.4%, 9.6%]
12-Month		
< 140 (mmHg)	48.5% (80/165)	[40.6%, 56.4%]
≥ 140 and < 160 (mmHg)	32.1% (53/165)	[25.1%, 39.8%]
≥ 160 and < 180 (mmHg)	15.8% (26/165)	[10.6%, 22.2%]
≥ 180 (mmHg)	3.6% (6/165)	[1.3%, 7.7%]
24-Month		
< 140 (mmHg)	43.3% (65/150)	[35.3%, 51.7%]
≥ 140 and < 160 (mmHg)	36.0% (54/150)	[28.3%, 44.2%]
≥ 160 and < 180 (mmHg)	14.0% (21/150)	[8.9%, 20.6%]
≥ 180 (mmHg)	6.7% (10/150)	[3.2%, 11.9%]
36-Month		
< 140 (mmHg)	40.3% (56/139)	[32.1%, 48.9%]
≥ 140 and < 160 (mmHg)	34.5% (48/139)	[26.7%, 43.1%]
≥ 160 and < 180 (mmHg)	18.7% (26/139)	[12.6%, 26.2%]
≥ 180 (mmHg)	6.5% (9/139)	[3.0%, 11.9%]

[†] By Clopper-Pearson exact confidence interval

Figure 3. Systolic Blood Pressure Measurement Change Over Time Per Subject Analysis (Intent-to-Treat Population)



Change in renal function

In addition, renal function was maintained (i.e., did not worsen) from pre-procedure to 36-month follow-up based on serum creatinine levels and eGFR, further demonstrating the clinical utility of the Herculink Elite stent and suggesting that revascularization with the Herculink Elite stent does not adversely affect renal function.

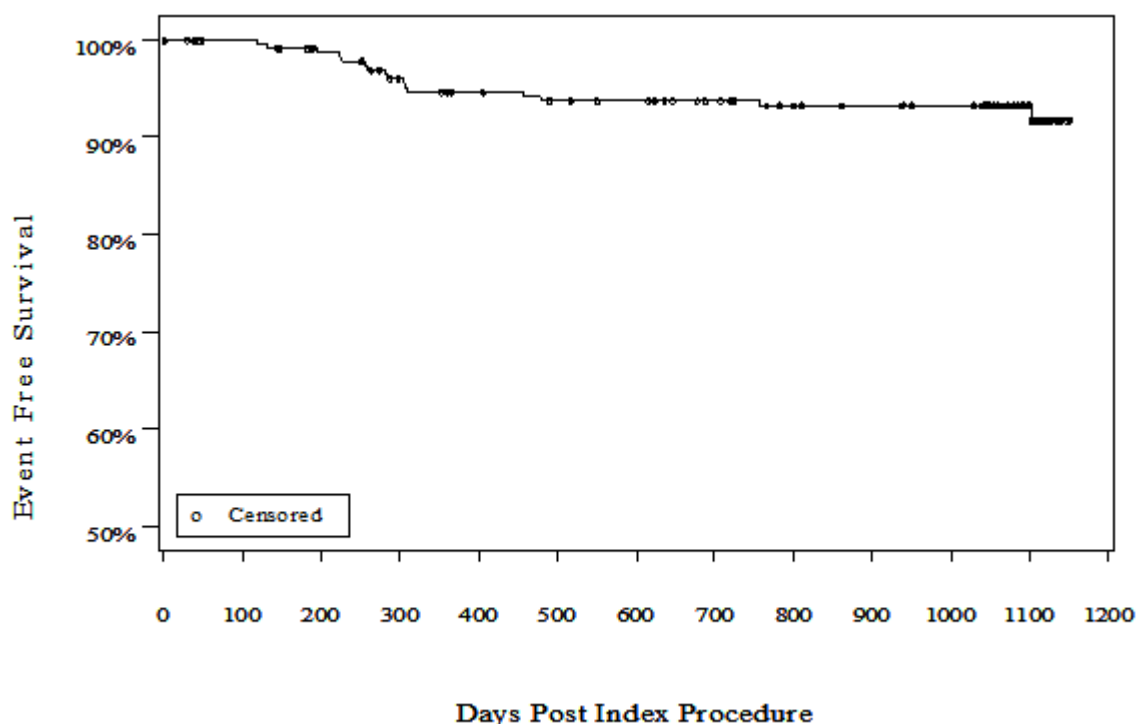
Primary and Secondary Patency

Primary and secondary patency at 9 months were 88.2% (186/211) and 95.2% (200/210), respectively. At 24 months primary and secondary patency were 84.9% (152/179) and 95.9% (163/170), and at 36 months were 82.9% (126/152) and 95.8% (136/142), respectively.

Target Lesion Revascularization

Kaplan-Meier Survival Analysis yields an 87.6% freedom from all Target Lesion Revascularization (TLR) through 36 months. Clinically indicated TLR through 9 months was determined based on the angiographic core laboratory reported percent diameter stenosis of $\geq 60\%$. Kaplan-Meier Survival Analysis yields a 91.8% freedom from clinically indicated TLR through 36 months (**Figure 4**).

Figure 4. Kaplan-Meier Survival Curve: Freedom from Clinically Indicated Target Lesion Revascularization through 1151 Days (Intent-to-Treat Population)



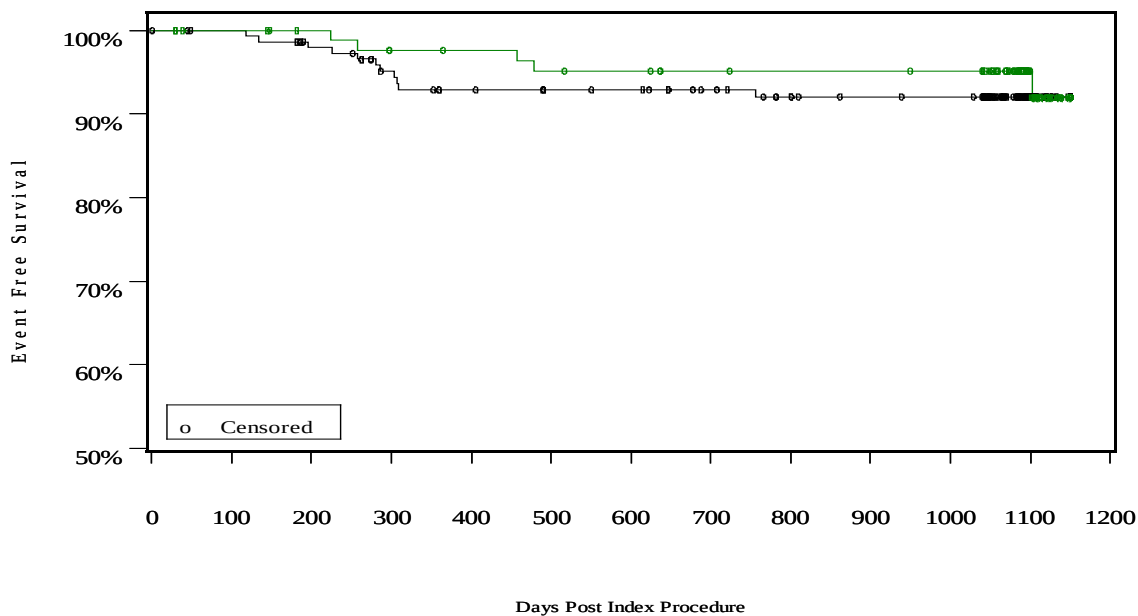
Days Post Index Procedure	0	(0, 30]	(30, 270]	(270, 365]	(365, 730]	(730, 1095]	(1095, 1151]
Number at Risk	241	241	238	217	203	183	86
Number Censored	0	3	14	9	18	96	85
Number of Events	0	0	7	5	2	1	1
Event Free (%)	100%	100%	96.9%	94.7%	93.7%	93.2%	91.8%
Standard Error (%)	0.0%	0.0%	1.1%	1.5%	1.6%	1.7%	2.2%

Subgroup Analyses

There were 126 female and 76 male subjects enrolled in the HERCULES study. The reference vessel diameter (RVD) was smaller for female subjects, 5.0 ± 0.9 mm versus 6.1 ± 1.0 mm. There was no difference in the 9-month restenosis rate between male and female subjects, 11.7% versus 9.8% ($p = 0.8157$), respectively. There was no difference in the composite rate of all cause death, ipsilateral nephrectomy, embolic events resulting in kidney damage, all through 30 days, and clinically indicated target lesion revascularization (TLR) up to 270 days between female and male subjects. There was no statistical difference in freedom from clinically indicated TLR at 3 years for female and male subjects, 92.1% versus 92.0% (Log Rank, $p=0.5515$), respectively (**Figure 5**). There was no difference in outcomes for female verses male subjects with respect to freedom from death, freedom from ipsilateral nephrectomy and freedom from site reported embolic events resulting in kidney damage, all through 1151 days. Although the

eGFR was slightly lower for female subjects, there were no statistically significant differences in estimated eGFR between male and female subjects at baseline or 3 year follow-up. The baseline mean systolic blood pressure (SBP) was higher for female subjects, 165.5 ± 19.4 mmHg versus 157.1 ± 15.5 mmHg for male subjects. At 9 months, the mean SBP was significantly reduced for both female and male subjects, 146.4 ± 23.2 mmHg versus 143.4 ± 17.7 mmHg, respectively. The SBP improvements were sustained through 3 years, with slightly lower SBP for male subjects at that time point. The key differences in antihypertensive medication intake between female and male subjects were: fewer female than male subjects were on ACE inhibitors at baseline and 30 days post procedure, and at 9 months more female than male subjects were on diuretics. At 3 years, there were no significant differences, although more female than male subjects were on diuretics.

Figure 5. Kaplan-Meier Survival Curve: Freedom from Clinically Indicated Target Lesion Revascularization through 1151 Days (Intent to Treat Population: Female vs. Male)



Black line: Female (n=151)

Green line: Male (n=90)

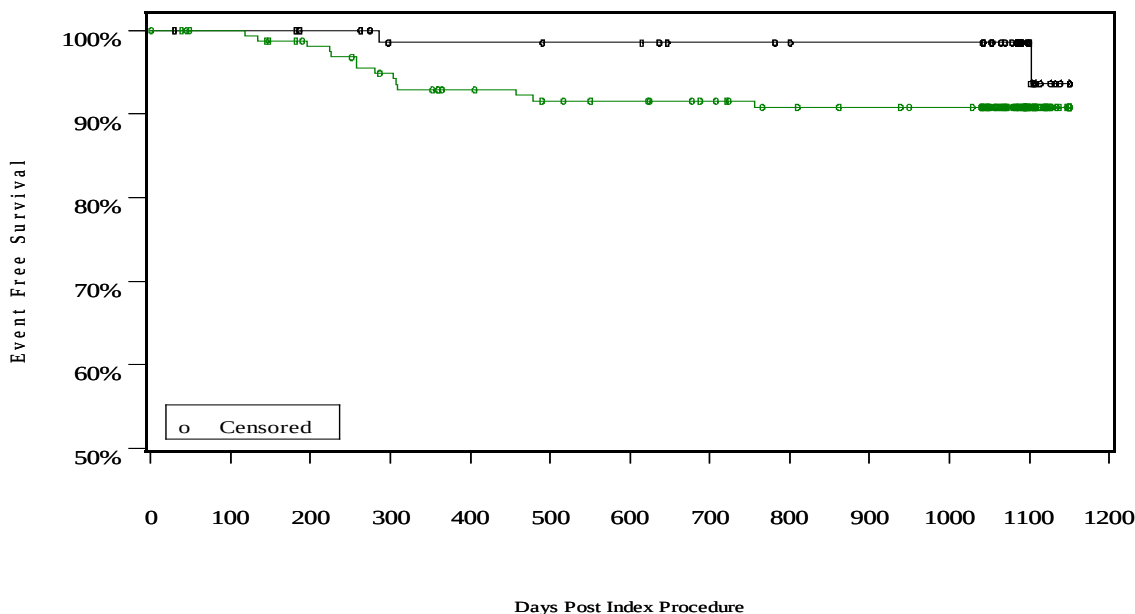
Days Post Index Procedure	0	(0, 30]	(30, 270]	(270, 365]	(365, 730]	(730, 1095]	(1095, 1151]
Female							
Number at Risk	151	151	150	135	124	111	47
Number Censored	0	1	10	6	13	63	47
Number of Events	0	0	5	5	0	1	0
Event Free (%)	100%	100%	96.5%	92.9%	92.9%	92.1%	92.1%
Standard Error (%)	0.0%	0.0%	1.5%	2.2%	2.2%	2.3%	2.3%
Male							
Number at Risk	90	90	88	82	79	72	39
Number Censored	0	2	4	3	5	33	38
Number of Events	0	0	2	0	2	0	1
Event Free (%)	100%	100%	97.6%	97.6%	95.1%	95.1%	92.0%
Standard Error (%)	0.0%	0.0%	1.7%	1.7%	2.4%	2.4%	3.9%
Tests Between Groups							
	Test	Chi-Square	DF	p-value			
	Log-Rank	0.355	1	0.5515			
	Wilcoxon	0.702	1	0.4022			

Note: Lesions at risk gives the number of lesions at risk of an event at the start of the interval, while lesions censored and number of events are the incremental counts of lesions censored or with events during the interval. The intervals are denoted as half-open bracket expression, where the start of interval 'I' is exclusive and the end of the interval 'J' is inclusive.

There were 39 bilateral subjects and 163 unilateral subjects. Females accounted for 64.1% (25/39) of bilateral subjects while males accounted for 62.0% (101/163) of unilateral subjects. At 9 months, there was no difference in the restenosis rate between bilateral and unilateral subjects, 9.5% versus 11.0%, respectively. There was no difference in the composite rate of all cause death, ipsilateral nephrectomy, embolic

events resulting in kidney damage, all through 30 days, and clinically indicated target lesion revascularization (TLR) up to 270 days between bilateral and unilateral subjects. At 3 years, by Kaplan-Meier Survival Analysis, freedom from clinically indicated TLR for bilateral versus unilateral subjects was 93.6% versus 90.8% (Log Rank, $p=0.0960$), respectively (**Figure 6**). Freedom from death, by Kaplan-Meier Survival Analysis, was no different for bilateral versus unilateral subjects, 86.3% versus 91.0%, (Log Rank $p = 0.2793$), respectively. There was no difference in freedom from ipsilateral nephrectomy and freedom from site reported embolic events resulting in kidney damage, all through 1151 days. The baseline mean systolic blood pressure (SBP) was similar for bilateral and unilateral subjects. At 9 months, the mean SBP was significantly reduced for both groups. The SBP improvements were sustained through 3 years, with slightly lower SBP for unilateral subjects at that time point and more unilateral subjects having SBP < 140 mmHg. There were no differences between bilateral and unilateral subjects with respect to sCr measurements or eGFR.

Figure 6. Kaplan-Meier Survival Curve: Freedom from Clinically Indicated Target Lesion Revascularization through 1151 Days (Intent to Treat Population: Bilateral vs. Unilateral)



Black line: Bilateral (n=78)

Green line: Unilateral (n=163)

Days Post Index Procedure	0	(0, 30]	(30, 270]	(270, 365]	(365, 730]	(730, 1095]	(1095, 1151]
Bilateral							
Number at Risk	78	78	76	70	65	58	26
Number Censored	0	2	6	4	7	32	25
Number of Events	0	0	0	1	0	0	1
Event Free (%)	100%	100%	100%	98.5%	98.5%	98.5%	93.6%
Standard Error (%)	0.0%	0.0%	0.0%	1.5%	1.5%	1.5%	5.0%
Unilateral							
Number at Risk	163	163	162	147	138	125	60
Number Censored	0	1	8	5	11	64	60
Number of Events	0	0	7	4	2	1	0
Event Free (%)	100%	100%	95.5%	92.9%	91.5%	90.8%	90.8%
Standard Error (%)	0.0%	0.0%	1.7%	2.1%	2.2%	2.3%	2.3%
Tests Between Groups							
Test	Chi-Square	DF	p-value				
Log-Rank	2.770	1	0.0960				
Wilcoxon	3.916	1	0.0478				

Note: Lesions at risk gives the number of lesions at risk of an event at the start of the interval, while lesions censored and number of events are the incremental counts of lesions censored or with events during the interval. The intervals are denoted as half-open bracket expression, where the start of interval 'i' is exclusive and the end of the interval 'j' is inclusive.

Study Strengths and Weaknesses

HERCULES was a prospective multicenter study evaluating outcomes in patients who had suboptimal PTRa and subsequent stenting. Study strengths included a prespecified, standardized definition for suboptimal PTRa ensuring physicians would use similar

criteria lesion inclusion into the trial. Restenosis, the primary endpoint, was independently evaluated by a duplex ultrasound core laboratory or an angiographic core laboratory. Because blood pressure was being evaluated, a standardized methodology for blood pressure measurements was utilized throughout the study. An independent clinical events committee determined whether target lesion revascularization (TRL) was clinically indicated. An independent data safety and monitoring board (DSMB) provided safety oversight for the study. Adding to scientific knowledge, brain natriuretic peptide (BNP) levels were measured at baseline, within 24 hours post-procedure, and at 30 days post procedure to evaluate whether they were predictive of systolic blood pressure response post-PTRA.

Limitations of the trial were that HERCULES was a non-randomized, single arm study that enrolled a majority of Caucasian patients.

8.2 Materials Required

- Introducer sheath / guiding catheter in the appropriate size and configuration for the selected Stent Delivery System (Refer to **Table 1**).
- 2 – 3 syringes (10 – 20 cc)
- 1,000 u/500 cc normal saline
- 0.014" (0.36 mm) diameter guide wire of appropriate length
- 60% contrast diluted 1:1 with normal saline
- Inflation device
- Three-way stopcock
- Torque device (if applicable)
- Guide wire introducer

8.3 Stent Inspection Prior To Use

Prior to using the RX Herculink Elite Renal Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent is located between the radiopaque balloon markers. Do not use if any defects are noted.

8.4 Lesion Preparation

1. Standard percutaneous technique should be used to place the introducer sheath / guiding catheter in the vessel. An appropriate sized (0.014") guide wire should be advanced across the lesion and into the common vessel.
2. Pre-dilate the lesion with an appropriate size balloon dilatation catheter to closely match the lumen diameter proximal and distal to the lesion.
3. Withdraw the balloon dilatation catheter leaving the guide wire in place.

8.5 Guide Wire Lumen Flush

1. Remove the protective cover from the tip.
2. Using the flush tool, flush the guide wire lumen with HepNS until fluid exits the guide wire exit notch.

8.6 Stent Delivery System Preparation

1. Prepare an inflation device / syringe with diluted contrast medium.
2. Attach the inflation device / syringe to the stopcock; attach to the inflation port.
3. With the tip down, orient the Delivery System vertically.
4. Open the stopcock to the Delivery System; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the Delivery System; purge the inflation device / syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. **Note:** If air is seen in the shaft, repeat Delivery System Preparation steps 3 through 5 to prevent uneven stent expansion.
7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the Delivery System, leave on neutral.

8.7 Stent Delivery Procedure

1. Wipe the exposed guide wire with Heparinized saline to remove residual blood or contrast medium.
2. Fully open the hemostatic valve. Maintain neutral pressure on the inflation device.
3. Backload the Delivery System onto the proximal portion of the guide wire while maintaining guide wire position across the target lesion.
4. Advance the Delivery System over the guide wire to target lesion. Utilize radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm stent position. If applicable tighten the hemostatic valve.
Note: If during the process of moving the Delivery System into position you notice the stent has moved on the balloon, do not deploy the stent. The entire system should be **removed as a single unit**. See *Stent / System Removal – Precautions* section for specific removal instructions.
5. The stent is now ready to be deployed.

8.8 Stent Deployment Procedure

CAUTION: Refer to product label for *in vitro* stent outer diameter, deployment pressure, and RBP.

1. Slowly inflate the delivery balloon to low pressure; hold until balloon inflation is observed both proximally and distally to the stent. Continue balloon expansion to the specified stent deployment pressure. Confirm complete expansion of the stent / balloon fluoroscopically. If necessary, the delivery balloon can be used to post dilate the stent to optimize stent apposition.

Do not exceed RBP: A larger PTA catheter may be used to dilate the stent. Do not expand the 4.0 mm – 6.0 mm stents beyond 7.0 mm. Do not expand 6.5 mm – 7.0 mm **stents beyond 8.0 mm**.

2. After stent deployment, draw negative pressure on the inflation device for 30 seconds or until the delivery balloon is fully deflated.
3. Return the inflation device to neutral pressure to allow the balloon to refold during removal through the guide catheter.

-
4. With the inflation device on **neutral pressure**, carefully withdraw the delivery catheter with the guide wire remaining across the lesion.

Note: Should **unusual resistance** be felt **at any time** during either lesion access, or removal of an undeployed stent, the Stent System, wire, and guiding catheter should be **removed as a single unit**. See *Stent / System Removal – Precautions* section for specific removal instructions.

5. Confirm optimal stent apposition using standard angiographic techniques. If necessary, post dilate within stent. Post dilatation balloon diameters should closely match vessel reference diameter

9.0 REFERENCES

The physician should consult current literature on current medical practice on balloon dilatation and placement of balloon expandable stents.

10.0 PATENTS AND TRADEMARKS

This product and / or its use may be covered by one or more of the following United States Patents: 6,296,655; 6,419,693; 6,428,568; 6,482,166; 6,568,235; 6,589,207; 6,651,478; 6,736,843; 6,827,734; 6,835,059; 6,840,081; 7,060,218. Additional patents pending.

Herculink Elite is a registered trademark of the Abbott Group of Companies.

Plavix is a registered trademark of Sanofi-Aventis.

Abbott Vascular

Santa Clara, CA 95054-2807 USA

CUSTOMER SERVICE

TEL: (800) 227-9902

FAX: (800) 601-8874

Outside USA TEL: (951) 914 -4669

Outside USA FAX: (951) 914 -2531

Graphical Symbols for Medical Device Labeling

 Manufacturer	 Sterilized using irradiation
 Catalogue number	 Outer diameter
 French size	 Stent length
 Consult instructions for use	 Date of manufacture
 Contents (numeral represents quantity of units inside)	 Use by
 Do not reuse	 Batch code
	 MR Conditional

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RX Herculink Elite Biliary Stent System

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

1.0 DEVICE DESCRIPTION

The **RX Herculink Elite Biliary Stent System** includes:

- A balloon expandable L605 cobalt chromium alloy stent pre-mounted on the balloon of a rapid exchange (RX) stent delivery system
- Two radiopaque markers located underneath the balloon which identify the stent position and fluoroscopically mark the working length of the balloon
- Proximal shaft markers to aid with delivery catheter position, relative to a biliary guiding catheter tip
- A third marker located approximately 30 cm from the center of the balloon that aids in locating the guide wire exit lumen and facilitating catheter removal and exchange

The delivery system can be utilized to optimize the stent wall apposition post stent deployment.

Table 1. *In Vitro Device Specifications**

Expanded Stent Diameter (mm)	Stent Lengths (mm)	<i>In Vitro</i> * Stent Deployment Pressure (atm)	Rated Burst Pressure RBP (atm)	Recommended Minimum Guiding Catheter ID (F) / (inches) / (mm)	Recommended Minimum Sheath Introducer** (F) / (inches) / (mm)
4.0	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
4.5	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
5.0	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
5.5	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
6.0	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
6.5	12, 15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80
7.0	15, 18	11	14	6 / 0.067 / 1.70	5 / 0.071 / 1.80

* All data provided is based on *in vitro* testing. Assure full deployment of the stent (see *Clinician Use Information* section 8.8 *Stent Deployment Procedure*). Deployment pressures should be based on stricture characteristics.

** See individual manufacturer specifications for (F) equivalent

2.0 HOW SUPPLIED

Sterile. This device is sterilized with electron beam radiation. Non-pyrogenic. Do not use if the package is open or damaged.

Storage. Store in a dry, dark, cool place.

Contents. One (1) **RX Herculink Elite Biliary Stent System**, one (1) Protective / Regrooming sheath, one (1) flush tool

3.0 INDICATIONS

The **RX Herculink Elite Biliary Stent System** is intended for palliation of malignant strictures in the biliary tree.

4.0 CONTRAINDICATIONS

The **RX Herculink Elite Biliary Stent System** is contraindicated for use in:

- Stenting a perforated duct where the leakage from the duct can be enhanced by the prosthesis
- Patients with bleeding disorders
- Severe ascites

5.0 WARNINGS

The long term safety and effectiveness of this device in the biliary system have not been established.

Should **unusual resistance** be felt **at any time** during stricture access or Delivery System removal, the introducer sheath / guiding catheter and stent system should be removed **as a single unit**. Applying excessive force to the Stent Delivery System can potentially result in loss or damage to the Stent and Delivery System components. (See *Stent / System Removal – Precautions*.)

Stenting across a major bifurcation may hinder or prevent future diagnostic or therapeutic procedures.

Once fully deployed, the stent cannot be repositioned.

Persons allergic to L605 cobalt chromium alloy may suffer an allergic reaction to this implant.

Only physicians familiar with the complications, side effects and hazards commonly associated with biliary stent placement should use this device.

The RX Herculink Elite Biliary Stent System is intended to perform as a system. The stent should not be removed for use in conjunction with other dilatation catheters, nor should the RX Herculink Elite Biliary Stent System be used in conjunction with other stents.

The safety and effectiveness of multiple overlapping stents have not been established. However, when multiple stents are required, stent materials should be of similar composition.

6.0 PRECAUTIONS

6.1 Stent Delivery System Handling – Precautions

- **For single use only.** Do not resterilize or reuse. Note product "Use By" date.
- **Do not remove stent from its delivery balloon.**
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important during stent system removal from the packaging, placement over a guide wire and advancement through a guiding catheter or introducer sheath.

-
- Do not "roll" the mounted stent with your fingers as this action may loosen the stent from the delivery balloon.
 - Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

6.2 Stent Placement – Precautions

- Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use balloon purging technique described in the *Clinician Use Information* section.
- The inflated balloon diameter of the system used to deploy the stent should approximate the diameter of the bile duct. Oversizing of the stent can result in a ruptured bile duct. To ensure full expansion of the stent, the balloon should be inflated to a minimum of nominal pressure.
- Implanting a stent may lead to dissection of the duct distal and / or proximal to the stent and may cause acute closure of the duct requiring additional intervention (surgical intervention, further dilatation, placement of additional stents, or other).
- Do not expand the stent if it is not properly positioned in the bile duct. (See *Stent / System Removal - Precautions*.)
- Balloon pressures should be monitored during inflation. **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** Use of pressures higher than specified on product label may result in a ruptured balloon with possible bile duct damage or perforation.

Do not attempt to pull an unexpanded stent back through the introducer sheath / guiding catheter; dislodgment of the stent from the balloon may occur.

6.3 Stent / System Removal – Precautions

Should **unusual resistance** be felt **at any time** during either stricture access or removal of the Delivery System post-stent implantation, the entire system should be removed **as a single unit**.

When removing the Delivery System as a single unit:

- DO NOT retract the Delivery System into the introducer sheath / guiding catheter.
- Position the proximal balloon marker just distal to the tip of the introducer sheath / guiding catheter.
- Advance the guide wire in the anatomy as far distally as safely possible.
- Secure the Delivery System to the introducer sheath / guiding catheter; then remove the introducer sheath / guiding catheter, guide wire and Delivery System as a **single unit**.

Failure to follow these steps and / or applying excessive force to the Delivery System can potentially result in loss or damage to the stent and / or Delivery System components.

If it is necessary to retain guide wire position for subsequent biliary access, leave the guide wire in place and remove all other system components.

6.4 Post Implant – Precautions

Great care must be exercised when **crossing a newly deployed stent** with a guide wire or balloon catheter to avoid disrupting the stent geometry.

Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the Herculink Elite stent, in single and in overlapped configurations up to 33 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for any duration of MRI scan that would otherwise be safe for the patient without implant.

MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the Herculink Elite stent.

The Herculink Elite stent should not migrate in this MRI environment. Magnetic force on the Herculink Elite stent was tested according to ASTM F2052-06e. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating.

Stent heating was derived by using the measured non-clinical, *in vitro* temperature rise according to ASTM F2182-09 in a GE Signa HDx 3 Tesla scanner and in a GE 1.5 Tesla coil in combination with the local specific absorption rates (SARs) in a digitized human heart model. The temperature rise was derived by a validated calculation. At overlapped lengths up to 33 mm, the Herculink Elite stent produced a non-clinical maximum local temperature rise of less than 3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for an MRI sequence of 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 33 mm in length or stents with fractured struts are unknown.

Image artifact may be present when scanning the Herculink Elite stent as demonstrated in non-clinical testing performed according to ASTM F2119-07 in a GE Signa HDx 3 Tesla scanner. The image artifact (both inside and outside the device lumen) extends approximately 7 mm from the device using the spin echo sequence (TR = 500 ms; TE = 20 ms; flip angle = 90°) and 13 mm from the device using the gradient echo sequence (TR = 100 ms; TE = 15 ms; flip angle = 30°). MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the Herculink Elite stent. Therefore, it may be necessary to optimize the MR imaging parameters in the presence of Herculink Elite stents.

7.0 POTENTIAL ADVERSE EVENTS

Potential complications associated with the use of a biliary stent may include, but are not limited to, the following:

- Abscess
- Bile duct occlusion / obstruction
- Bile duct injury, including rupture and perforation
- Cholangitis
- Death
- Hypersensitivity or allergic reaction to drugs
- Infection
- Pancreatitis
- Parenchymal hemorrhage
- Peritonitis
- Sepsis
- Tumor overgrowth at the stent ends

8.0 CLINICIAN USE INFORMATION

8.1 Materials Required

- Introducer sheath / guiding catheter in the appropriate size and configuration for the selected Stent Delivery System (Refer to **Table 1**).
- 2 – 3 syringes (10 – 20 cc)
- 1,000 u/500 cc normal saline
- 0.014" (0.36 mm) diameter guide wire of appropriate length
- 60% contrast diluted 1:1 with normal saline
- Inflation device
- Three-way stopcock
- Torque device (if applicable)
- Guide wire introducer

8.2 Stent Inspection Prior To Use

Prior to using the **RX Herculink Elite Biliary Stent System**, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent is located between the radiopaque balloon markers. Do not use if any defects are noted.

8.3 Stricture Evaluation / Biliary Drainage

Standard percutaneous transhepatic cholangiography should be performed to assess the biliary tree followed by the passage of a guide wire through the stricture and the placement of an internal / external biliary drainage catheter.

8.4 Stricture Pre-dilatation

1. Standard percutaneous technique should be used to place an introducer sheath / guiding catheter in the biliary tree. A 0.014" (0.36 mm) diameter guide wire should be advanced across the stricture and into the common bile duct.
2. Stricture and bile ducts may need to be pre-dilated with balloon dilatation. Pre-dilatation catheter diameters should closely match the duct diameter proximal and distal to the stricture to be treated.

8.5 Guide Wire Lumen Flush

1. Remove the protective cover from tip.
2. Using the flush tool, flush the guide wire lumen with normal saline until fluid exits the guide wire exit notch.

8.6 Stent Delivery System Preparation

1. Prepare an inflation device / syringe with diluted contrast medium.
2. Attach the inflation device / syringe to the stopcock; attach to the inflation port.
3. With the tip down, orient the Delivery System vertically.
4. Open the stopcock to the Delivery System; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the Delivery System; purge the inflation device / syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. **Note:** If air is seen in the shaft, repeat Balloon Preparation steps 3 through 5 to prevent uneven stent expansion.
7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the Delivery System, leave on neutral.

8.7 Stent Delivery Procedure

1. Wipe the exposed guide wire with normal saline.
2. Maintain neutral pressure on inflation device.
3. Backload the Delivery System onto the proximal portion of the guide wire while maintaining guide wire position across the stricture.
4. Advance the Delivery System over the guide wire to target stricture. Utilize radiopaque balloon markers to position the stent across stricture; perform cholangiography to confirm stent position.

Note: If during the process of moving the Delivery System into position you notice the stent has moved on the balloon, do not deploy the stent. The entire system should be removed as a single unit. See *Stent / System Removal - Precautions* section for specific Delivery System removal instructions.

5. The stent is now ready to be deployed.

8.8 Stent Deployment Procedure

CAUTION. Refer to product label for *in vitro* stent outer diameter, deployment pressure, and RBP.

1. Slowly inflate the delivery balloon to low pressure; hold until balloon inflation is observed both proximally and distally to the stent. Continue balloon expansion to the specified stent deployment pressure. Confirm complete expansion of the stent / balloon fluoroscopically. If necessary, the delivery balloon can be used to post dilate the stent to optimize stent apposition.

Do not exceed RBP. A larger dilatation catheter may be used to dilate the stent.

Do not expand the 4.0 mm - 6.0 mm diameter stent beyond 7.0 mm. Do not expand the 6.5 mm - 7.0 mm diameter stent beyond 8.0 mm.

2. After stent deployment, draw negative pressure on the inflation device for 30 seconds or until the delivery balloon is fully deflated.
3. Return the inflation device to neutral pressure to allow the balloon to refold during removal through the guide catheter.
4. With the inflation device on neutral pressure, carefully withdraw the delivery catheter with the guide wire remaining across the stricture.

Note: Should **unusual resistance** be felt at **any time** during either stricture access or removal of an undeployed stent, the Stent System, guide wire and guiding catheter should be **removed as a single unit**. See *Stent / System Removal – Precautions* section for specific removal instructions.

5. Confirm optimal stent apposition using standard cholangiographic techniques. If necessary, post dilate within the stent. Post dilatation balloon diameters should closely match bile duct reference diameter.

9.0 REFERENCES

The physician should consult current literature on current medical practice on balloon dilatation and placement of balloon expandable stents.

10.0 PATENTS AND TRADEMARKS

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Additional patents pending.

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Abbott Vascular

Santa Clara, CA 95054-2807 USA

CUSTOMER SERVICE

TEL: (800) 227-9902

FAX: (800) 601-8874

Outside USA TEL: (951) 914-4669

Outside USA FAX: (951) 914-2531

Graphical Symbols for Medical Device Labeling

	
Manufacturer	Sterilized using irradiation
	
Catalogue number	Outer diameter
	
French size	Stent length
	
Consult instructions for use	Date of manufacture
	
Contents (numeral represents quantity of units inside)	Use by
	
Do not reuse	Batch code
	
	MR Conditional

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