Supplemental material

Randomized Trial of a Drug Coated Balloon Angioplasty in Failing AV Fistulae

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For the Lutonix AV Clinical Trial Investigators

Appendix 1. Inclusion and exclusion criteria

Inclusion criteria

1. Age ≥21 years
2. Willing and able to sign informed consent
3. Arteriovenous fistula located in the arm presenting with any clinical, physiological or hemodynamic abnormalities warranting angiographic imaging as defined in the K/DOQI guidelines
4. Native AV fistula was created ≥30 days prior to the index procedure and had undergone one or more hemodialysis sessions utilizing two needles and no hemodialysis catheter had been present for ≥30 days (immature fistulae were not allowed)
5. Venous stenosis of an AV fistula meeting the following criteria:
    a) Target lesion was located from the anastomosis to the axillary-subclavian vein junction, as defined by insertion of the cephalic vein
    b) Lesion length ≤10cm
    c) Reference vessel diameter 4-12mm
    d) ≥50% stenosis by angiographic measurement
    e) At least one clinical, physiological or hemodynamic abnormality attributable to the stenosis as defined in the K/DOQI guidelines
6. Successful predilation of the target lesion with a percutaneous transluminal angioplasty (angioplasty) balloon defined as:
    a) No clinically significant dissection
    b) No extravasation requiring treatment
    c) Residual stenosis ≤30% by angiographic measurement
    d) Ability to completely efface the waist using the pre-dilation balloon
7. Intended target lesion or if a tandem lesion (≤ 2cm apart) could be treated with ≤120 mm of drug coated balloons in length

Exclusion criteria

1. Women who were pregnant, lactating, or planning on becoming pregnant during the study
2. Hemodialysis access located in the leg
3. Subject had more than two lesions in the access circuit
4. Subject had a secondary non-target lesion that could not be successfully treated
5. Target lesion located central to the axillary-subclavian vein junction
6. The subject had a secondary lesion located in the central venous system (central to the axillary-subclavian vein junction) which, in the opinion of the investigator, is clinically significant (treatment of an asymptomatic lesion was not allowed)
7. A thrombosed access or an access with thrombosis treated ≤30 days prior to the index procedure
8. Surgical revision of the access site planned or expected ≤6 months after the index procedure
9. Prior surgical interventions of the access site ≤30 days before the index procedure
10. Planned concomitant procedure (e.g. coil embolization) during the index procedure
11. Known contraindication (including allergic reaction) or sensitivity to iodinated contrast media, that could not be adequately managed with pre-and post-procedure medication
12. Known contraindication (including allergic reaction) or sensitivity to paclitaxel.
13. Subjects who were taking immunosuppressive therapy or are routinely taking ≥10 mg of prednisone per day;
14. Subject had another medical condition, which, in the opinion of the investigator, might cause him/her to be noncompliant with the protocol or confound the data interpretation
15. Subject had a life expectancy <12 months
16. Anticipated for a kidney transplant via a living donor
17. Anticipated conversion to peritoneal dialysis in the next 6 months
18. Subject had one of the following:

a) Bare metal stent in the target or secondary non-target lesion
b) Covered stent in the target or secondary non-target lesion

19. Subject had an infected AV access or systemic infection;
20. Currently participating in an investigational drug, biologic, or device study, or previous enrollment in the study

Appendix 2

Definitions

Access Circuit	The area from the AV access anastomosis to the superior vena cava-right atrial junction.
Access Circuit Primary Patency	Interval following intervention until the next access circuit thrombosis or repeated intervention. Ends with treatment of a lesion anywhere within the access circuit.
Adverse Event – AE	Any unfavorable and unintended sign, symptom, or disease temporally associate with the use of an investigational product, whether or not related to the investigational product.
Serious Adverse Event - SAE	An AE that: • Results in death, • Is life threatening, • Requires inpatient hospitalization or prolongation of existing hospitalization (>24hrs), • Results in persistent or significant disability/incapacity, or • Is a congenital anomaly/birth defect. • Requires intervention to prevent permanent impairment or damage
Anticipated Adverse Event	Any AE whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the CIP, predefined in the CIP and/or IFU.
Adverse Device Effect -ADE	An AE related to the use of the study device.

Serious Adverse Device Effect - SADE	A SADE is an ADE that has resulted in any of the consequences characteristic of a SAE.
Unanticipated Adverse Device Effect - UADE	A UADE is an ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Anastomosis	The site(s) of surgical connection between an AV access graft or artery (fistula) and venous structures.
Arteriovenous Fistula	Surgically created communications between the artery and vein in an extremity. Direct communications are called arteriovenous fistulae (AVFs).
Arteriovenous Graft	A natural or synthetic tube structure used for AV access.

Clinical or Physiological Abnormalities	Per K/DOQI guideline, stenoses should be treated in the presence of the following clinical or physical abnormalities.
	• Decreased access blood flow (<500mL/min, 25% decrease in flow)
	• Elevated venous pressures
	• Decreased dialysis dose (Kt/V)
	• Abnormal physical exam:
	  o Diminished or abnormal thrill (focal, systolic only, etc)
	  o Pulsatility
	  o Flaccid access
	  o Abnormal bruit
	  o Arm or hand swelling
	• Prolonged bleeding
	• Difficult puncture
	• Infiltration
	• Recirculation
	• Pulling clots

Clinical Success	The resumption of dialysis for at least one session after the index procedure.

Clinically driven reintervention	Clinically driven reintervention is defined as a lesion that is ≥50% stenosis and at least one clinical, physiological or hemodynamic abnormality attributable to the stenosis defined in the K/DOQI guidelines.
	• Decreased access blood flow (<500mL/min, 25% decrease in flow)
	• Elevated venous pressures
	• Decreased dialysis dose (Kt/V)
	• Abnormal physical exam:
	  o Diminished or abnormal thrill (focal, systolic only, etc)
	  o Pulsatility
	  o Flaccid access
	  o Abnormal bruit
	  o Arm or hand swelling
	• Prolonged bleeding
	• Difficult puncture
	• Infiltration
	• Recirculation
	• Pulling clots

Device Deficiency - DD	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance and may include malfunctions, use errors, and inadequate labeling
Device Malfunction	Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Device Success	Successful delivery to the target lesion, deployment, and retrieval at index procedure. If a device is inserted into the subject but not used due to user error (e.g. inappropriate balloon length or transit time too long), this device will not be included in the device success assessment
Discharge	The time point at which the subject was released from the admitting hospital or transferred to another facility.
Hemodynamic Success	Reduction of venous dialysis pressures, reduction of static intragraft/cuffed brachial static pressure ratios and increase in access volume flows.
Investigational Device	Lutonix 035 Drug Coated Balloon PTA Catheter, Model 9010
Kidney Disease Outcomes Quality Initiative-K/DOQI	K/DOQI™ has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD) and related complications since 1997.
Lutonix DCB	Lutonix 035 Drug Coated Balloon PTA Catheter, the same device as the previously approved product for superficial femoral and popliteal arteries (with exception of expanded balloon size range).
Procedural Success	At least one indicator of hemodynamic success (e.g., physical examination with restoration of a thrill, direct measurement of flow) in the absence of peri-procedural (index procedure and through hospital stay) Serious Adverse Device Effects (SADEs).

Reference Vessel Diameter	According to K/DOQI guidelines "the diameter of the immediately upstream or downstream normal vessel", whichever is smallest. • Perianastomotic stenoses: If there is no usable adjacent normal vein to use, such as in stenosis beginning at the anastomosis and ending in an aneurysmal vein, the adjacent arterial diameter may be used as the RVD.
Screen Failures	Subjects screened and who have given their informed consent, but not meeting all study entry criteria and hence are not randomized, are considered screening failures and will be documented as such on the Screening Logs.
Secondary Non-Target Lesion	A secondary non-target lesion in the access circuit which may be treated as per the clinical protocol.
Society of Interventional Radiology	The Society of Interventional Radiology (SIR) is a national organization of physicians, scientists and allied health professionals dedicated to improving public health through disease management and minimally invasive, image-guided therapeutic interventions.
Stenosis	Narrowing of the vessel. Percent (%) stenosis or residual stenosis is measured in comparison to the reference vessel diameter (RVD).
Study Device	Lutonix 035 Drug Coated Balloon PTA Catheter, Model 9010 (investigational) or Standard PTA Catheter
Successful Pre-dilation	Treatment of the lesion with an angioplasty balloon (including fiber/ultra high pressure) resulting in: a) No clinically significant dissection b) No extravasation requiring treatment c) Residual stenosis ≤30% by angiographic measurement d) Ability to completely efface the waist using the pre-dilation balloon
Target Lesion	Lesion(s) that are to be treated with a study device during the index procedure.

Target Lesion Primary Patency	Target Lesion Primary Patency (TLPP) is defined as the interval following index procedure intervention until clinically driven reintervention of the target lesion or access thrombosis through 6 months.
Thrill	The vibration or tremble of blood flow in a graft or fistula.
Treatment Area	The entire treated vessel segment(s) in which the study device angioplasty balloons were inflated (the injury segment) in access circuit including the Target Lesion(s).

Appendix 3

Details of Study Device and Procedure

The drug coated balloon used in the study (Lutonix 035 DCB Catheter, Lutonix, Minneapolis, MN) is an over-the-wire, 0.035" guidewire compatible percutaneous angioplasty catheter with a paclitaxel-based coating on the balloon portion of the catheter. Paclitaxel is a well-characterized anti-proliferative agent, and was the active pharmaceutical ingredient, while excipients polysorbate and sorbitol were also present on the balloon. The balloon was coated with a uniform 2 μg/mm2 of paclitaxel. Balloon diameters from 4-12 mm were available. In contrast to the pre-dilation balloon, the drug coated balloon is a partially compliant low pressure balloon with rated burst pressure 10-12 atmospheres depending on diameter. When determining percent stenosis for eligibility, stenosis was measured from the fistulogram images by determining the minimal luminal diameter of the stenosis and the diameter of the adjacent normal vessel (reference), then applying the formula % stenosis=[1-(minimal luminal diameter/reference)] x 100. All fistulograms were analyzed by the Core Lab (Yale Cardiovascular Research Group, New Haven, CT) in a blinded fashion via quantitative vessel analysis software (QAngio XA, MEDIS, Leiden, The Netherlands) using an interpolated reference approach. Study and control balloon diameter were identical to that of the high pressure predilation balloon, the diameter of which was selected at the investigator's discretion with the intention of 1 mm overdilation compared to the diameter of the adjacent normal vessel. Drug coated balloon length was selected such that there was at least 5 mm extra length on either end compared to the pre-dilation balloon; this was done to minimize "geographic miss". The control balloon was of similar design to the study balloon. Depending on the arm of the study to which the patient was randomized, either the drug coated balloon or control balloon was inflated to at least nominal pressure at the same site as predilation and remained fully expanded for a minimum of 30 seconds in order to allow maximal drug transfer to the vessel wall. Following drug delivery, additional measures such as prolonged angioplasty were allowed in both arms of the study to achieve ≤30% stenosis.

Appendix 4

Statistical Analysis

OVERVIEW OF STUDY DESIGN AND STATISTICAL PLAN

The clinical study was a prospective, multi-center, single-blind, randomized safety and effectiveness study with the primary objective to demonstrate superior effectiveness and non-inferior safety of the Lutonix AV DCB Catheter by direct comparison to standard PTA for treatment of recurrent lesions of native arteriovenous fistulae.

ANALYSIS POPULATIONS

All analyses including the primary analyses are primarily based on the mITT population. A Per Protocol analysis was performed for the primary endpoints. This served as a sensitivity analyses for the primary analyses. Additionally, an as-treated analysis set was created based on the actual treatment received instead of the randomized treatment.

- The ITT population consists of all enrolled subjects who have signed the Informed Consent Form and have been randomized.
- The Modified ITT (mITT) population consists of any subjects in the ITT population who are treated with Lutonix AV DCB Catheter or standard PTA.
- A Per-Protocol (PP) population consists of any subjects in the mITT population who do not have any major protocol deviation. The protocol deviations that are considered to have a “major” grade were defined a priori in the analysis plan.

Given that all enrolled subjects were randomized and received the assigned treatment, ITT and as-treated population are the same as the mITT population.

ASSESSMENT OF COMPARABILITY OF TREATMENT GROUPS AND POOLABILITY OF SITES

To demonstrate the comparability of the Control to Test subjects, the treatment groups were compared with respect to demographics and baseline characteristics and other covariates using t-tests or Wilcoxon nonparametric tests for means and Fisher’s Exact tests for proportions.

Demographics, baseline characteristics and other covariates were also compared between the treatment groups by sites using descriptive statistics. Both primary endpoints are summarized by treatment group and by site. This can help identify any confounding covariates that can potentially explain the variability of the treatment effect across sites.

No site was allowed to enroll more than 20% (~56 subjects) of the overall number of subjects to ensure the study to be a reasonably well-balanced, multicenter study. Sites with less than 10 randomized subjects were sorted by site number and pooled by order to form pooled sites with at least 10 randomized subjects each.

For the primary effectiveness endpoint, an analysis was performed to examine the potential for interaction of site and treatment group. A Cox regression model was fit that includes fixed effect for treatment group, site and the interaction of treatment group and site. If the p-value for the interaction term is <0.15, it is considered evidence of a possible significant interaction effect, and additional analyses would be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful.

For the primary safety endpoint, an analysis was performed as well to examine the potential for interaction of site and treatment group. A logistic regression model was fit that includes fixed effect for treatment group, site and the interaction of treatment group and site. If the p-value for the interaction term is <0.15, it is considered evidence of a possible significant interaction effect, and additional analyses would be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful.

There was no need to present the primary endpoints by geography, as all subjects were enrolled at sites in the U.S.

HANDLING OF MISSING DATA

The primary analysis of the primary effectiveness endpoint is a survival analysis. As a supportive analysis, the primary safety endpoint was also analyzed using survival analysis techniques. In survival analyses, unobserved endpoints are a standard part of

the analysis; they are known as “censored observations”. As long as the censoring is unrelated to the treatment, this method of handling missing endpoints produces unbiased estimates of the freedom-from-event rates.

For both primary endpoints, the reason for the censoring of all subjects with missing endpoints is reported; a worst-case analysis was performed for each primary endpoint, in addition to the standard analysis. For the primary effectiveness endpoint, the worst case analysis was based on a survival analysis. For the primary safety endpoint, it was based on a binary analysis. In a worst-case analysis, an event is assumed to have occurred at the time the subject discontinued participation in the study for all such subjects in the Test group. In the Control group, all subjects with missing data are assumed *not* to have had an event.

In addition, a tipping-point analysis was also performed for both primary endpoints using a proportion-based binary analysis, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. These analyses constitute sensitivity analyses of the effect of missing data on the study results.

STATISTICAL SOFTWARE AND AE CODING

SAS version 9.3 (TS1M2) was used for all programming and analysis. MedDRA dictionary version 16.1 was used for coding for all adverse events.

PRIMARY ENDPOINTS

1.1.1.1 PRIMARY EFFECTIVENESS ENDPOINT

The Primary Endpoint is Target Lesion Primary Patency (TLPP) evaluated at 6 months. TLPP ends with the next clinically driven reintervention of the target lesion or access thrombosis prior to Day 180. In order to demonstrate clinically acceptable effectiveness, this randomized study assessed superiority of the rate of TLPP at 6 months of the Lutonix AV DCB Catheter by direct comparison to standard PTA for treatment of AV fistulae. If a subject has an abandoned AV access circuit, the subject was censored at the date of abandonment.

If Core Lab or CEC data were missing, the corresponding site reported re-intervention data were used. Subjects who lost TLPP prior to Day 180 were considered loss of TLPP at event date. All other subjects without loss TLPP prior to Day 180 were censored at Day 180 or the last available visit date for subjects discontinued prior to 6-month visit.

1.1.1.2 PRIMARY EFFECTIVENESS ENDPOINT HYPOTHESIS TEST

The primary effectiveness endpoint is TLPP at 6 months. Objective: To assess if the 6 months TLPP for Lutonix AV DCB Catheter is superior to the primary patency rate for standard uncoated balloon, by direct comparison:

H_0: The (survival) rate $S_1(t)$ of subjects in the DCB treatment group with TLPP through $t \leq 6$ month post index procedure is less than or equal to that $S_2(t)$ of PTA treatment group. (i.e. $S_1(t) \leq S_2(t)$, for $t \leq 6$ months)

H_1: The (survival) rate $S_1(t)$ of subjects in the DCB treatment group with TLPP through $t \leq 6$ month post index procedure is greater than that $S_2(t)$ of PTA treatment group. (i.e. $S_1(t) > S_2(t)$, for $t \leq 6$ months

Rejection of the null hypothesis signifies that the 6 month TLPP of Lutonix AV DCB Catheter is superior to the 6 month TLPP of standard uncoated balloon.

A Kaplan-Meier analysis was used to estimate the survival rate of TLPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA was used to test the primary hypothesis to determine if DCB is superior to PTA. The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value of the test, the confidence intervals of the rate at Day 180 (6 month) in each group are provided.

1.1.1.3 SUPPORTIVE ANALYSIS AND SENSITIVITY ANALYSIS (EFFECTIVENESS)

1.1.1.3.1 PROPORTION-BASED ANALYSIS

The primary effectiveness endpoint was analyzed as a proportion-based binomial rate. Subjects were considered a failure if there was a clinically-driven reintervention of the target lesion or access thrombosis before Day 180. Subjects who discontinued prior to

Day 150 and did not have loss of TLPP were considered as 'not evaluable (NE)' and were not included in the proportion calculation.

1.1.1.3.2 ALTERNATIVE DEFINITIONS

Two alternative definitions were created to compare loss of TLPP at 6 months between treatment groups for the circumstance when the AV access circuit was abandoned. The first alternative definition did not take into account reason for abandonment; the second alternative definition considered a subject meeting the primary endpoint (loss of patency), if the abandonment was due to any reason except renal transplant. Subjects who were on the living donor list at the time of screening were excluded per exclusion criterion #16, however it is not feasible to exclude subjects that may receive a deceased donor transplant over the course of the 24 month follow-up of the study. Thus, shortly after the transplant is performed the circuit may be abandoned, however, the access could still be patent at this time.

Statistically, subjects who lost TLPP prior to Day 180 were considered loss of TLPP at event date. All other subjects without loss of TLPP prior to Day 180 were censored at Day 180 or the last available visit date for subjects discontinued prior to 6-month visit. A Kaplan-Meier analysis was used to estimate the survival rate of TLPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA was used, one-sided p-value is presented, and the confidence intervals of the rate at Day 180 (6 month) in each group are provided.

1.1.1.3.3 WORST-CASE ANALYSIS

The worst-case analysis was based on a survival analysis. In a worst-case analysis, an event of loss TLPP was assumed to have occurred at the time the subject discontinued participation in the study for all such subjects in the DCB treatment group. In the PTA treatment group, all subjects with missing data were assumed *not* to have had an event of loss TLPP until Day 180.

1.1.1.3.4 TIPPING-POINT ANALYSIS

A tipping-point analysis was performed using a proportion-based binary analysis, in which assumptions about missing data were varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. These analyses constituted sensitivity analyses of the effect of missing data on the study results.

1.1.1.4 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is freedom from localized or systemic serious adverse events through 30 days that reasonably suggests the involvement of the AV access circuit. Subjects who discontinued prior to Day 30 (except death) and did not have an event, were considered as not evaluable and not included in the proportion calculation.

Objective: To assess if the 30-day primary safety rate for Lutonix AV DCB Catheter is non-inferior to that of standard uncoated balloon, by direct comparison:

H_0: The primary safety rate p_1 in the DCB treatment group through 30 days post index procedure is inferior to that p_2 of the PTA treatment group. (i.e. $p_1 \leq p_2 - \delta$)

H_1: The primary safety rate p_1 in the DCB treatment group through 30 days post index procedure is non-inferior to that p_2 of the PTA treatment group. (i.e. $p_1 > p_2 - \delta$)

Where $\delta = 10\%$ is the non-inferiority margin, which is the range of difference that is considered not clinically important.

A non-inferiority Farrington and Manning Exact Test was used to test the primary safety hypothesis. The test is successful if the one-sided p-value is less than 0.025. In addition to the p-value of the test, the confidence intervals of the rate in each group and the difference between the two groups are provided.

1.1.1.4.1 SUPPORTIVE ANALYSIS AND SENSITIVITY ANALYSIS (SAFETY)

1.1.1.4.1.1 KAPLAN-MEIER ANALYSIS

If subject had an event prior to Day 30, the date of the event occurrence was used. All other subjects without an event prior to Day 30 were censored at Day 30 or the last available visit date for subjects discontinued prior to Day 30.

A Kaplan-Meier analysis was used to estimate the survival rate in the DCB and PTA groups. Standard errors for Kaplan-Meier estimates were calculated by Greenwood formula, and the corresponding non-inferiority test for the estimates were generated following normal approximation.

1.1.1.4.1.2 WORST CASE ANALYSIS

The worst-case analysis was based on the proportion-based binary analysis (e.g. the primary safety endpoint). In a worst-case analysis, an event was assumed to have occurred at the time the subject discontinued participation in the study for all such subjects in the DCB treatment group. In the PTA treatment group, all subjects with missing data were assumed *free* from an event.

1.1.1.4.1.3 TIPPING POINT ANALYSIS

A tipping-point analysis was performed using a proportion-based binary analysis, in which assumptions about missing data were varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. These analyses constituted a sensitivity analysis of the effect of missing data on the study results.

SECONDARY ENDPOINTS

1.1.1.5 SECONDARY ENDPOINTS WITH HYPOTHESIS TEST

The following secondary endpoints had hypothesis tests. No secondary endpoints were tested unless both primary hypotheses are successful. The testing of the secondary objectives are performed in a hierarchical fashion in the order in which they are listed below. This means that as soon as a null hypothesis is *not rejected*, no further

hypotheses are tested. This hierarchical testing scheme ensures that the study-wide Type 1 error rate remains at 0.025 one-sided when all of the secondary endpoints are tested at two-sided α=0.05 or equivalently at one-sided α=0.025.

Given that the effectiveness primary endpoint was not met, no hypothesis testing of the pre-specified secondary endpoints was performed and only descriptive statistics of the results are provided.

Hypothesis-Tested Secondary Endpoints:

- TLPP at 12 months
- Number of interventions required to maintain target lesion patency at 12 months
- ACPP at 6 months
- ACPP at 12 months

1.1.1.6 SECONDARY ENDPOINTS WITH DESCRIPTIVE STATISTICS

The following secondary endpoints were summarized with descriptive statistics and confidence intervals using the mITT population. For categorical variables summary statistics will include frequency counts and percentages. In addition, 95% CI for the percentages may be provided. For continuous variables, summary statistics included mean, standard deviation, minimum, median, and maximum. Ninety-five percent (95%) confidence intervals may be provided for the mean.

Effectiveness

- Device, Procedural, and Clinical Success
- ACPP evaluated at 3, 9, 18 and 24 months
- TLPP evaluated at 3, 9, 18, and 24 months
- TLPP evaluated at 6 months for subjects in whom a fiber pre-dilation balloon was used before the Lutonix AV DCB as compared to those in whom a non-fiber pre-dilation balloon
- Abandonment of permanent access in the index extremity at 3, 6, 9, 12, 18 and 24 months

- Number of interventions required to maintain target lesion patency at 3, 6, 9, 18 and 24 months
- Number of interventions required to maintain access circuit patency at 3, 6, 9, 12, 18 and 24 months

Safety

- Rate of device and procedure related adverse events assessed at 1, 3, 6, 9, 12, 18 and 24 months

1.1.1.7 EXPLORATORY AND SUBGROUP ANALYSIS

The following exploratory and subgroup analyses were performed:

Responder analysis:

Based on the primary effectiveness endpoint at 6 months, baseline and procedure information summarized for the DCB and control subjects to illustrate potential trend in subject based on outcomes.

Outcome by Period of Randomization:

Primary effectiveness outcome was evaluated according to the time of enrollment as follows: subjects randomized through first 3 months, second 3 months and third 3 months.

Subgroup analyses:

The primary endpoints were analyzed by the following subgroups:

- Gender
- Age
- Ethnicity
- Race
- Target Lesion Length (site reported, Core Lab)
- Target Lesion Location
- Treatment of Non-target lesion during index procedure

- Previous interventions
- Stents present in access circuit (from previous intervention)
- Baseline RVD
- Final residual stenosis (site reported, Core Lab)
- Inflation pressure
- Transit time
- Inflation time

The performance factors (final residual stenosis, inflation pressure, transit time, inflation time) were explored in all combinations of pairs, triplets, and for all conditions met.

Descriptive statistics are presented for each of the subgroup categories.

1.1.1.8 POST-HOC ANALYSIS

To assess if the 9 month TLPP for Lutonix AV DCB Catheter is superior to the primary patency rate for standard PTA by direct comparison, hypothesis testing for superiority was conducted in the same manner as for the primary effectiveness endpoint (6 months).

A Kaplan-Meier analysis was used to estimate the survival rate of TLPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA was used to test the hypothesis to determine if DCB is superior to PTA at 9 months (Day 270). The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value of the test, the confidence intervals of the rate at Day 270 in each group are provided.