

Statistical Analysis Plan for
Lutonix® ISR Study

Protocol: CL0018-01

Sponsor: Lutonix, Inc
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Analysis Plan Sign-off

[REDACTED] _____ Date _____

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1 PURPOSE

This analysis plan describes the analysis of the CL0018-01 protocol database. The CL0018-01 protocol was initiated as a randomized comparison of the LUTONIX® Drug Coated Balloon (DCB) in patients presenting with claudication or ischemic rest pain (Rutherford Category 2-4) and occlusion or $\geq 50\%$ stenosis of a previously deployed nitinol stent(s) in the femoropopliteal artery that is appropriate for angioplasty (e.g. In-stent Restenosis or ISR). Subjects were to be randomized in a 2:1 ratio of drug coated balloon to control PTA. In March 2016, the study was converted to an open label study with primary effectiveness and safety endpoints performance goals. The updated study would continue to enroll LUTONIX® Drug Coated Balloon subjects in addition to the originally randomized set of DCB subjects until a total of 98 DCB subjects were enrolled. The originally randomized PTA control subjects would be summarized to provide additional information on the success of this type of procedures in ISR subjects.

This statistical analysis plan (SAP) addresses an interim descriptive summary of the ISR data that Lutonix agreed to present to the FDA as part of the review of the SFA Global Registry data. As part of that review, the FDA agreed to evaluate the performance of the LUTONIX® Drug Coated Balloon in subjects with long lesions (≥ 14 cm) and ISR subjects.

1.1 Scope

This analysis plan describes the planned descriptive analysis of the Lutonix DCB and PTA subjects in the CL0018-01 study of subjects with ISR.

1.2 Changes from Last Approved Version of the SAP or Protocol

This is first version of the SAP.

As noted above, the protocol was converted from a randomized to open-label study March 2016.

1.3 Timing of Analyses

This interim analysis is to be based on available data as of April 28, 2016. A revised CEC adjudication data set will be obtained if it becomes available. This study does not include any interim hypothesis testing of the primary effectiveness and safety performance goals in the open-label protocol.

1.4 Statistical Analysis

The analyses will be completed by Lutonix, Inc staff or contract programmers working under the company operating procedures. The CR Bard SOPs on the validation of statistical output will be used.

1.5 Software

Statistical summaries and any inferential analyses will be completed using SAS Version 9.3 or later. Figures may be completed using SAS or with R Version 3.1.2 or later. Any data for figures generated using R will be made available through comma separated value (CSV) files generated using the SAS system and will be saved with unique dated names.

1.6 Applicable Documents

Document	Content
CL0018-01r04 SFA ISR protocol - to FDA - 2-19-16.pdf	CL0018-01 Protocol
Lutonix_SFA ISR_Annnotated_eCRF 2.2 24Mar2014.pdf	Annotated CRFs for study

2 DEFINITIONS

Abbreviation/Acronym	Definition
CEC	Clinical Events Committee
CI	Confidence Interval
DCB	Drug coated balloon
ISR	In-Stent Restenosis
ITT	Intent-to-Treat
Lutonix DCB	LUTONIX® Drug Coated PTA Dilatation Catheter
mITT	Modified Intent-to-Treat
OPG	Objective Performance Goal
SAP	Statistical Analysis Plan
SD	Standard Deviation
SFA	Superficial Femoral Artery
SOP	Standard Operating Procedure
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

3 STUDY OBJECTIVES AND ENDPOINTS

To demonstrate efficacy and safety of the LUTONIX® Drug Coated Balloon for treatment of SFA ISR by comparison to an objective performance goal (OPG).

3.1 Primary Endpoints

3.1.1 Primary Effectiveness Endpoint

The primary effectiveness measure is the primary patency at 12 months.

Primary Patency is defined as Freedom from CEC-adjudicated Clinically-Driven TLR and from Core laboratory-adjudicated Binary Restenosis. Binary restenosis is based on threshold Doppler PSVR ≥ 2.5 (together with waveform analysis & color mosaic appearance) or based on angiographic $\geq 50\%$ diameter stenosis (if angiography is performed although not required per protocol).

3.1.2 Primary Safety Endpoint

Freedom from all-cause perioperative (≤ 30 day) death and freedom at 1 year from index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death.

3.2 Secondary Endpoints

The following endpoints will be reported:

- Efficacy measurements of Device, Technical and Procedural Success will be assessed following the procedure
- Major vascular complications will be assessed within 30 days following the procedure
- Primary patency at 6 and 24 months

The following secondary endpoints will be assessed at 6, 12, and 24 months

- Secondary patency
- TLR, Total and Clinically Driven
- Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization)
- Change in Rutherford Classification from baseline
- Change in resting Ankle Brachial Index (ABI) from baseline
- Change in Walking Impairment Questionnaire (WIQ) from baseline
- Change in quality of life from baseline as measured by the EQ-5D

The following safety endpoints will be assessed at 1, 6, 12, 24, and 36 months

- Composite safety (criteria of the primary safety endpoint)
- All-cause death
- Amputation (major and minor separately)
- Target vessel revascularization (TVR)
- Target limb intervention

4 OVERVIEW OF TRIAL DESIGN

The study is a current a prospective, multicenter, single arm investigation of the safety and effectiveness of the LUTONIX® Drug Coated PTA Dilatation Catheter in treating ISR subjects.

The study will enroll patients presenting with claudication or ischemic rest pain (Rutherford Category 2-4) and occlusion or $\geq 50\%$ stenosis of a previously deployed bare nitinol stent(s) or drug-eluting stent if placed ≥ 6 months prior to the index procedure in the femoropopliteal artery that is appropriate for

angioplasty. After successful protocol-defined pre-dilatation, subjects are treated with the LUTONIX® Drug Coated Balloon.

Per the definition section of the protocol, all eligible subjects having signed the informed consent form and who have a DCB passed into their body will be considered enrolled.

4.1 Randomization

This is currently a non-randomized study. This study does include a small cohort of PTA subjects who were randomized to control under the original study protocol.

4.2 Blinding

Subjects enrolled under protocol versions 2.0 and 3.0 are blinded to their treatment until after the completion of the 12 month visit. All Duplex Ultrasound operators, core lab evaluators, and members of the Clinical Events Committee (CEC) will be blinded to the subject's treatment assignment. Blinding is not applicable to subjects enrolled under protocol versions 4.0 or greater due to the design change from randomized to open-label.

4.3 Sample Size Considerations

The protocol identifies a total sample size of 127 subjects inclusive of the LUTONIX® Drug Coated Balloon subjects and the originally randomized PTA control subjects from up to 30 US clinical sites. A sample size of 98 LUTONIX® Drug Coated Balloon subjects is required for completion of the performance goal analyses included in the updated protocol. While this SAP addresses an interim descriptive summary of the ISR study, the sample size calculations are provided below and additional details on assumption used to support the OPG and assumed response rates are included in the protocol in Sections 15.5.1 through 15.5.4.

Effectiveness OPG Sample Size

The primary effectiveness performance goal for 12-month primary patency response is 45% to be evaluated using a one-sided 0.025 exact binomial test ($H_0: p \leq 0.45$ vs $H_1: p > 0.45$) and the assumed response rate for the DCB subjects is 63% (0.63). A sample size of 83 subjects with outcomes provides 90% power based on the exact binomial test. The sample size was adjusted to 98 to allow for up to 15% missing or incomplete assessments.

Safety OPG Sample Size

The primary safety performance goal for 12-month safety outcome is 69% to be evaluated using a one-sided 0.05 exact binomial test ($H_0: p \leq 0.69$ vs $H_1: p > 0.69$) and the assumed safety response rate for the DCB subjects is 84.9% (0.849). A sample size of 79 subjects with outcomes provides 90% power based on the exact binomial test. Fewer subjects are expected to have missing results for this endpoint, so adjusting for 10% missing or incomplete data provides a sample size of 88 treated subjects. Hence, this is not a driver for the overall study sample size.

5 DATA STRUCTURE AND HANDLING

5.1 Visit Schedule and Visit Windows

The following table captures the visit schedule as shown in the CL0018-01 study protocol:

EVENT	Pre-Procedure	Procedure	Post-Procedure	1 Month ¹	6 Month	12 Month	24 Month	36, 48, & 60 months ¹	Repeat Angio/Revasc
Visit Window	30 Days	--		±14 days	±30 days	±30 days	±60 days	±60 days	-
Inc/Exc Criteria	✓	✓							
Inf. Consent	✓								
Med Hx	✓								
Pregnancy Test ²	✓								
Physical Exam	✓		✓	✓ ³	✓	✓	✓		✓ ⁵
Medication Compliance	✓			✓	✓	✓	✓	✓	✓
Resting ABI	✓ ⁴		✓ ⁵	✓ ³	✓	✓	✓		✓ ⁵
Rutherford Classification	✓				✓	✓	✓		✓ ⁵
WIQ & EQ5D Questionnaires	✓				✓	✓	✓		
Angiogram		✓							✓
Adverse Event Monitoring		✓	✓	✓	✓	✓	✓	✓	✓
Duplex Ultrasound ⁶				✓ ⁷	✓	✓	✓		✓

¹Follow-up can be by telephone or clinical visit

²For females of childbearing potential

³Required only if clinical visit occurs

⁴Resting ABI is required within 90 days prior to index procedure.

⁵Not required, but encouraged to capture if possible

⁶DUS to be performed after Clinical Assessment

⁷DUS may be capture anytime 0-6 weeks post procedure

6 STATISTICAL ANALYSES

6.1 General Considerations

All CRF data will be provided in listings sorted by subject number in the final analysis, but only selected listings may be provided with the interim analysis. Summary tables will be generated using descriptive

statistics according to the treatment received. The numeric descriptive statistics include the n (observed data), mean, standard deviation (SD), median, minimum value, and maximum value. Categorical summaries will show the number and percent of subjects in the levels associated with the variable summarized. Percentages will be calculated based on the total number of subjects with non-missing data for the assessment. The denominator should be included in each table to indicate the set of subjects included in each analysis. Descriptive information associated with Kaplan-Meier estimates includes the number of subjects available at the beginning of a visit window, the cumulative number of subjects with an event, the cumulative number of censored subjects, the number of subjects ongoing at the end at the relative target visit day, and survival rate or cumulative event rate. All confidence intervals presented with two-sided 95% CIs.

For Kaplan-Meier endpoints, relative day will be calculated as the event or last follow-up date minus the treatment date plus 1.

No inferential analyses have been identified.

Formatting considerations are as follows:

- Output will be provided in RTF documents and optionally converted to PDF
- Document page sizes will be based on 8”x11” paper
- One inch margins will be provided on the sides
- Listings will be provided on landscape pages while tables will be generated on portrait format pages
- Time New Roman font will be used with font sizes not smaller than 9 point
- The left margin on a portrait page should be 1.25” and the top margin on landscape output should be 1.25”; otherwise margins should be 1.0” on other sides.
- The header will display the company name, protocol name, and indicate the study database used
- The footer will show the program name, the source data, and date and time the program was run.

There is no planned inferential testing for this protocol outside of covariate and site evaluations. Should other post-hoc testing be performed, then a two-sided 0.05 or a one-sided 0.025 p-value would be identified as statistically significant. Any post-hoc should be clearly identified in the applicable report or paper.

6.2 Analysis Populations

This section covers population definitions identified in the protocol. There is no plan to do any per-protocol analyses as part of the interim descriptive summary.

The protocol identified an Intent-to-Treat (ITT) population consisting of all subjects who signed the informed consent and are determined by the site to be suitable to receive treatment with the LUTONIX® Drug Coated Balloon.

The Modified Intent-to-Treat (mITT) population consisting of all ITT subjects who were treated with the Lutonix DCB. For this study and the interim analysis, this is inclusive of an As-Treated (AT) population as subjects will be summarized according to the treatment they received.

A Per-Protocol (PP) population removes subjects who have any major protocol violations. The PP population will consist of any subjects in the mITT population who do not have any major protocol violations. The protocol violations that are considered to have a “major” grade will be defined a priori.

A Safety Population (SP) will be constructed based on mITT subjects that have some evidence of follow-up (e.g. at least a discharge date).

All baseline, demographic, patient history information, and all primary and secondary outcomes will be reported using the mITT population. The primary effectiveness and safety endpoints will also be summarized for the ITT population. The Safety Population will be used for any adverse event summaries.

6.3 Adjustment for Multiplicity of Testing

There is no testing performed for this interim analysis.

6.4 Handling of Missing Data

The primary and secondary endpoints will be analyzed using survival analysis techniques. In survival analyses, unobserved endpoints are a standard part of the analysis; they are known as “censored observations”. This method of handling missing endpoints produces unbiased estimates of the endpoints rates if the censoring is unrelated to the unobserved endpoints. The reason for the censoring of all subjects with missing endpoints will also be reported. As there can be considerable bias in analyses of subjects with a known result for time points where substantial subjects have not reached the time point, binary 12 month outcomes will not be summarized.

6.5 Subject Disposition

Study accountability information will include summarized through:

- The number and percent of subjects enrolled in the CL001-18 study
- The number of subjects in the ITT, mITT, and Safety Population
- The overall study completion status
- The duration of follow-up and availability for analysis of the 12-month primary patency and primary safety.

6.6 Demographics and Baseline Characteristics

Descriptive summaries of demographics information will be provided include gender, ethnicity, race, medical history variables, previous target limb interventions, baseline vital signs (height (cm), weight (kg), BMI (kg/m²), blood pressure, ABI, Rutherford Classification, PSVR, and previous treatments of the target lesion. For the ABI and Rutherford Classification, the post-baseline values and shift from baseline will also be provided for 6 and 12 months using available data. PSVR will be summarized descriptively by visit.

6.7 Procedure Information

Descriptive summaries of procedure information will include several summaries:

- Concomitant medications used during the procedure,
- Procedure overview: access method, number of treated lesions, number of patent outflow vessels, treated vessel(s), inflow vessels treated,

- Procedure details: arteries treated, total lesion length, lesion length by treated lesion, maximum baseline percent stenosis, baseline percent stenosis by lesion, maximum baseline RVD, RVD by lesion, subjects with one or more calcified lesion, highest TASCA II grade of calcified lesion,
- Pre-Tx Dilatation: Was pre-treatment dilatation performed, number of dilatations performed, maximum balloon diameter, total balloon length, did a dissection occur, highest dissection grade
- Study Device Dilatation: Number of balloons used per subject, maximum balloon diameter by subject, total balloon length by subject (sum of balloons used), average inflation time by subject, maximum pressure by subject, any dissection by subject, highest dissection grade by subject, any dissection by lesion, worst dissection grade by lesion, bailout stenting by subject, was lesion covered by subject, post-tx dilatation performed by subject, any dilatations after final procedure by subject, any malfunctions or complication during procedure by subject, were all devices successfully removed by subject, any additional treatments during the initial procedure.

6.8 Primary Effectiveness Endpoint

6.8.1 Endpoint Definition

The primary efficacy endpoint is primary patency at 12 months. Primary Patency is defined as Freedom from CEC-adjudicated Clinically-Driven TLR and from Core laboratory-adjudicated Binary Restenosis. Binary restenosis is based on threshold Doppler PSVR ≥ 2.5 (together with wave form analysis & color mosaic appearance) or based on angiographic $\geq 50\%$ diameter stenosis (if angiography is performed although not required per protocol).

6.8.2 Summaries

For the Kaplan-Meier analysis of the primary patency, subjects with an event will have event time that is the earliest of a TLR failure onset or the first confirmed patency failure on DUS. For a subject without a failure, the subjects will be censored at the time of the last DUS assessment where they are confirmed to be patent.

The Kaplan-Meier estimates will be provided along with two-sided 95% CIs (based Kaplan-Meier methodology) for the rate will be primary patency survival rate at 1 month (30 days), 6 months (183 days), and 12 months (365 days).

Kaplan-Meier curves for the primary patency survival by treatment will be provided.

6.8.3 Pooling Analyses

The Kaplan-Meier estimate of the response rate at 12 months (e.g. Day 365) for each site will be provided. For this analysis, sites with 3 or fewer subjects will be pooled into a single “Small Sites” group. A proportional hazards model will be used to assess the homogeneity of the response rates and a p-value of less than or equal to 0.15 will be considered statistically significant.

6.8.4 Handling of Missing data and Sensitivity Analyses

There are no additional planned sensitivity analyses for this interim analysis.

6.8.5 Covariate and Subgroup Analyses

There are no planned covariate analyses for the interim analysis.

6.9 Primary Safety Endpoint

6.9.1 Definition

The primary safety endpoint is composite of freedom from all-cause perioperative (≤ 30 day) death and freedom at 1 year from the following: index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death. These events are called “safety events” in the following text.

6.9.2 Supportive Summaries

The Kaplan-Meier estimates will be provided along with two-sided 95% CIs for the rate will be primary safety survival rate at 12 months (365 days). Additional time points of 1 month and 6 months will be included in the same table for convenience though they are considered secondary endpoints in the protocol.

Kaplan-Meier figures will be provided for the primary safety survival rate through 365 days.

6.9.3 Covariate and Subgroup Analyses

No covariate or subgroup analyses are planned for the primary safety endpoint.

6.9.4 Handling of Missing data and Sensitivity Analyses

There are no additional planned sensitivity analyses for this interim analysis.

6.10 Secondary Endpoints

These endpoints will be analyzed using Kaplan-Meier estimates if possible or using the number and percent of subjects with an event or based on available data at a specific time point. When calculating survival information for secondary variables, if a subject has a specific event then the onset is based on the first event. For subjects without survival events, the subject will be censored at the last visit where the subject had a visit or contact.

Secondary endpoints are:

- Device, Technical, and Procedural success (binary outcomes)
- Occurrence of major vascular complications within 30 days following the procedure. Major vascular complications are hematoma at access site > 5 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, any transfusion reported unless clearly indicated to be other than a catheterization complication, vascular surgical repair (binary outcome)
- Freedom separately from each of the following adverse events at 30 days and at 6, and 12 months to be summarized using Kaplan-Meier estimates:

- All-cause death
- Death related to index limb
- Index limb amputation (major and minor reported separately)
- Target Lesion Revascularization (Total and Clinically Driven TLR at 1-month, 6-months, and 12 months)
- Target Vessel Revascularization (TVR)
- Any index limb revascularization
- Composite of all-cause perioperative (≤ 30 day) death and from the following: index limb amputation, index limb reintervention, and index-limb-related death,
- Endpoints analyses using available results by time point using categorical or numeric descriptive methods as appropriate:
 - Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization) (binary outcome)
 - Change in Rutherford Classification from baseline (available data by time point)
 - Change in resting Ankle Brachial Index (ABI) from baseline (available data by time point)
 - Change from Baseline in WIQ by Visit (available data by time point)
 - Change from Baseline in EQOL-5 by Visit (available data by time point)
 - Secondary patency by Visit (binary outcome, available data by time point)

6.11 Adverse Events

All adverse events reported in the study will be summarized by class showing the number of events and number and percent of subjects with one or more events. An overall adverse events analysis summary will be provided to show the percent and count of subject with one or more AEs, one or more unexpected device related event, one or more procedure related event, one or more device related event, and one or more serious events. A listing of deaths will be provided if narratives are not included as part of the study report.

6.12 Device Malfunctions

Device malfunctions will be listed.

6.13 Protocol Deviations

Protocol deviations were collected on all subjects within the database. A summary of protocol deviation types will be provided showing the total number of protocol deviations by type and the number and percent of subjects with each protocol deviation type.

7 VERSION HISTORY

SAP Version	Date	Comments
01	June 8, 2016	Initial version

8 REFERENCES

Not applicable

9 Table of Contents for Tables, Listings, and Figures

Tables

Number	Title
14.1-1	Subject Disposition, All Subjects
14.1-2	Subject Evaluable for Primary Effectiveness and Primary Safety Endpoints, mITT Subjects
14.1-3	Number of Protocol Deviations per Subject, All Subjects
14.1-4	Protocol Deviations, All Subjects
14.2-1	Demographic Information, mITT Subjects
14.2-2	Selected Medical History, mITT Subjects
14.2-3	Previous Interventions, mITT Subjects
14.2-4.1	ABI Assessments by Visit, mITT Subjects
14.2-4.2	Rutherford Classification by Visit, mITT Subjects
14.2-4.3	PSVR by Visit, mITT Subjects
14.2-4.4	Walking Impairment Questionnaire by Visit, mITT Subjects
14.2-4.5	EQOL-5 Scores by Visit, mITT Subjects
14.2-5	Cardiac Medications at Baseline, mITT Subjects
14.2-6	Baseline Angiographic Data, mITT Subjects
14.2-7	Procedural Data, mITT Subjects
14.3-1	Freedom from Primary Safety Events with Kaplan-Meier Method, Safety Subjects
14.3-2.1	Primary Patency with Kaplan-Meier Method, mITT Subjects
14.3-2.2	Primary Patency with Kaplan-Meier Method, ITT Subjects
14.3-2.3	Primary Patency with Kaplan-Meier Method by Study Site, mITT Subjects
14.4-1	Clinically-Driven TLR-Free Survival with Kaplan-Meier Method, mITT Subjects
14.4-2	Secondary Endpoints at 30 Days, 6 Months, and 12-Months with Kaplan-Meier Method, mITT Subjects [Note this includes Total TLR-Free success]
14.4-3	Major Vascular Complications with 30 Days, mITT Subjects
14.4-4	Sustained Clinical Benefit by Visit, mITT Subjects
14.4-5	Acute Procedural Assessments, mITT Subjects
14.4-6	Secondary Patency by Visit, mITT Subjects
14.7-1	Overall Site Reported Adverse Events, Safety Subjects
14.7-2	All Site Reported Adverse Events by Category, Safety Subjects

Figures

Number	Title
14.3-1	Primary Safety Endpoint Survival, mITT Subjects

Number	Title
14.3-2	Primary Patency Survival, mITT Subjects
14.4-1	Clinically Driven TLR-Free Survival, mITT Subjects
14.4-2	TVR-Free Survival, mITT Subjects

10 Programming Instructions and Mock Outputs

Mock tables were provided in the document titled:

ISR Mock Tables 20160608.docx

Mock listings will not be provided. Listing will be created to match the order of the CRFs to the extent possible and contain all of the variables displayed on annotated CRFs.

Programming instructions for additional variables have been provided in these additional documents:

ISR ADSL Version 01.docx	Subject level flags
ISR ADEF Version 01.docx	Subject response variables
ISR CVPROC Version 02.docx	Subject level procedural information variables