Statistical Analysis Plan

A Study to EXhibit Percutaneous coronary Artery dilatation with Non-Slip Element balloon

(EXPANSE-PTCA)

(Study Protocol Number: RDX-CL-5000)

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to outline the data handling methods and planned analyses to be used for the Infraredx EXPANSE-PTCA study.

The results of the analyses documented here are to be presented in the final clinical study report. Selected analyses may also be presented in interim reports, DSMB reports, and manuscripts reporting study results, as deemed appropriate by the authors. Additional analyses of the study data beyond the analyses pre-specified in this plan are expected, and therefore the SAP does not preclude *ad hoc* analyses that may provide additional useful information on the study device.

2. Abbreviations and Definitions

Abbreviation / Term	Definition
CEC	Clinical Events Committee
MACE	Major adverse cardiac event
MLD	Minimum lumen diameter
PCI	Percutaneous coronary intervention
PG	Performance goal
PMA	Premarket approval
SAP	Statistical analysis plan
TIMI	Thrombolysis in myocardial infarction

3. Study Design

The study is a prospective, multi-center, single arm clinical study. Subjects will be followed through hospital discharge.

4. Randomization and Blinding

The study is non-randomized; no blinding of the subject or site staff is intended.

5. Analysis Population

The primary analysis will be based on all available data on all subjects enrolled, referred to in ICH E9 (“Statistical Principles for Clinical Trials”) as the *full analysis set*. As the study is a treatment-only, single arm design, summaries of results will principally be presented for the entire study population.

6. Study Endpoints

The endpoints of the study are intended to evaluate the safety and effectiveness of the Lacrosse NSE ALPHA coronary dilatation catheter during percutaneous coronary intervention (PCI) in subjects with stenotic coronary arteries.

6.1. Primary Endpoint

The primary endpoint is defined as device procedural success, defined as:

- Successful delivery, inflation, deflation, and withdrawal of the study balloon; and
- No evidence of device-related vessel perforation, flow limiting dissection (grade C or higher per Clinical Events Committee (CEC) adjudication) or reduction in thrombolysis in myocardial infarction (TIMI) flow from baseline (per core laboratory assessment); and
- Final TIMI flow grade of 3 at the conclusion of the PCI procedure per core laboratory assessment.

This endpoint will be presented as the proportion of subjects experiencing device procedural success. The proportion of target lesions meeting the primary endpoint will be concurrently calculated and presented as a secondary endpoint, as noted below.

6.2. Secondary Endpoints

The secondary endpoints for the study are:

1. Angiographic procedural success, defined as final diameter stenosis ≤50% in at least one of the Lacrosse NSE ALPHA attempted lesions following completion of the interventional procedure, including adjunctive stenting per core laboratory assessment.
2. Major adverse cardiac events (MACE) through hospital discharge per CEC adjudication. MACE is defined as a composite of:
   - All-cause death
   - Myocardial infarction
   - Clinically indicated target lesion revascularization
3. Stent thrombosis within the target vessel(s) through hospital discharge using ARC-2 definitions for definite & probable, per CEC adjudication.
4. Clinically significant arrhythmia (defined as those requiring intervention) through hospital discharge, per CEC adjudication.
5. Occurrence of Lacrosse NSE balloon rupture, per device deficiency case report form.
6. Change in minimum lumen diameter (MLD), measured by quantitative coronary angiography, following use of Lacrosse NSE ALPHA, per core laboratory assessment.
7. Device procedural success defined as for the primary endpoint, calculated and presented per target lesion.

Secondary endpoints 1 through 5 are defined at a subject level and will be presented as the proportion of subjects experiencing the above events. In cases where multiple events per subject may be observed (e.g., adverse events), the primary analysis will be at the subject level but total event counts will also be reported. Secondary endpoints 6 and 7 are defined at the lesion level and statistical analyses of these endpoints will account for within-subject correlation as some subjects will have more than one target lesion, using generalized estimating equations with an exchangeable correlation structure.

7. General Statistical Considerations

The following general comments apply to all statistical analyses and data presentations.

7.1. Descriptive Statistics

Continuous data will be summarized using descriptive statistics: mean, standard deviation, median, and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For endpoints analyzed at the subject level that can occur more than once in a single subject, such as adverse events, the percentage will be based on the number of subjects experiencing the event; both subject and event counts will be reported. For endpoints analyzed at the lesion level (secondary endpoints 6 and 7 as defined above), the lesion-level analysis will be considered primary.

7.2. Significance Level

Hypothesis testing of the primary endpoint (against a predefined performance goal as defined below) will be performed using one-sided hypothesis tests at an alpha level of 0.05. Other statistical analyses will be performed using two-sided hypothesis tests at an alpha level of 0.05.

7.3. Duration Variables

Study Day 0 is the day of study device deployment (index procedure). Study day is calculated relative to day 0 and will appear in the listings where applicable:

Study Day = (Date of Event – Date of Study Device Deployment)

Duration variables will be calculated using the general formula:

[(end date – start date)]

7.4. Missing Data

All available data in the full analysis set will be used to evaluate study outcomes. Methods for replacing missing data, such as last value carried forward or multiple imputation, will not be employed for primary analyses; however, a sensitivity analysis of the primary endpoint incorporating worst-case assumptions (e.g., missingness equals failure) will be performed.

7.5. Software

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4 or higher, SAS Institute Inc. Cary, NC) or R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

8. General Statistical Summaries

8.1. Subject Disposition

Subject accountability and study discontinuation will be summarized. Subject accountability at each visit will be summarized as the number of subjects with complete visits, missed visits, or study discontinuations prior to the visit. All subjects who do not complete the study will be tabulated by reason for discontinuation.

8.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized. Demographic variables will include, but are not limited to, age, gender and ethnicity.

8.3. Medical History

Medical history will be summarized. Medical history variables will include, but are not limited to, those related to the study disease history and current status as well as relevant concomitant conditions.

8.4. Adverse Events

An overall summary of adverse events will be presented. The summary will include the number and percentage of subjects who report at least one adverse event and the total number of adverse events. Complete subject listings of all adverse events will be provided. Adverse events as adjudicated by the CEC will be considered primary for the purpose of categorization, tabulation and reporting.

Adverse events adjudicated by the CEC as *definitely* or *probably* will be considered related adverse events for data analytic purposes. Events adjudicated by the CEC as *possibly*, *unlikely* or *not related* will not be considered related adverse events for data analytic purposes.

9. Analysis of Study Endpoints

9.1. Primary Endpoint

The primary endpoint will be presented as the proportion of subjects experiencing device procedural success.

These results will then be compared to a performance goal derived from studies of comparable products. As clinical evidence from FDA premarket approval (PMA) application submissions on similar products (e.g., AngioSculpt, Fx miniRAIL) involve a substantially different definition of the primary endpoint, the performance goal is based on recent studies in the LOX product code, as follows:

Device	N	Endpoint	Success Rate
Sapphire II PRO	61	Successful use, no perf or grade C dissection, no reduction in TIMI, final TIMI 3	96.7% (59/61)
Emerge	60	Successful use, no perf or grade C dissection, no reduction in TIMI, final TIMI 3	98.3% (59/60)
Mini Trek Rx	71	Successful use, no clinically significant perf or grade C dissection, no clinically significant arrhythmias, no reduction in TIMI, final TIMI 3	98.5% (66/67[1])
		TOTAL	97.9% (184/188)

1 Angiographic documentation associated with predilation with the study device was not available for 4 patients; accordingly, patient-level analysis related to the primary endpoint was performed for 67 patients.

The sample-size weighted rate of endpoint success in the above trials is then 97.9% as shown above.

Results are also available from the Scoreflex NC trial (Kandzari et al.), which included a comparable primary endpoint which was achieved in 93.5% (187/200) of study subjects; as the product and intended patient population in the Scoreflex NC trial are substantially more similar to those in the present study than in the LOX studies cited above, it is prudent to account for these results.

To do so without overreliance on Scoreflex NC alone, we therefore adjust the tabulated outcomes from the LOX studies above by half of the difference compared to Scoreflex NC, or (97.9% - 93.5%) / 2 = 2.2%, to get a final value of 95.7%.

The studies cited above did not have statistical performance goals defined, while other trials with similar purposes and populations (e.g., AngioSculpt) used different endpoints; however, in general in the PCI space statistical margins such as 7% (e.g., FX miniRAIL), 9.4% (e.g., Asahi Intecc) and 10% (e.g., XIENCE) have been applied. Therefore, a value of 8%, within the typical range, will be applied.

With this statistical margin (i.e., delta), the performance goal is then 87.7%. Formally, the hypotheses to be tested for the primary endpoint are then as follows:

$H0: r \leq PG$

$HA: r > PG,$

where r is the proportion of endpoint successes and PG is the performance goal of 87.7% = 0.877.

The hypotheses will be tested at a one-sided alpha level of 0.05 and endpoint success will be declared if the performance goal is met (i.e., if the null hypothesis above is rejected in favor of the alternative hypothesis). For primary analysis, this endpoint will be tested on all subjects with available data, with a worst-case sensitivity analysis also incorporated as noted below.

Among the 200 subjects intended for enrollment, a subgroup of at least 30 is intended to be cases of in-stent restenosis. The value of 30 is a commonly used benchmark and is chosen to provide a reasonable sample size to characterize outcomes in this subgroup,[4] as well as a feasible target from a clinical perspective. The ISR subgroup is not intended for formal statistical hypothesis testing independent of the entire study cohort as the study is powered for the full 200 subjects planned for enrollment; hence no decision rule specific to ISR cases is defined. However, key outcomes, including the primary endpoint, will be compared between the *de novo* and ISR cohorts to assess any statistically significant differences. This testing will be performed on an exploratory basis and hence no alpha allocation for multiplicity is necessary, nor will overall analytical conclusions be driven by the number of ISR cases.

To obtain at least 30 ISR subjects, enrollment will continue until both the overall target of 200 and the ISR cohort of 30 have been obtained. More specifically, enrollment of non-ISR subjects will be capped at 170 such that if and when this maximum has been achieved without 30 ISR subjects,

only ISR subjects will be permitted to be enrolled until the minimum of 30 has been reached, for a total of 200 subjects.

9.2. Secondary Endpoints

Secondary endpoints 1 through 5 (as stated and numbered above) are defined at a subject level and will be presented as the proportion of subjects experiencing the above events. In cases where a subject-level analysis is specified but multiple events per subject may be observed (e.g., adverse events), the primary analysis will be at the subject level but total event counts will also be reported. Secondary endpoints 6 and 7 are defined at the lesion level and statistical analyses of these endpoints will account for within-subject correlation as some subjects will have more than one target lesion. For these endpoints, generalized estimating equations will be applied, using an exchangeable (within-subject) correlation structure.

Secondary endpoints defined as continuous measures (e.g., MLD) will be summarized according to the general principles stated above.

Secondary endpoints as defined in this protocol are not intended for labeling claims and hence no formal statistical hypotheses are defined *a priori.* Multiplicity of testing and associated alpha allocation (i.e., between the primary and secondary endpoints) is therefore not applicable to the current investigation.

10. Determination of Sample Size

Based on the performance goal and hypothesis testing specified above, sample size and power were computed using SAS version 9.4 PROC POWER, assuming an exact test of a single binomial outcome against a performance goal (the null hypothesis). Postulating a primary endpoint success rate at the subject level of 93.5%, as observed in the Scoreflex NC trial, and with a null hypothesis of 87.7% per the performance goal constructed from the available literature, a sample size of 200 subjects provides 84% power to meet the endpoint using hypothesis testing as defined above. Under modest assumptions for missing data on study outcomes (e.g., 5% missingness), the power remains above 80%.

This sample size also reflects clinical trial practice in the space and in the study population of interest and matches the sample sizes from relevant regulatory studies including the Scoreflex NC and AngioSculpt primary clinical investigations.

11. Additional Analyses

11.1. Subgroup Analyses

No *a priori* subgroup analyses of interest are specified, although subgroup analyses may be performed on an *ad hoc* basis.

11.2. Interim Analysis

No formal interim analysis for the purpose of early stopping for efficacy will be performed. Analysis for the purpose of evaluating safety and futility (which do not require alpha-spending) or for the use of safety and review committees may be performed.

11.3. Pooling of Data

As this investigation is a multi-center study, poolability of the primary endpoint will be assessed using Pearson's chi-square test, where sites enrolling fewer than 5 subjects will be dropped from the poolability analysis for sites, such that poolability findings will only be applied to sites with enrollment of at least 5 subjects. A resulting p-value less than 0.15 will be cause for investigation of potential causes of heterogeneity across clinical sites. Additionally, descriptive statistics for the primary endpoint will be tabulated and presented by site, including small (less than 5 subjects) sites.

12. Changes in Planned Analyses

Any deviations or changes from this SAP deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described with justification and rationale.

13. Revision History

Revision	DCO#	Date	Revision Description
A	2021-10-004	13Oct2021	Initial release.