ILUMIEN IV: OPTIMAL PCI

(ABT-CIP-10233)

Statistical Analysis Plan (SAP)

October 10, 2022

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Abbott	[redacted] Study Name: ILUMIEN IV
Statistical Analysis Plan	

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1.0 INTRODUCTION

This document is a statistical analysis plan for the ILUMIEN IV trial (refer to ABT-CIP-10233 for the clinical investigational plan).

2.0 TRIAL OBJECTIVES

The objective of this clinical investigation is to demonstrate the superiority of an Optical Coherence Tomography (OCT)-guided stent implantation strategy as compared to an angiography-guided stent implantation strategy in achieving larger post-PCI lumen dimensions and improving clinical cardiovascular outcomes in patients with high-risk clinical characteristics and/or with high-risk angiographic lesions. In addition, embedded within the ILUMIEN IV protocol is a separate pre-specified powered analysis of XIENCE to be conducted in randomized ILUMIEN IV subjects with in-stent restenosis (ISR). The objective of the analysis is to demonstrate the safety and effectiveness of XIENCE in the treatment of ISR lesions. This is described in further detail in Appendix C.

3.0 TRIAL DESIGN

This is a prospective, single-blind clinical investigation randomizing subjects to OCT-guided coronary stent implantation vs. angiography-guided coronary stent implantation in a 1:1 ratio. The clinical investigation will be conducted at approximately 125 centers in North America (US and Canada), Western Europe, and Asia-Pacific. Up to 3656 randomized subjects and approximately 375 roll-in subjects will be enrolled in the clinical investigation. No site may enroll more than 15% of the total subjects. Subjects participating in this clinical investigation will be followed for 2 years. The expected duration of enrollment is approximately 2 years. The total duration of the clinical investigation is expected to be approximately 5 years.

The sample size is driven by the primary endpoint of target vessel failure (TVF). Because of the event driven nature of this primary endpoint, the statistical power of the trial is a function of the number of endpoint events, and not a direct function of the number of patients enrolled. As a result, the number of patients is not an endorsement of the statistical power of the trial. If event rates are lower than anticipated, more patients will be required to obtain a sufficient number of endpoint events.

Subjects will be randomized in a 1:1 ratio according to an electronic randomization system. Randomization will be stratified by medically treated diabetes, presentation with a biomarker positive ACS (NSTEMI or recent STEMI), and site.

Each operator will complete OCT-guided stenting roll-in cases (up to 3, if needed) according to a pre-specified stent optimization protocol on patients meeting study inclusion/exclusion criteria. Within 72 hours of receipt, the core lab will determine accurate OCT measurements and stent optimization protocol compliance. OCT Core laboratory approval of each operator is required to proceed to the randomization phase.

Subjects will be considered enrolled in the trial once informed consent has been obtained and the subject is randomized. The trial will utilize a Clinical Events Committee (CEC) to review adverse events for adjudication of trial endpoints.

4.0 TRIAL ENDPOINTS

There are two powered primary endpoints, one powered major secondary endpoint and multiple descriptive non-powered secondary endpoints in this clinical investigation.

4.1 Primary Endpoints

4.1.1 Imaging Outcome (powered): Minimal Stent Area (MSA), continuous measure

The primary imaging endpoint is Final Post-PCI MSA (per target lesion basis) in each randomized arm, as measured at an independent OCT core laboratory, which is blinded to imaging modality assignment.

4.1.2 Clinical outcome (powered): Target Vessel Failure (TVF)

The primary clinical endpoint is the time-to-first event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition), or ischemia-driven target vessel revascularization (ID-TVR) assessed at 2 years.

Testing between OCT and angiography will be done in a hierarchical manner as follows:

1. Superiority of MSA in OCT-guided arm vs. Angiography-guided arm

2. Superiority of TVF in OCT-guided arm vs. Angiography-guided arm

4.2 Major Secondary Endpoint

4.2.1 Target vessel failure (TVF) excluding periprocedural MI

The major secondary endpoint is time-to-first event rate of the composite outcome of cardiac death, target vessel-related spontaneous myocardial infarction, or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years.

4.3 Non-Powered Secondary Endpoints

The trial has a number of non-powered secondary endpoints such as procedural outcomes, additional procedural and clinical endpoints, patient reported outcomes (PRO) and cost-effectiveness measures. See Section 5.4 for a full listing.

5.0 STATISTICAL METHODS

5.1 Analysis Populations

5.1.1 Intent-to-Treat (ITT) Population

[redacted]

5.1.2 Per-Protocol (PP) Population

[redacted]

5.2 Primary Endpoints

5.2.1 Primary Endpoint of Minimal Stent Area (MSA)

The primary imaging endpoint is Final Post-PCI MSA (per target lesion basis) in each randomized arm, as measured at an independent OCT core laboratory, which is blinded to imaging modality assignment.

5.2.2 Hypothesis

Let M(OCT) be the MSA in OCT-guided arm, while M(Angio) is MSA in angiography-guided arm. The following hypothesis will be tested:

$$H_0: M(Angio) - M(OCT) \geq 0$$

$$H_1: M(Angio) - M(OCT) < 0$$

The null hypothesis will be tested at the one-sided 2.5% significance level and [redacted]

5.2.3 Analysis Method

The mean of the MSA will be estimated in both OCT-guided and angiography-guided arm. [redacted]

5.2.4 Sample Size

[redacted] a sample size of 1600 subjects will provide at least 95% power to demonstrate superiority of treatment difference.

5.2.5 Analysis Populations

The primary endpoint of MSA will be tested in the ITT population, as defined in section 5.1 above, and for only those ITT subjects in whom one or more stents were implanted at a target lesion will be excluded from this endpoint analysis.

As a secondary analysis, the primary endpoint of MSA will be tested for the PP population as defined in section 5.1 above, and for only those PP subjects in whom one or more stents were implanted at a target lesion.

5.2.6 Poolability Analysis

[redacted]

[redacted]

5.2.7 Sensitivity Analyses

[redacted]

5.2.8 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the primary endpoint of MSA across study subgroups for the following baseline variables:

- Gender: male vs. female
- Age (e.g., < 65, ≥ 65)
- Race (all categories as well as white vs non-white)
- Ethnicity (Hispanic or Latino vs not Hispanic or Latino)
- ACS vs. non-ACS
- Diabetes vs. non-diabetes
- Long or multiple lesions (defined as intended total stent length in any single target vessel ≥28 mm) vs. short and single lesions
- Bifurcations: yes vs. no
- Angiographic severe calcification vs. non-calcification
- In-stent restenosis: yes vs. no
- Medication-treated diabetes mellitus vs. others

[redacted]

5.3 Primary Endpoint of Target Vessel Failure

The primary clinical endpoint is the time-to-first event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition), or ischemia-

driven target vessel revascularization (ID-TVR) assessed at 2 years. For patients with multiple target vessels, TVF in either or both target vessels constitutes an endpoint event.

5.3.1 Hypothesis

The following hypothesis will be tested only in the final analysis.

$$H_0: H(OCT) / H(Angio) \geq 1$$

$$H_1: H(OCT) / H(Angio) < 1$$

where H(PCT) and H(Angio)are the hazard function for the OCT-guided arm and angiography-guided arm. The null hypothesis will be tested at the one-sided 2.5% significance level.

5.3.2 Analysis Method

The primary endpoint of TVF is defined as the time to the first TVF. [redacted]

5.3.3 Sample Size

[redacted] will achieve power of 90% at a one-sided significance level of 0.025. [redacted] approximately 2490 patients [redacted]

5.3.4 Analysis Populations

The primary analysis population for the primary endpoint of TVF will be the ITT population as defined in section 5.1 above.

As a secondary analysis, the primary endpoint of TVF will be tested for the PP population as defined in section 5.1 above. [redacted]

5.3.5 Poolability Analysis

[redacted]

5.3.6 Sensitivity Analysis

[redacted]

[redacted]

5.3.7 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of primary endpoint of TVF across study subgroups for the following baseline variables:

- Gender: male vs. female
- Age (e.g., < 65, ≥ 65)
- Race (all categories as well as white vs non-white)
- Ethnicity (Hispanic or Latino vs not Hispanic or Latino)
- ACS vs. non-ACS
- Diabetes vs. non-diabetes
- Long or multiple lesions (defined as intended total stent length in any single target vessel ≥28 mm) vs. short and single lesions
- Bifurcations: yes vs. no
- Angiographic severe calcification vs. non-calcification
- In-stent restenosis: yes vs. no
- Medication-treated diabetes mellitus vs. others

[redacted]

5.3.8 Additional Analyses to Assess Impact of COVID-19

[redacted]

[redacted]

Abbott will also collect and report COVID-19 test results (positive, negative, or symptomatic and managed as COVID-19 but with no test, inconclusive test, or invalid test) using a COVID-19 Assessment Log. Additionally, protocol deviations associated with COVID-19 results will be reported.

5.4 Major Secondary Endpoint of TVF Excluding Periprocedural MI and Hypothesis

The major powered secondary endpoint is the time-to-first event rate of the composite outcome of cardiac death, target vessel-related spontaneous MI or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years. For patients with multiple target vessels, TVF excluding periprocedural MI in either or both target vessels constitutes an endpoint event.

5.4.1 Hypothesis

The following hypothesis will be tested for the analysis on TVF excluding periprocedural MI.

$$H_0: H(OCT) / H(Angio) \geq 1$$

$$H_1: H(OCT / H(Angio) < 1$$

where H(OCT) and H(Angio) are hazard function for the OCT-guided arm and angiography-guided arm. The null hypothesis will be tested at the one-sided 2.5% significance level.

5.4.2 Analysis Methodology

[redacted]

[redacted]

5.4.3 Sample Size

[redacted]

5.4.4 Analysis Population

The major secondary endpoint analysis population will be the ITT population as defined in section 5.1 above.

As a secondary analysis, the major secondary endpoint will be tested for the PP population as defined in section 5.1 above. [redacted]

5.4.5 Poolability Analysis

[redacted]

5.4.6 Sensitivity Analysis

[redacted]

[redacted]

5.4.7 Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of the major secondary endpoint across study subgroups for the following baseline variables:

- Gender: male vs. female
- Age (e.g., < 65, ≥ 65)
- Race (all categories as well as white vs non-white)
- Ethnicity (Hispanic or Latino vs not Hispanic or Latino)
- ACS vs. non-ACS
- Diabetes vs. non-diabetes
- Long or multiple lesions (defined as intended total stent length in any single target vessel ≥28 mm) vs. short and single lesions
- Bifurcations: yes vs. no
- Angiographic severe calcification vs. non-calcification
- In-stent restenosis: yes vs. no
- Medication-treated diabetes mellitus vs. others

[redacted].

5.4.8 Additional Analyses to Assess Impact of COVID-19

[redacted]

5.5 Secondary Endpoints

Descriptive endpoints are reported using only summary statistics and no hypothesis test will be performed.

Procedural outcomes

OCT-defined (OCT core laboratory assessed). Subjects in the angiography-guided arm will

undergo a post-PCI OCT run, blinded to the operator. Assessed per target lesion.

1) Stent expansion. Stent expansion is defined by the MSA achieved in the proximal and distal stented segments relative to their respective reference lumen areas. The stent length is divided into 2 equal segments (proximal and distal) except for lesions containing a bifurcation (visually estimated side branch ≥2.5 mm). When there is a bifurcation present, rather than splitting the stent into two halves, the division occurs at the proximal most side branch.

   - Acceptable stent expansion (categorical variable): The MSA of the proximal segment is ≥90% of the proximal reference lumen area and the MSA of the distal segment is ≥90% of the distal reference lumen area.
   - Unacceptable stent expansion (categorical variable): The MSA of the proximal segment is <90% of the proximal reference lumen area, and/or the MSA of the distal segment is <90% of the distal reference lumen area.

   In case either segment (proximal or distal) of the stent meets criteria for unacceptable stent expansion, the stent is considered to have unacceptable stent expansion. Both segments of the stent must meet acceptable stent expansion criteria to be considered acceptable.

   In case a respective reference segment cannot be measured the determination will be made with only one of the two reference (proximal or distal) segments.

   Note: If acceptable stent expansion (by operator assessment) is not achieved in either the distal or proximal segments of the stent in the OCT-guided arm according to the Post-PCI OCT, further post-stent expansion with higher pressures and/or larger balloons must be performed per protocol if the POST-PCI OCT EEL measurements now suggest a larger balloon be used. See CIP Section 6.5.3.7 for more details.

   - Post-PCI stent expansion (%) (continuous variable): The MSA divided by the average of proximal and distal reference lumen areas x 100.

2) Mean stent expansion (%) (continuous variable): The mean stent area (stent volume/analysed stent length) divided by the average of proximal and distal reference lumen areas x 100.

3) Intra-stent plaque protrusion and thrombus

Defined as a mass attached to the luminal surface or floating within the lumen, meeting the following criteria: Protrusion/thrombus is defined as any intraluminal mass protruding at least 0.2 mm within the luminal edge of a stent strut, and will be further classified as Major and Minor:

- Major: Protrusion area/Stent area at site of tissue protrusion ≥10% and the minimal intrastent flow area (MSA – protrusion area) is unacceptable (<90% of respective proximal or distal reference area
- Minor: Protrusion area/Stent area at site of tissue protrusion is <10%, or is ≥10% but the minimal intraluminal flow area (MSA – protrusion area) is acceptable (≥90% of respective proximal or distal reference area

Note: It is recommended that if protrusion is detected by operator assessment in the OCT-guided arm during the procedure and meets the criteria for major protrusion, then thrombus aspiration, further high-pressure balloon inflation and/or an additional stent be considered.

4) Untreated reference segment disease

Defined as focal disease with untreated MLA <4.5 mm^2 within 5 mm from the proximal and/or distal stent edges.

Sub-classified by the amount of untreated lipid plaque, divided into 3 grades:

i. Low (≤90° of lipid arc)

ii. Medium (>90°-<180° of lipid arc)

iii. High (≥180° of lipid arc)

Note: If untreated reference segment disease with an MLA <4.5 mm^2 is detected by operator assessment in either the proximal reference (inflow disease) or distal reference (outflow disease) segment lumen in the OCT-guided arm, an additional stent must be placed to treat it, unless there are anatomic reasons that the disease should not be covered (e.g. diffuse distal disease or significant vessel tapering, etc.)

5) Edge dissections

Edge dissections will be tabulated as:

i. Major (%): ≥60 degrees of the circumference of the vessel at site of dissection and ≥3 mm in length

ii. Minor (%): any visible edge dissection <60 degrees of the circumference of the vessel or <3 mm in length

Edge dissections will be further classified as:

i. Intimal (limited to the intima layer, i.e. not extending beyond the internal elastic lamina)

ii. Medial (extending into the media layer)

iii. Adventitial (extending through the external elastic membrane/lamina)

Note: If a major edge dissection is detected by operator assessment in the OCT-guided arm, it is recommended that an additional stent be placed to cover the dissected segment, particularly if the site of dissection is at the distal stent edge.

6) Stent Malapposition

Defined as frequency (%) of incompletely apposed stent struts (defined as stent struts clearly separated from the vessel wall (lumen border/plaque surface) without any tissue behind the struts with a distance from the adjacent intima of ≥0.2 mm and not associated with any side branch).

Malapposition will be further classified as:

- Major: if associated with unacceptable stent expansion (as defined above)
- Minor: if associated with acceptable stent expansion (as defined above)

Note: If malapposition is detected by operator assessment during the procedure in the OCT-guided arm and meets the criteria for major malapposition (i.e. malapposition associated with unacceptable stent expansion), further stent expansion must be performed. The degree of stent underexpansion (acceptable or unacceptable) should guide the intervention rather than amount of malapposition.

Stent Malapposition will be tabulated as:

i. Major (%)

ii. Minor (%)

iii. All (Major and Minor) (%)

7) Border detection (angiography arm post-PCI only, blinded to investigator)

The visibility of the vessel external elastic lamina (EEL) border by OCT will be evaluated at both reference sites (proximal and distal) and the MSA, after intervention and then classified into 3 grades:

i. Good: ≥75% (270°) of visible circumference

ii. Moderate: ≥50% (180°) - <75% (270°) of visible circumference

iii. Poor: <50% (180°) of visible circumference

8) Intra-stent lumen area (intra-stent flow area)

Defined as stent area minus any protrusion as defined above in secondary endpoint 3 (Intra-stent plaque protrusion and thrombus).

9) Effective lumen area (total flow area)

Defined as intra-stent lumen area plus any area of malapposition between the stent and the vessel wall (lumen border/plaque border).

Additional Procedural Endpoints

10) Angiographic Endpoints (QCA). (Angiographic core laboratory assessed). Assessed per target lesion.

i. Final (post-PCI) minimal lumen diameter

ii. Final (post-PCI) percent diameter stenosis

iii. Acute lumen gain post-intervention

iv. Maximum device size (stent or post-dilatation balloon)/reference vessel diameter ratio

v. Post-PCI target vessel TIMI flow rate

vi. Angiographic complications – worst (anytime during the procedure) and final (post PCI and all imaging) - Angiographic dissection ≥ NHLBI type B, perforations (Ellis classification), intra-procedural thrombotic events (including slow-flow, no-reflow, side branch closure, distal embolization, and intra-procedural stent thrombosis, as per the standard angiographic core laboratory definitions

11) Device Usage Endpoints (site reported; assessed per subject):

i. Total stent length

ii. Total number of stents

iii. Maximal stent size

iv. Post dilatation (yes/no)

v. Total number of post-dilation balloons

vi. Maximal post-dilatation balloon size

vii. Maximal device size (stent or post-dilatation balloon)

viii. Maximum inflation pressure (atm.; stent or post-dilatation balloon)

12) Procedure time (first angiogram to guide catheter removal), fluoroscopy time, radiation exposure

13) Contrast use; contrast induced nephropathy (defined as serum creatinine rise >25% or absolute increase >0.5 mg/dL (44.2µmol/L)); need for renal replacement therapy

14) Procedural success (must be present in all treated lesions and vessels):

Defined as A) angiographic core laboratory-assessed final (post-PCI) lesion angiographic diameter stenosis <30% and target vessel TIMI III flow without any of the angiographic complications listed in 10(vi) above; plus B) the absence of site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

15) Procedural complications

Defined as A) angiographic core laboratory-assessed complications listed in 10(vi) above occurring anytime during the procedure; or B) site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

16) OCT performance success (site reported) (OCT arm only):

OCT imaging performed both pre- and post-PCI

17) OCT imaging-related procedural complications (CEC adjudicated)

Any procedural complications (e.g. angiographic dissection, perforation, thrombus, acute closure, etc.) requiring any active intervention (e.g. prolonged balloon inflations, additional stent implantation, pericardiocentesis, intubation, hemodynamic support or pressors, defibrillation or cardioversion) or death adjudicated by the CEC as definitely or likely attributable to the physical performance of OCT-imaging (e.g. passing the catheter through the vasculature or stent, or injecting contrast to clear the blood for imaging). For this definition, adverse events that arise due to changes in PCI strategy as the result of OCT findings are NOT considered OCT imaging-related procedural complications.

18) Additional interventions on the basis of the pre-PCI or post-stent OCT-imaging run that would not have been performed based on angiographic guidance alone (site reported; assessed per subject; OCT Arm Only):

i. Use of larger balloon

ii. Use of higher inflation pressures

iii. Use of additional balloons

iv. Use of additional stent(s)

v. Performance of atherectomy

vi. Other interventions

Reason(s) for additional interventions will be documented by the site (e.g. more calcium

than anticipated, greater stent under-expansion than appreciated angiographically, greater malapposition than appreciated angiographically, greater tissue protrusion or thrombus burden than appreciated angiographically, more severe edge dissection than appreciated angiographically, residual reference segment disease not appreciated angiographically, other)

Clinical outcomes at 30 days, 1 year, and 2 years (unless otherwise noted)

19) Target lesion failure (TLF; cardiac death, TV-MI or ischemia-driven target lesion revascularization (ID-TLR)

20) All-cause mortality

21) Cardiac and non-cardiac mortality

22) All MI

23) TV-MI, non-TV-MI and indeterminate vessel MI

24) Periprocedural MI and non-periprocedural MI

25) All revascularization

26) ID-revascularization and non-ID-revascularization

27) ID-TVR, ID-TLR, ID-non-TLR TVR, and ID-non-TVR

28) Definite, probable and definite/procedure stent thrombosis (ARC definition)

29) Relationship between immediate post-procedure OCT parameters (e.g. MSA, procedural success, malapposition, dissection, protrusion, etc.) and 2-year endpoint rates (e.g. TVF, TLF, all-cause mortality, cardiac death, TV-MI, all MI, ID-TLR, ID-TVR, and stent thrombosis)

30) TVF excluding periprocedural MI (i.e. the composite of cardiac death, target vessel-related spontaneous MI, or ID-TVR) (at 30 days and 1 year)

In addition, the following outcomes using the SCAI definition of periprocedural MI will be reported as sensitivity analyses at 30 days, 1 year and 2 years:

31) TV-MI$_{SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)

32) Periprocedural MI$_{SCAI}$ (by SCAI definition)

33) All MI$_{SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)

34) TVF$_{SCAI}$; the composite of cardiac death, TV-MI$_{SCAI}$ or ID-TVR

Patient Reported Outcomes (PRO)

Patient Reported Outcome questionnaires will be incorporated into this study to provide a complementary evaluation of the effectiveness of OCT-guided stent implantation. The following instruments will be administered during this study at baseline (optional post-procedure), 30 day, 12 month and 24 month follow-up:

- EuroQoL 5D (EQ-5D-5L) survey to assess overall health status

5.5.1 Analysis Method

Analyses of all secondary endpoints will be performed according to their randomized group regardless of the device attempted or implanted. All continuous secondary endpoints will be summarized descriptively by number of observations available, mean, standard deviation, median, minimum, maximum; categorical secondary endpoints will be summarized by, the number within each category and the percentage out of the total number of available observations for each randomized arm and overall subjects.

Procedural outcome and Additional Procedural Endpoints

For continuous endpoints, the summary statistics will be presented by randomized arm. Changes from baseline to follow-up, where applicable, will be assessed by ANCOVA, adjusting for the baseline measurement in each group, and least square means, differences thereof and 95% CI of the differences will be reported.

For categorical endpoints, the percentages of each category will be presented by randomized arm and compared using a 95% confidence interval for the difference.

Clinical outcomes

The endpoints will be summarized via Kaplan Meier estimates and a Kaplan-Meier plot. The following statistics will be reported at 1 year and 2 years: estimated event rates and its 95% confidence interval (CI), log-rank p-value, and hazard ratios with 95% Wald CI's obtained via Cox proportional hazards regression.

Relationship between immediate post-procedure OCT parameters and 2-year endpoint rates will be explored using univariate and Cox multiple regression.

Patient Reported Outcomes (PRO)

The end point of PRO will be summarized by randomized arm. [redacted]

5.6 Interim Analysis

[redacted]

5.7 Overall Sample Size

The sample size required for evaluation of the first primary endpoint of MSA is 1600 randomized subjects. [redacted]

5.8 Trial Success

The trial has two primary endpoints for MSA and TVF to compare the effectiveness of the OCT-guided PCI against the angiography-guided PCI. Both primary endpoints must be met in order to claim the study success.

5.9 Multiplicity Adjustment

ILUMIEN IV study is powered for testing the two hypotheses for the primary endpoints in a hierarchical order:

[redacted]

[redacted]

[redacted]

6.0 ADDITIONAL DATA

6.1 Baseline and Demographic Characteristics

Descriptive statistics of continuous variables will be presented by randomized arm and include sample size, mean median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented by randomized arm. Baseline characteristics will be tabulated and compared between the two randomized arms by 95% confidence intervals of the difference.

6.2 Mortality

The number of deaths will be summarized by frequencies and percentages by randomized arm. Kaplan-Meier survival curves will be used to present deaths through longer term follow-up.

6.3 Adverse Events

Adverse events, serious adverse events and unanticipated adverse device effects (UADE) will be summarized from the time of index procedure in terms of number of events, the percentage of subjects with events.

6.4 Withdrawal

Withdrawals will be summarized for subjects who have withdrawn from the trial and will include days to withdrawal and reason for withdrawal.

6.5 Protocol Deviation

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported. All protocol deviations will be reviewed by Abbott throughout the trial for identification of protocol deviations that are thought to be major.

Major protocol deviations include enrollment of a subject:

- whose informed consent was not obtained,
- who did not meet all of the inclusion or exclusion criteria,
- who had a procedure where the physician did not attempt OCT image acquisition in all

target lesions prior to or after stent placement in the OCT arm,

- who had at least one target vessel not assessed with blinded post-PCI OCT in the angiography arm,
- who had at least one target vessel receiving subsequent treatment following the intended blinded post-PCI OCT in the angiography arm,
- who did not receive any post-PCI cardiac enzyme draws

All major protocol deviations will be summarized in the final study report.

6.6 Data for Roll-in Subjects

No hypotheses tests will be performed for the roll-in subjects. Data collected for the roll-in subjects will be summarized using descriptive statistics.

7.0 Bibliography

[redacted]

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[redacted]

APPENDIX C: Pre-specified Powered Analysis of XIENCE in the In-Stent Restenosis (ISR) Population

Introduction

Abbott is evaluating the safety and effectiveness of treating in-stent restenosis (ISR) lesions with the XIENCE family of stents within the ILUMIEN IV trial. The trial enrolls patients undergoing planned XIENCE stent implantation during a clinically indicated PCI procedure who satisfy the eligibility criteria described in **Section 5.4** of the CIP. A pre-specified powered analysis of XIENCE is being conducted in randomized ILUMIEN IV subjects with ISR and is described below. The XIENCE ISR analysis is intended to support an indication expansion for treatment of ISR lesions with the XIENCE family of stents in the USA. The XIENCE ISR analysis will be conducted after the last enrolled patient reaches 2 years of follow-up.

The XIENCE ISR analysis is independent of the main ILUMIEN IV study objective outlined in **Section 1.1** of the CIP, which is to demonstrate the superiority of an OCT-guided stent implantation strategy as compared to an angiography-guided stent implantation strategy.

Objective

The objective of the XIENCE ISR analysis is to demonstrate the safety and effectiveness of XIENCE in the treatment of ISR lesions.

Analysis Population

[redacted].

Primary Endpoint

The primary endpoint for the XIENCE ISR analysis is target lesion failure (TLF_{ISR}). TLF_{ISR} is the event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition in Appendix B), or ischemia-driven target lesion revascularization (ID-TLR), assessed at 1 year. For subjects with multiple target vessels, TLF_{ISR} in any vessel with at least one XIENCE stent implanted on an ISR target lesion constitutes an endpoint event. The primary endpoint TLF_{ISR} is assessed to evaluate the safety and effectiveness of XIENCE in ISR lesions. This endpoint must be met to demonstrate success for XIENCE in ISR lesions.

[redacted]

Statistical Considerations

The hypothesis for the XIENCE ISR analysis is as follows:

$$H0: TLF_{ISR} \geq PG$$
$$Ha: TLF_{ISR} < PG$$

where PG (performance goal) equals 20%. The null hypothesis will be tested using a one-sided alpha of 2.5%.

[redacted]

Sample Size and Power

A sample size of 228 subjects will provide approximately 90% power to reject the null hypothesis [redacted]

For the determination of binary event rates at time points such as 1 year, the denominators are defined as below based on the type of events.

- Death/MI/Revascularization (DMR) event

  Subjects will be included in the analysis if they either had the DMR event by the analysis time point or they did not have the DMR event but had follow-up visit falling into the specific window. In other words, subjects will be included in a given analysis if it can be determined whether or not the subject would have had the DMR event by the time point.

- Special events such as Stent Thrombosis (ST)

  Subjects will be included in the analysis if they either had the specific event (for example, for analysis on ST, only ST is considered) by the analysis time point or they did not have the event but had follow-up visit falling into the specific window. In other words, subjects will be included in a given analysis if it can be determined whether or not the subject would have had the specific event by the time point.

Subgroup Analyses

Subgroup analyses will be performed to examine the consistency of TLF_{ISR} across study subgroups for the following baseline variables:

- Gender: male vs. female
- Age (e.g., < 65, ≥ 65)
- Race (all categories as well as white vs non-white)
- Ethnicity (Hispanic or Latino vs not Hispanic or Latino)
- ACS vs. non-ACS
- Diabetes vs. non-diabetes
- Long or multiple lesions (defined as intended total stent length in any single target vessel ≥28 mm) vs. short and single lesions
- Bifurcations: yes vs. no
- Angiographic severe calcification vs. non-calcification
- OCT-guided treatment vs. angiography-guided treatment
- Medication-treated diabetes mellitus vs. others

[redacted]

Poolability Analysis

[redacted]

Non-powered Secondary Endpoints

Non-powered secondary endpoints for the XIENCE ISR analysis to be assessed at 1 year are as follows:

1. Cardiac death $_{ISR}$

2. TV-MI$_{ISR}$
3. ID-TLR$_{ISR}$
4. Stent thrombosis $_{ISR}$
5. All-cause mortality $_{ISR}$

In addition, the following outcomes will be reported as sensitivity analyses at 1 year:

6. TV-MI$_{ISR,SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)
7. Periprocedural MI$_{ISR,SCAI}$ (by SCAI definition)
8. All MI$_{ISR,SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)
9. TLF$_{ISR,SCAI}$; the composite of cardiac death, TV-MI$_{ISR,SCAI}$ or ID-TLR

Note: In the XIENCE ISR analysis population, TV-MI$_{ISR}$ and TV-MI$_{ISR,SCAI}$ include MI events with confirmed target vessel involvement and indeterminate vessel MI events

The analysis procedures used for the analysis of the primary endpoint and secondary endpoints for the XIENCE ISR population will be the same as used for the endpoints for the full ILUMIEN IV population as described previously in this SAP.

The XIENCE ISR analysis is independent of the main ILUMIEN IV study objective; therefore, multiplicity adjustment of the primary endpoint TLF$_{ISR}$ is not required.

Additional Analyses to Assess Impact of COVID-19

[redacted]

Sensitivity Analyses

[redacted]

Other Study Considerations

Unless otherwise noted in this appendix, study conduct for the ISR analysis population is the same as for the full ILUMIEN IV population. This consideration applies to risks and benefits, investigator records and reporting, adverse events, clinical data handling, monitoring, compliance, suspension or premature termination of the clinical investigation, ethical considerations, clinical investigation conclusion, publication policy and results reporting on clinicaltrials.gov website.

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Statistical Analysis Plan	

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