Abbott

Statistical Analysis Plan Cover Page

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FUSION Statistical Analysis Plan
Validation of OCT-based FUnctional diagnoSIs of corONary stenosis (FUSION)
Study Document No: [redacted]
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Sponsor [redacted]

Statistical Analysis Plan

CRD_1006 FUSION

Validation of OCT-based FUnctional diagnoSIs of corONary stenosis (FUSION)

Statistical Analysis Plan (SAP)

[redacted]

February 2nd, 2021

[redacted]

Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for CIP CL 1009385, the validation of OCT-based functional diagnosis of coronary stenosis (FUSION) clinical investigation. This plan is based on the [redacted] Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective is to validate the diagnostic performance of virtual flow reserve (VFR) by comparing it against a reference standard, fractional flow reserve (FFR).

1.3 Clinical Investigation Design

This study is a single-arm, prospective, multi-center study collecting OCT pullback images of lesions pre-PCI and (optional) post-PCI procedure, and the corresponding pressure tracings and physiology indices. No investigational device will be used in this study. VFR will be calculated offline using the OCT pullback images. Up to 30 centers in the US will enroll approximately N=310 patients. There will be no clinical follow-up after completion of the PCI procedure. [redacted]

1.4 Endpoints

There are two co-primary endpoints and multiple secondary endpoints in this clinical investigation.

1.4.1 Co-Primary Endpoints

The co-primary endpoints of the study will be the sensitivity and specificity of VFR against FFR, each of which will be tested against a prespecified performance goal.

1.4.2 Secondary Endpoints

Secondary endpoints will be descriptive in nature and will include the following:

- Overall diagnostic accuracy
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Correlation between VFR and FFR
- Area under curve (AUC) against FFR.

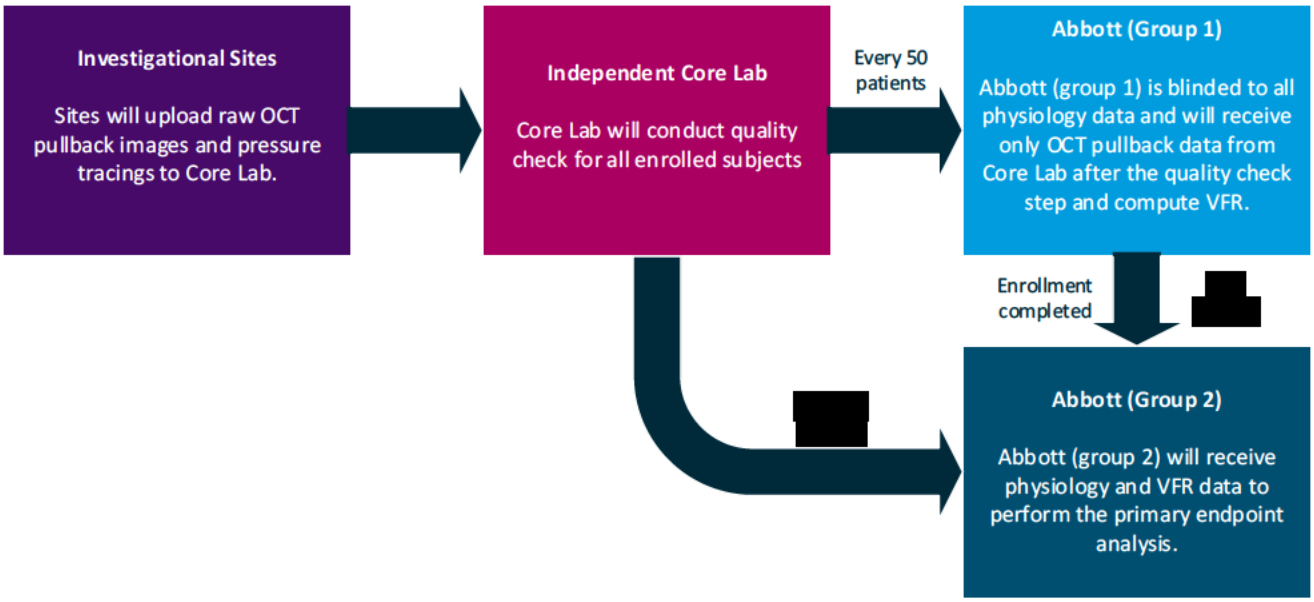
1.5 Randomization

This study is a single-arm study. Therefore, there will be no randomization.

1.6 Blinding and Quality Check

Investigational sites will directly upload and transfer the raw unidentified pullback images and pressure tracings to an independent core laboratory. The core laboratory will perform a quality check on OCT pullbacks and pressure tracings. Once the quality check is completed for [redacted], these OCT pullbacks will be transferred to Abbott personnel (Group 1) to analyze VFR (**Figure**). All Abbott personnel who are responsible for the calculation of VFR (Group 1) will be blinded to all physiology data (Pd/Pa, RFR, and FFR snapshots as well as RFR pullback). Abbott personnel responsible for performing the primary endpoint analysis (Group 2) will be blinded to the VFR data until all patients have been enrolled and all VFR data have been cleaned and generated. Additional data transfer detail is outlined in the data management plan (DMP) document.

Figure 1: Blinding/Unblinding Flowchart



The clinical investigation will utilize an independent OCT and physiology core laboratory for the assessment and evaluation of all OCT pullbacks and pressure tracings required during the clinical investigation period. All clinical investigation-required OCT pullbacks and pressure tracings must be submitted to the core laboratories by uploading the assessments directly to the core laboratories' database.

Pressure tracings will also be reviewed for pressure drift and significant artifacts per the core laboratory's standard operational procedure. Reasons of rejection for each unacceptable pressure tracing will be documented by the core laboratory. All the remaining acceptable pressure tracings will be subsequently transferred to the sponsor.

To ensure timely feedback on the quality of OCT pullbacks and pressure tracings, as well as a balanced baseline FFR distribution in line with study assumptions, the core lab will send data quality and baseline FFR data to Abbott (group 2) for [redacted] (**Figure**). Based on this information, Abbott may choose to work with the sites on improving data quality as well as rebalancing the FFR distributions via encouraging or capping enrollment in certain subgroup(s).

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Primary Analysis Population

The primary analysis population will include all subjects who have signed informed consent, met all inclusion and exclusion criteria, and have acceptable OCT pullbacks and pressure tracings for computing both the VFR and FFR indices.

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results within treatment arm will be summarized with the numbers of observations, means, and standard deviations. Optionally, quartiles, minimums, maximums, and 95% confidence intervals for the means may be included as per the table mockups.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, diabetic status, etc.), results within treatment arm will be summarized with subject counts and percentages/rates. Optionally, exact 95% Clopper-Pearson confidence intervals may be included as per the table mockups.

2.2.3 Correlation

The correlation between VFR and FFR will be estimated as the R^2 correlation coefficient from the simple linear regression model using VFR value as the independent variable and FFR as the dependent variable. The point estimate and 95% confidence interval for this statistic will be reported.

2.2.4 Area Under Curve (AUC)

AUC will be estimated as the area under the ROC curve. To construct a ROC curve, the specificity on the x-axis and sensitivity on the y-axis will be plotted. (Šimundić, 2009 Jan) Sensitivity and specificity are calculated at various values of VFR and FFR, and the AUC curve will be drawn using logistic regression.

The point estimate and 95% confidence interval for this statistic will be reported.

2.3 Endpoint Analysis

All endpoint analyses are diagnostic measures intended to evaluate the performance of the VFR algorithm versus the gold standard, FFR.

2.3.1 Diagnostic Definitions

2.3.1.1 FFR Definition of Disease State

FFR with a binary cut-off of 0.80 will be used as the reference standard for comparison, and an FFR value ≤ 0.80 will be considered positive (ischemia-causing) and an FFR value > 0.80 will be considered negative (non-ischemia-causing).

2.3.1.2 VFR Definition of Disease State

VFR with a binary cut-off of 0.80 will be used as the reference standard for comparison, and a VFR value ≤ 0.80 will be considered positive (ischemia-causing) and a VFR value > 0.80 will be considered negative (non-ischemia-causing).

2.3.1.3 Diagnostic Definitions

The following 2x2 table provides diagnostic definitions of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) within the context of this study.

	FFR ≤ 0.80	**FFR > 0.80**
VFR ≤ 0.80	True Positive (TP)	False Positive (FP)
VFR > 0.80	False Negative (FN)	True Negative (TN)

The following sections contain these diagnostic definitions of TP, TP, FN, and TN to explain how to calculate the endpoint data.

2.3.2 Co-Primary Endpoints

The co-primary endpoints of the study will be the sensitivity and specificity of VFR against FFR, each of which will be tested against a prespecified performance goal. These two endpoints will be described further in the following sections.

2.3.2.1 Co-Primary Endpoint: Overall Sensitivity

The first co-primary endpoint is the overall sensitivity of VFR against FFR.

2.3.2.1.1 Hypothesis

Let Sens(VFR) be the overall sensitivity of VFR, while PG_{sens} is the performance goal for this primary endpoint. The following hypothesis will be tested:

$$H_0: \text{Sens(VFR)} \leq PG_{sens}$$

$$H_1: \text{Sens(VFR)} > PG_{sens},$$

[redacted]

2.3.2.1.2 Analysis Method

The overall sensitivity of the hybrid approach will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. Sensitivity is defined as the proportion of VFR positive lesions (Šimundić, 2009 Jan) in the group of FFR positive lesions, which can be expressed in the following way:

$$Sensitivity = \frac{TP}{TP + FN}$$

Where TP denotes the number of True Positives (both VFR and FFR positive) and FN denotes the number of False Negatives (VFR negative but FFR positive).

[redacted]

2.3.2.2 Co-Primary Endpoint: Overall Specificity

The second co-primary endpoint is the overall specificity of VFR against FFR.

2.3.2.2.1 Hypothesis

Let Spec(VFR) be the overall specificity of VFR, while PG_{spec} is the performance goal for this primary endpoint. The following hypothesis will be tested:

H_0: Spec(VFR) ≤ PG_{spec}
H_1: Spec(VFR) > PG_{spec},

[redacted]

2.3.2.2.2 Analysis Method

The overall specificity will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. Specificity is defined as the proportion of VFR negative lesions in the group of FFR negative lesions (Šimundić, 2009 Jan), which can be expressed in the following way:

$$Specificity = \frac{TN}{TN + FP}$$

Where TN denotes the number of True Negatives (both VFR and FFR negatives) and FP denotes the number of False Positives (VFR positive but FFR negative).

[redacted]

2.3.3 Secondary Endpoints

All secondary endpoints will be summarized descriptively on the primary analysis population. No hypothesis testing will be performed for these endpoints.

2.3.3.1 Secondary Endpoint #1: Overall Diagnostic Accuracy

The overall diagnostic accuracy will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. Overall diagnostic accuracy is defined as the proportion of correctly classified lesions among all lesions (Šimundić, 2009 Jan), which can be expressed in the following way using definitions from Section 2.3.1.3:

$$Overall\ Diagnostic\ Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

Where TP denotes the number of True Positives, TN denotes the number of False Negatives, TN denotes the number of True Negatives, and FN denotes the number of False Negatives.

The point estimate and 95% confidence interval for this statistic will be reported.

2.3.3.2 Secondary Endpoint #2: Positive Predictive Value (PPV)

PPV will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. PPV is defined as the proportion of lesions with the disease and with a positive test result among the group of lesions with a positive test result (Šimundić, 2009 Jan), which can be expressed in the following way using definitions from Section 2.3.1.3:

$$PPV = \frac{TP}{TP + FP}$$

Where TP denotes the number of True Positives and FP denotes the number of False Positives.

The point estimate and 95% confidence interval for this statistic will be reported.

2.3.3.3 Secondary Endpoint #3: Negative Predictive Values (NPV)

NPV will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. NPV is defined as the proportion of lesions without the disease and with a negative test result among the group of lesions with negative test results (Šimundić, 2009 Jan), which can be expressed in the following way using definitions from Section 2.3.1.3:

$$NPV = \frac{TN}{TN + FN}$$

Where TN denotes the number of True Negatives and FN denotes the number of False Negatives.

The point estimate and 95% confidence interval for this statistic will be reported.

2.3.3.4 Secondary Endpoint #4: Correlation between VFR and FFR

The correlation between VFR and FFR will be estimated at the lesion level as the R^2 correlation coefficient from the simple linear regression model using VFR value as the independent variable and FFR as the dependent variable.

[redacted]

2.3.3.5 [redacted]

[redacted]

2.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this study. As such, no formal statistical rule for early termination of the trial is defined.

2.6 Timing of Analysis

The primary endpoint analysis will be conducted after at least 310 subjects have undergone a procedure and usable VFR and FFR readings have been obtained.

2.7 Study/Trial Success

The clinical investigation will be deemed a success if both primary endpoint hypotheses are rejected at the 0.025 level.

2.8 Subgroups for Analysis

[redacted]

2.9 Handling of Missing Data

Every effort will be taken to obtain complete data for all subjects. Any subject without a pair of qualified FFR and VFR measurements will be excluded from analysis.

[redacted]

2.10 Poolability Issue

[redacted]

2.11 Multiplicity Issues

Since the endpoints are co-primary and both must be passed to declare study success, there is no need for multiple comparison adjustment.

2.12 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

2.13 Sensitivity Analysis

Generalized linear models may be utilized to adjust for within-subject correlation.

2.14 Exploratory Analysis

Exploratory analysis may be performed comparing VFR with RFR and Pd/Pa as per the table mock-ups.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following demographic, medical history and vessel characteristic variables may be summarized for the subjects in the primary analysis population:

- Age (year)
- Gender

- Race
- Previous myocardial infarction (MI) in non-target vessel
- Previous PCI
- History of hypertension
- History of hyperlipidemia
- History of cerebrovascular accident (CVA)
- History of transient ischemic attack (TIA)
- Peripheral vascular Disease
- Diabetes mellitus
- Current smoker or recent smoker (within 30 days)
- Renal dysfunction (serum creatinine > 2.0 mg/dL)
- Clinical presentation (Stable angina, Unstable angina, Silent Ischemia)
- Target vessel (LAD, Circumflex or ramus, RCA)
- LVEF (%)
- NYHA
- Lesion length (mm)
- Reference vessel diameter (mm)
- Diameter stenosis (%)

3.2 Adverse Events

All adverse events will be summarized as reported by investigator for all subjects who are enrolled in this trial in terms the number of events and the percentage of subjects with events.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, etc. will be summarized.

3.4 Protocol Deviation

Protocol deviations will be summarized by category for subjects in whom a protocol deviation was reported.

3.5 Descriptive Endpoints or Additional Data

If applicable, additional analyses may be performed as per the table mock-ups.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.2 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AUC	Area Under Curve
CIP	Clinical Investigation Plan
CRF	Case Report Form
CVA	Cerebrovascular Accident
FFR	Fractional Flow Reserve
FN	False Negative
FP	False Positive
LAD	Left Anterior Descending [Artery]
LCB	Lower Confidence Bound
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
NPV	Negative Predictive Value
NYHA	New York Heart Association
Pd/Pa	Ratio of resting distal coronary pressure to aortic pressure
PCI	Percutaneous Coronary Intervention
PG	Performance Goal
PPV	Positive Predictive Value
RCA	Right Coronary Artery
RFR	Resting Full-cycle Ratio
ROC	Receiver Operating Characteristic
SAP	Statistical Analysis Plan
TIA	Transient Ischemic Attack
TN	True Negative
TP	True Positive
VFR	Virtual Flow Reserve

6.0 REFERENCES

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