Statistical Analysis Plan

NCT Number: NCT02468778
SHIELD II
Supporting Patients Undergoing High-Risk PCI Using a High-Flow PErcutaneous Left Ventricular Support Device
Study Document No: SJM-CIP-10148
Version E
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Sponsor

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Supporting Patients Undergoing High-Risk PCI Using a High-Flow PErcutaneous Left Ventricular Support Device

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[redacted]

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Clinical Investigation Plan (CIP) 10148, the SHIELD II clinical investigation. This plan is based on the Version J Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective of the SHIELD II clinical investigation is to assess the safety and effectiveness of the HeartMate PHP compared to Impella in supporting patients with severe symptomatic coronary artery disease but with stable cardiovascular function, who are undergoing elective or urgent high-risk PCI, and a heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option.

1.3 Clinical Investigation Design

SHIELD II is a prospective, randomized, open-label, multi-center clinical investigation that will register subjects at up to 120 sites in the U.S. Subjects in this clinical investigation will be randomly assigned to the HeartMate PHP or Impella in a 2:1 ratio. The primary endpoint is a composite endpoint at 90 days, including cardiovascular death, myocardial infarction (MI), stroke, unplanned repeat revascularization, bleeding of BARC 3 or 5 up to 14 days post-device removal, severe hypotension and change in aortic insufficiency from baseline to 90 days by echocardiographic assessment. HeartMate PHP will be tested for non-inferiority in the primary endpoint compared to Impella. Any Impella device approved for use in high-risk PCI can be used as the control device. All registered subjects will be followed for 90 days. This clinical investigation is conducted to support the pre-market approval of the HeartMate PHP for the indication of high-risk PCI.

The SHIELD II clinical investigation is divided into two phases chronologically: a feasibility phase, which includes subjects registered under the CIP versions 2-4[†] prior to January 30, 2017, and a pivotal phase, which includes subjects to be registered under version F or a later version of the CIP. Both phases consist of a non-randomized roll-in cohort and a randomized cohort. The roll-in cohort is designed to prevent a learning curve from biasing the clinical investigation results.

There were 195 subjects, including 75 HeartMate PHP roll-in and 120 randomized subjects, registered at 48 U.S. sites in SHIELD II prior to January 30 ,2017, and these subjects are now considered in the feasibility phase of the clinical investigation. All registered subjects in the

[†] Previous versions of the SHIELD II CIP in the feasibility phase were designated numerically from version 1 to version 5 (no subjects were registered under versions 1 and 5 of the CIP). Starting from the pivotal phase, the CIP is designated alphabetically and starts as version F.

feasibility phase were already beyond the time point of the 90-day follow-up visit, and the feasibility phase of the clinical investigation reached its end in 2017.

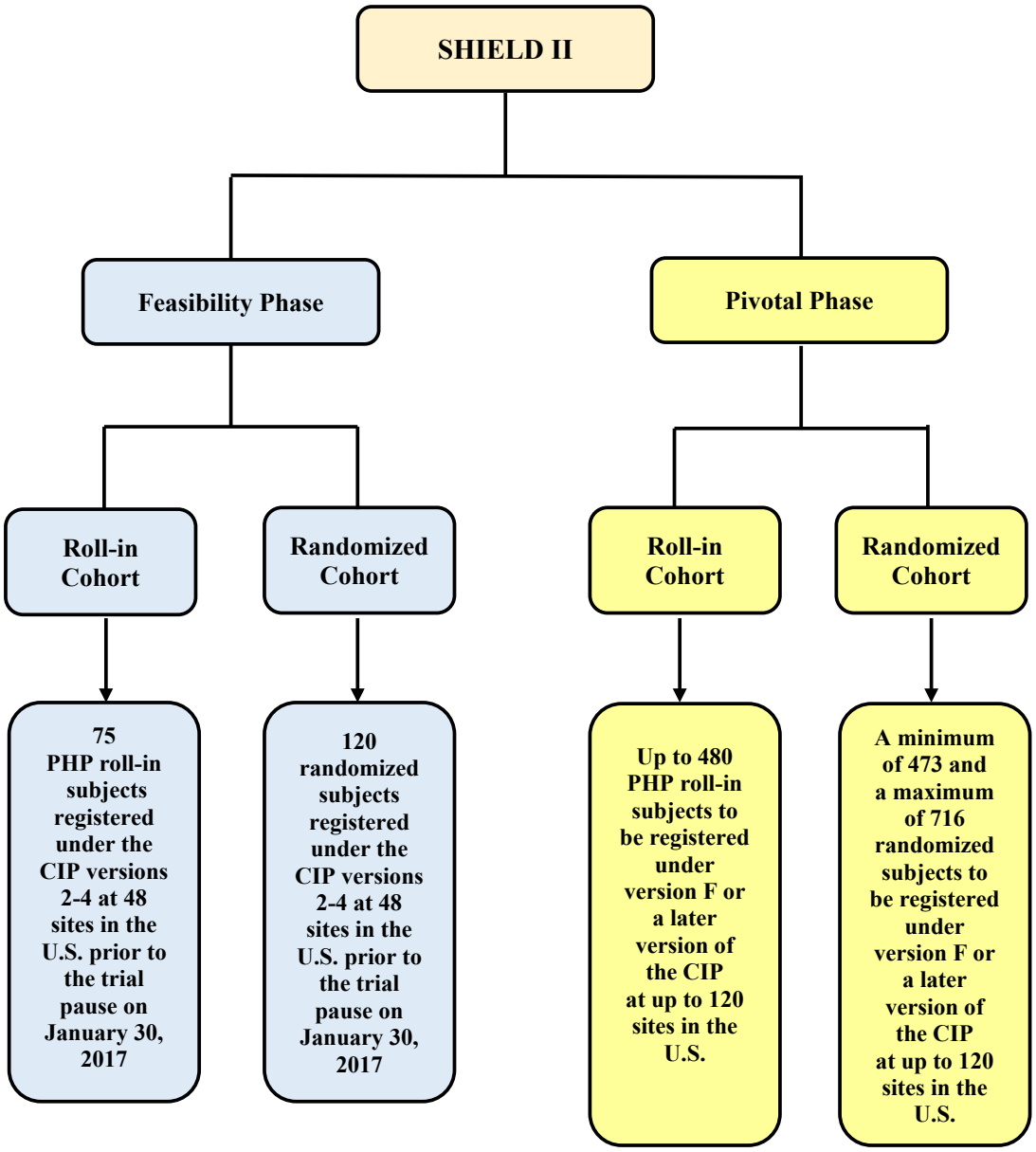
In the pivotal phase, each operator will be required to actively participate in treating a minimum of 1 and up to 2 HeartMate PHP subjects first before becoming qualified to randomize subjects. Since only sites experienced in the use of Impella will be invited to participate in this clinical investigation, no roll-in subjects using Impella will be required in the pivotal phase. With an estimation of 2 operators per site, up to 480 HeartMate PHP roll-in subjects will be registered at up to 120 sites in the U.S. in the roll-in cohort. For the randomized cohort of the pivotal phase, a minimum of 473 subjects will be randomized. [redacted] Each site will be allowed a maximum of 60 randomized subjects. The overall design of the SHIELD II clinical investigation is shown in **Figure 1.**

[redacted] Both roll-in and randomized subjects will follow all the clinical investigation procedures outlined in the CIP. The results of the roll-in cohort will be analyzed as adjunctive data, separate from the results of the randomized cohort. In addition, data in the feasibility phase of the clinical investigation will also be analyzed separately from data in the pivotal phase of the clinical investigation. Hypothesis testing of the primary endpoint will be performed for the randomized cohort in the pivotal phase to support regulatory approval.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis section of this clinical investigation plan for details.

Figure 1: Overall Design of the SHIELD II Clinical Investigation

The SHIELD II trial Pivotal Phase will not enroll patients in Europe.



* The feasibility phase of the clinical investigation has already completed the 90-day follow-up and reached its end as of the release of Revision F of this CIP.

1.4 Endpoints

The primary endpoint analysis will be based on adverse events collected after the start of the index procedure.

1.4.1 Primary Endpoint

The primary endpoint of the clinical investigation is a composite endpoint at 90 days, including the following components representing important safety and effectiveness endpoints:

- Cardiovascular Death
- Myocardial infarction (MI)
- Stroke
- Any unplanned repeat revascularization (PCI or CABG)
- Bleeding (BARC 3 or 5) up to 14 days post-device removal
- Severe hypotension, defined as: systolic blood pressure (SBP) or augmented diastolic pressure (whichever is greater) <90 mmHg while on device support requiring (1) more than one administration of OR (2) continuous infusion of inotropic/pressor medications to restore hemodynamics
- Change in aortic insufficiency from baseline to 90 days by echocardiographic assessment and defined as:

Baseline Assessment	90 Day Assessment
None	Moderate OR Severe
Trace	Moderate OR Severe
Mild	Moderate OR Severe

1.5 Randomization

1.5.1 Stratified Randomization

For the randomized cohort of the pivotal phase, up to 716 subjects will be randomized. Each site will be allowed a maximum of 60 randomized subjects. Subjects will be randomly assigned in a 2:1 fashion to either HeartMate PHP or Impella in SHIELD II. [redacted]

1.5.2 Timing of Randomization

Randomization assignments will be given through EDC Study Site Portal after subjects have signed the ICF and met all eligibility requirements. Subjects will be considered registered in the clinical investigation once randomized and must follow all CIP requirements. Randomized subjects who do not undergo device placement due to previously undiagnosed anatomic abnormalities (e.g. peripheral vascular disease) which precludes device placement, will be considered registered and in the intent-to-treat (ITT) population, and they must follow all CIP requirements. Once a subject is randomized, PCI should be performed as soon as possible.

1.6 Blinding

This is an open-label clinical investigation. The subjects and the investigators will not be blinded to the treatment assignment. Nevertheless, measures of blinding will be taken to minimize bias and will be applied to the randomized cohorts of both the feasibility and pivotal phases.

[redacted]

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

All analysis populations will be applied to the randomized cohorts of both the feasibility phase and the pivotal phase. The two phases will be analyzed separately.

2.1.1 Intent-to-Treat (ITT) Population

The ITT population [redacted]

2.1.2 As-Treated (AT) Population

The AT population [redacted]

2.1.3 Per-Protocol (PP) Population

The PP population [redacted]

[redacted]

[redacted]

2.2 Statistical Methods

Descriptive analysis will be performed to summarize baseline, hemodynamic measures, clinical and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in the following sections will be used.

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, with quartiles, minimums, maximums, and 95% confidence intervals for the means. Differences between the treatment arms, where specified, will be summarized with differences of the two means, and 95% confidence intervals for the difference between the means.

2.2.2 Descriptive Statistics for Categorical Variables

For binary variables (e.g. gender, diabetic status, etc.), results within treatment arm will be summarized with subject counts and percentages/rates, and where applicable, with exact 95% Clopper-Pearson[1] confidence intervals. [redacted]

For events of interest, relative risks (i.e., the ratio of rates), confidence interval for the relative risks, the difference in rates and the confidence interval for difference in rates, and p-values may also be presented for hypothesis generating purposes. [redacted]

For the determination of event rates, the denominators are defined as below based on the type of events.

- Primary endpoint event and its components

The denominator of the primary endpoint event rate will exclude subjects in the analysis population who terminated from the study [redacted] without a primary endpoint event or any subject who completes the 90-day follow-up without aortic insufficiency data at either baseline or 90-day follow-up and without a primary endpoint event. The same denominator rule will apply to individual component of the primary endpoint except for change in aortic insufficiency, which is an imaging endpoint and will follow the denominator rule set forth for missing data handling.

- Site-reported Adverse Events, Adverse Device Effects and Adverse Event related Descriptive Endpoints

[redacted]

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Subjects who withdrew from the study will be censored at the date of withdrawal. Survival curves will be constructed using Kaplan-Meier[4] estimates. Summary tables for endpoints will include event (failure) rates, Greenwood standard error and confidence interval for the event rates.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint(s)

The primary endpoint, a composite of safety and effectiveness at 90 days, will be evaluated using the difference in event rates in the ITT population of the pivotal phase. The hypothesis test is designed to show non-inferiority of HeartMate PHP to Impella for the primary endpoint with one-sided alpha of 0.025. [redacted]

[redacted]

If non-inferiority is met, superiority testing will be performed with a two-sided alpha of 0.05. [redacted]

[redacted]

The data will be analyzed for superiority using Fisher's exact test.

2.4 Sample Size Calculations

It is assumed that the Impella will have a 90-day composite endpoint rate of 20%. [redacted]

[redacted]

[redacted] the non-inferiority margin (δ) is assumed to be 10%.

[redacted]

[redacted] a total of 473 subjects (315 for the HeartMate PHP arm and 158 for the Impella arm) will be registered in the randomized cohort of the pivotal phase. [redacted]

[redacted]

[redacted]

2.6 Timing of Analysis

For the randomized cohort of the pivotal phase, the analyses will be performed after all registered subjects have reached their 90-day follow-up visit, the database is locked, and the clinical investigation

becomes unblinded.

[redacted]

2.8 Subgroups for Analysis

The treatment comparisons for the primary endpoint will be analyzed within each of the subgroups below. [redacted]

Gender:
- Males
- Female

Race:
- White
- Black or African American
- Other

Age:
- 18 ≤ Age < 65
- Age ≥ 65

Atherectomy:
- Atherectomy is planned
- No Atherectomy is planned

STS score:
- STS score < 10
- STS score ≥ 10

2.9 Handling of Missing Data

All analyses will be based on available data with missing data excluded. [redacted]

2.10 Poolability Assessment

The SHIELD II study will have up to 120 sites. [redacted]

[redacted]

To evaluate the center effect on the primary endpoint, interaction effect between treatment and center on the primary endpoint will be tested against an alpha level of 0.15. [redacted]

2.11 Multiplicity Assessment

There is a single primary endpoint and no powered secondary endpoints. Therefore, no adjustment will be made for multiple testing.

2.12 Sensitivity Analysis

The following sensitivity analyses of the primary endpoint will be carried out:

Worst Case Scenario Analysis

[redacted]

Tipping Point Analysis

[redacted]

[redacted]

Multiple Imputation

[redacted]

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

Data in the feasibility phase of the clinical investigation will be analyzed separately from data in the pivotal phase of the clinical investigation. Data collected for both roll-in and randomized subjects will be summarized descriptively. The results of the roll-in cohort will be analyzed as adjunctive data, separate from the results of the randomized cohort.

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized: gender, age, height, weight, baseline risk factors, medical history, morphology, quantitative coronary angiography, echocardiogram, implant procedural characteristics, device usage, and quality of life, etc.

3.2 Adverse Events

The start of the index procedure will be a reference start time for summarizing all adverse events. All of the adverse device effects, serious adverse device effects, UADEs will be summarized for all subjects who registered in this trial in terms the number of events and the percentage of subjects with events.

All CEC adjudicated adverse events will also be summarized for all subjects who registered in the trial by treatment arms 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, lost-to-follow-up, etc. will be summarized by treatment arms at the 90-day follow-up visit.

3.4 Protocol Deviation

Protocol deviations will be summarized by category for subjects in whom a protocol deviation was reported. Number of protocol deviations and number of subjects with deviation will be summarized by deviation categories.

[redacted]

[redacted]

3.5.2 Exploratory Endpoints

- Quality of Life questionnaires including EQ-5D-5L and Seattle Angina Questionnaire (SAQ) at baseline and 90 days

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.3 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
AT	As-Treated Population
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CI	Cardiac Index
CIP	Clinical Investigation Plan
CO	Cardiac Output
CPO	Cardiac Power Output
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
EQ-5D	EuroQol Five Dimensions
ITT	Intent-to-Treat Population
LDH	Lactate Dehydrogenase
MAP	Mean Arterial Pressure
N	Sample Size
OUS	Outside the United States
PAP	Plumonary Artery Pressure
PCI	Percutaneous Coronary Intervention
PCWP	Pumlonary Capillary Wedge Pressure
PfHgb	Plasma-free Hemoglobin
PP	Per-Protocol Population
RAP	Right Atrial Pressure
SAE	Serious Adverse Event
SAP	Statically Analysis Plan
SAQ	Seattle Angina Questionnaire
UADE	Unanticipated Adverse Device Event
US	United States
USADE	Unanticipated Serious Adverse Device Event

[redacted]

[redacted]

[redacted]