Medtronic EXPAND I Feasibility Study

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Statistical Analysis Plan

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Medtronic
Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Sarah Verdoliva Boatman, Principal Statistician
2.0	• Document updated throughout to align with the removal of Cohort A (Moderate Symptomatic AS) in protocol revision D • Updated Kaplan-Meier standard error to use Greenwood's method • Remove required summary of domain scores for the efficacy endpoint change in KCCQ • Removal of "Additional details have been detailed in the SAP for the planned subgroup analyses (Section 7.9.4) including identification of the endpoints to be analyzed as well as the addition of subgroup analysis based on NT-proBNP which was identified as clinically important" from Section 7.11 as the details in this document align with the subgroup analyses as specified in CIP revision D • Added Section 9 (References)	Sarah Verdoliva Boatman, Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AS	Aortic stenosis
BMI	Body mass index
BSA	Body surface area
BVD	Bioprosthetic valve dysfunction
BVF	Bioprosthetic valve failure
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
DCS	Delivery catheter system
DVI	Doppler velocity index
E	Early diastolic mitral inflow velocity
e'	E prime; mitral annular early diastolic velocity

Abbreviation	Definition
E:e'	Ratio of early (E) mitral inflow velocity to early (e') mitral annular velocity
EOA	Effective orifice area index
EOAI	Effective orifice area index
GLS	Global longitudinal strain
KCCQ	Kansas City Cardiomyopathy Quality of Life
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PPM	Patient-prosthesis mismatch
PPI	Permanent pacemaker implant
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SVI	Stroke volume index
TAV	Transcatheter aortic valve
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiography
VARC-2	Valve Academic Research Consortium
VTI	Velocity time integral
6MWT	Six-minute walk test

3. Introduction

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports and study-specific publications for the Evolut™ EXPAND TAVR I Feasibility Study. This version of the analysis plan was developed under the approved Clinical Investigation Plan (CIP) and approved Case Report Form (CRF) Requirements.

4. Study Objectives

The primary objectives of this feasibility study are as follows:

1. Characterize the spectrum of cardiac function, symptomology, and severity of aortic stenosis in the study populations,
2. Estimate event rates for potential safety and effectiveness endpoints to be evaluated in pivotal studies for the proposed patient populations, and
3. Evaluate the effect of TAVR on cardiac function, functional capacity, effort tolerance, and patient-reported quality of life in the study populations.

The study objectives and associated endpoints are intended to fully characterize the spectrum of aortic stenosis (AS) severity, left ventricular (LV) function, and symptomology of patients with moderate

symptomatic and severe asymptomatic AS, provide information on event rates for pivotal sample size estimations, and refine the entrance criteria for future pivotal studies. The full list of protocol defined endpoints are detailed in Section 7.9. Of the protocol defined endpoints, the following key study endpoints have been identified:

Key Safety Endpoints:

- All-cause mortality at 30 days and 6 months
- All stroke (disabling and non-disabling) at 30 days and 6 months
- Valve-related dysfunction requiring repeat procedure at 30 days and 6 months
- New permanent pacemaker implant (PPI) at 30 days and 6 months

Key Efficacy Endpoints:

- Cardiovascular and heart failure hospitalizations at 30 days and 6 months
- Heart failure events at 30 days and 6 months
- Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months
- Change in Six-Minute Walk Test (6MWT) at 6 months
- Change in cardiac function by echo (LVEF, Peak GLS, E:e') at 6 months

5. Investigation Plan

5.1 Study Design

This is a prospective, descriptive, interventional, multi-center, single-arm, pre-market, feasibility study. The study will involve up to 75 subjects with severe, asymptomatic AS implanted using the Medtronic Evolut PRO+ TAVR system among up to 25 centers in the United States, Canada, Europe, Israel, Australia, and New Zealand. As not all patients consented for evaluation will go forward to implantation, the number of subjects consented for the study is expected to be higher than 75 (up to 150). No site will implant more than 15 total subjects without prior authorization from Medtronic in order to minimize bias.

5.2 Purpose

The purpose of this study is to obtain initial procedural safety and efficacy data on the use of the Medtronic self-expanding Evolut PRO+ TAVR system in patients with severe, asymptomatic AS. Data will be used to inform the design of pivotal studies to support expansion of the current indication to include these patient populations.

5.3 Follow-up and Study Duration

Subjects will be consented for follow-up through five years following implantation, and all implanted subjects will be followed per protocol through five years following implantation. Subject follow-up visits post-implantation will occur at discharge, 30 days, 6 months, and annually through five years. Subjects who exit from the study after implantation will not be replaced. The enrollment period is estimated to be between 9 and 20 months, and the estimated total study duration (first subject implanted to last subject completing his/her last follow-up exam) is estimated to be seven years.

5.4 Analysis Execution

The study endpoints are descriptive without formal statistical hypotheses. An initial analysis is anticipated when 50 to 75 subjects have completed the 6 month follow up exam. The analysis will be descriptive and no formal interim analyses are planned for the purpose of early stopping or sample size re-estimation. Additional analyses are planned when all 75 implanted subjects have completed his/her 6 month follow-up. Additional analyses may be performed following completion of annual follow-up. A final report will be prepared once all implanted subjects have completed his/her five-year follow-up and all data collection has ended.

6. Determination of Sample Size

The study is descriptive and the sample size of 75 subjects was not determined by statistical sample size methods. However, a sample size of 75 subjects is adequate to achieve the study objectives and for an assessment of the procedural safety and efficacy of the study device in the study populations.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be illustrated in a flow diagram. Subject visits will be tabulated and compliance to the visit schedule and visit windows will be summarized, and attrition will be identified and summarized. Tabulations will include the number of subjects enrolled, attempted implant, implanted, died, withdrawn, lost-to-follow-up, and completed the scheduled follow-up visit for each visit.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Deviations will be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations will be reported on the Study Deviation CRF. Deviations will be reported by deviation category and visit. For each category, both protocol deviation and subject counts will be reported. Percentages will be based on subject counts and the denominator will include all subjects eligible for the visit, where applicable.

7.1.3 Analysis Sets

The enrolled population will consist of all subjects who signed the informed consent. The following analysis sets are defined within the enrolled population:

1. **Attempted Implant set:** The attempted implant data set will include all subjects with an attempted implant procedure, where an attempted implant is defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, Transesophageal echocardiography (TEE) placed or any monitoring line placed. Day 0 is the date of first attempted procedure.
2. **Implanted set:** The implanted data set includes all subjects with an attempted implant where the study device is implanted, defined as when the transcatheter aortic valve (TAV) is fully released from the delivery catheter system (DCS). Day 0 is the date of first attempted procedure.

In general, the primary analysis of safety, clinical outcomes, and quality of life (QoL) outcomes will be performed using the Attempted Implant analysis set and primary analysis of echo-related outcomes will be performed using the Implanted analysis set. The primary analysis population for each endpoint are detailed in Section 7.9. Analysis performed using analysis sets other than the primary would be considered supportive.

7.2 General Methodology

Continuous variables will be summarized descriptively with number of observations, mean, standard deviations, median, first and third quartiles, minimums and maximums. Categorical data will be presented as counts and percentages.

For time-to-event outcomes using Kaplan-Meier methods, the time points of 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years will correspond to 30, 183, 365, 730, 1095, 1460, and 1825 days post-implant, respectively. For each applicable time point, the event or event-free rate, the number of subjects at risk, the number of subjects with an event, the Greenwood standard error of the estimate, and the log-log transformed 95% confidence interval using the Greenwood standard error will be reported. For subjects with an event, the date of event will be based on the first event occurrence. For subjects without an event, date of censoring will be based on the latest of all follow-up visits, assessments, and events (for non-death events).

All statistical analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) or other widely accepted statistical or graphical software.

7.3 Center Pooling

Data from all geographies and active centers will be included in the analyses; there are no planned poolability analyses.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing data. Missing (accidentally, due to withdrawal, missing follow-up or loss to follow-up, etc.), unused and spurious data will remain identifiable in the database. For time-to-event outcomes, dropouts will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. Unless otherwise specified, all analyses will be based on available data and missing data will not be imputed. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

In the case of partial dates, unknown portions will be imputed for the purposes of analysis. If only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of the known month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of the known year. Imputation of partial dates is subject to the restriction that pre-implant events must occur between the date of informed consent and the date of implant and post-implant events must occur after the date of implant.

7.5 Adjustments for Multiple Comparisons

The study is descriptive without formal hypothesis testing; methods for multiplicity adjustment are not applicable.

7.6 Demographic and Other Baseline Characteristics

Baseline demographics and clinical variables will be summarized descriptively for the attempted implant analysis set. Data will be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, first and third quartiles, minimums and maximums for continuous variables.

7.7 Treatment Characteristics

Implant procedure data will be summarized for the attempted implant analysis set. Data will be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, first and third quartiles, minimums and maximums for continuous variables.

7.8 Interim Analyses

An initial analysis is planned when the first 50 to 75 implanted subjects have completed his/her 6 month follow-up; however initial analyses may be performed earlier if enrollment is slower than expected. Initial analyses will assess all safety and efficacy endpoints based on available data. The analysis will be descriptive and no formal interim analyses are planned for the purpose of early stopping or sample size re-estimation.

7.9 Evaluation of Objectives

7.9.1 Safety Endpoints

The following safety endpoints are defined and will be analyzed:

1. All-cause and cardiovascular mortality at 30 days and 6 months
2. All stroke (disabling and non-disabling) at 30 days and 6 months
3. Myocardial infarction (periprocedural and spontaneous) at 30 days and 6 months
4. Acute kidney injury at 30 days and 6 months
5. Major vascular complications at 30 days and 6 months
6. Life-threatening bleed at 30 days and 6 months
7. New permanent pacemaker implantation (PPI) at 30 days and 6 months
8. New intraventricular conduction delays at 30 days and 6 months
9. New-onset atrial fibrillation at 30 days and 6 months
10. Valve-related dysfunction requiring repeat procedure at 30 days and 6 months

Safety endpoints will be adjudicated by the Clinical Events Committee (CEC) and analysis will be based on data collected on the CEC adjudication form. Safety endpoints will be analyzed with Kaplan-Meier survival analysis methods according to Section 7.2. Safety endpoints will be analyzed using the Attempted Implant population.

7.9.2 Efficacy Endpoints

7.9.2.1 Device success (VARC-2)

Device success is defined as meeting all of the following:

- Absence of procedural mortality, AND
- Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND
- Absence of patient prosthesis-mismatch AND mean aortic valve gradient < 20 mmHg (or peak velocity < 3 m/sec), AND
- Absence of moderate or severe prosthetic valve regurgitation.

Components of device success will be reported on the procedure CRF, the echo core lab CRF at discharge, and CEC CRF:

- Procedural mortality will be defined as any death occurring within 30 days of implant or prior to hospital discharge.
- Correct positioning of the single prosthetic heart valve into the proper anatomical location will be reported by the investigator on the procedure CRF.
- Absence of patient-prosthesis mismatch will be derived from the echo core lab data at discharge. Patient prosthesis mismatch is defined in Section 7.9.2.4.
- Mean aortic valve gradient < 20 mmHg (or peak velocity < 3 m/sec) will be derived from the echo core lab CRF at discharge
- Absence of moderate or severe prosthetic valve regurgitation will be derived from the echo core lab CRF at discharge

The endpoint will be reported as the count and percentage of subjects achieving device success with two-sided 95% exact binomial confidence interval. Subjects will be defined as success if all components are met. Subjects will be defined as failure if any one component with available data is not met, regardless if data are available for all components. Subjects missing data for any components and not meeting criteria for failure will be considered to have a missing outcome. The numerator will include the number of subjects with device success and the denominator will include subjects evaluable for device success (known status of success or failure). The components of device success will also be summarized descriptively. The endpoint will be analyzed using the Implanted set.

7.9.2.2 Cardiovascular and heart failure hospitalizations at 30 days and 6 months

Cardiovascular and heart failure hospitalization will be adjudicated by the CEC and analysis will be based on data collected on the CEC adjudication form. The endpoint will be analyzed with Kaplan-Meier survival analysis according to Section 7.2 for each time point. Analysis of the endpoint will use the Attempted Implant set.

7.9.2.3 Heart failure events at 30 days and 6 months

Heart failure events will be adjudicated by the CEC and analysis will be based on data collected on the CEC adjudication form. The endpoint will be analyzed with Kaplan-Meier survival analysis according to Section 7.2 for each time point. The primary analysis will use the Attempted Implant set.

7.9.2.4 Hemodynamic performance metrics by Doppler echocardiography at discharge, 30 days, and 6 months

The following hemodynamic performance metrics by Doppler echocardiography will be reported at discharge, 30 days, and 6 months:

- Mean aortic gradient
- Effective orifice area
- Degree of total, para, and transvalvular prosthetic regurgitation
- Incidence of moderate and severe patient-prosthesis mismatch (PPM)

Endpoint Definitions:
Mean aortic gradient will be reported in units of mmHg.

Effective Orifice Area (EOA) in cm^2 will be derived according to the following formula

EOA = LVOT $diameter_2$ x 0.785 x (LVOT VTI/Aortic valve VTI)

Where: LVOT VTI is the velocity time integral of the left ventricular outflow tract in cm, and aortic valve VTI is the velocity time integral of the aortic prosthesis in cm.

Degree of total, para, and transvalvular prosthetic regurgitation will be reported in categories of none, trace, mild, moderate, and severe.

Patient-prosthesis mismatch (PPM)[(1)] is defined as follows:

For subjects with body mass index (BMI) < 30 kg/cm2

- **Moderate PPM:** EOAI = 0.85 – 0.65
- **Severe PPM:** EOAI < 0.65

For subjects with BMI ≥ 30 kg/cm2

- **Moderate PPM:** EOAI = 0.70 – 0.60
- **Severe PPM:** EOAI < 0.60.

Note that in the above, Effective Orifice Area Index (EOAI) in cm^2/m^2 is defined as EOAI = EOA/BSA where EOA is the effective orifice area in cm^2 and BSA is the body surface area in m^2.

Analysis Methods:
Data for all endpoints will be reported on the core lab echo CRF. Mean aortic gradient and EOA will be summarized descriptively as continuous outcomes at each time point. Change from baseline in mean aortic gradient and EOA will also be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. The degree of total, para, and transvalvular prosthetic regurgitation and incidence of moderate and severe PPM will be summarized with frequency counts and percentages at each follow-up time point. Analysis of each hemodynamic performance outcome will use the Implanted set.

7.9.2.5 Change from baseline in New York Heart Association (NYHA) functional classification at 30 days and 6 months

New York Heart Association (NYHA) functional classification will be reported on the follow-up CRF by the investigator as Class I, II, III, or IV. NYHA class will be summarized with frequency counts and

percentages for each follow-up time point. At each follow-up time point, change in NYHA class from baseline will be reported descriptively both as categorical and continuous variable. Categorical summary of change will include a summary of subjects with change of 3, 2, 1, 0, -1, -2, and -3 as well as a summary of improved, no change, worsened, or died. Continuous change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. Analysis of the endpoint will use the Attempted Implant set.

7.9.2.6 Change in six-minute walk test (6MWT) from baseline at 6 months

The six-minute walk test (6MWT) measures the distance walked in meters (m). Distance walked at each time point will be summarized as a continuous outcome. The number of subjects unable to perform the test will be tabulated by reason at each visit. Change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. Analysis will be performed using the Attempted Implant set for all subjects able to complete the assessment at the follow-up visit.

7.9.2.7 Change in Kansas City Cardiomyopathy (KCCQ) from baseline at 30 days and 6 months

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered instrument and responses will be collected in the CRF. The domain and summary scores include: Physical Limitation, Symptom Stability, Symptom Frequency, Symptom Burden, Total Symptom Score, Self-efficacy, Quality of Life, Social Limitation, Overall Summary Score, and Clinical Summary Score. At each follow-up time point, each summary score will be summarized descriptively as continuous data. Change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. Analysis will be performed using the Attempted Implant set.

7.9.2.8 Change in left ventricular ejection fraction (LVEF) from baseline at 6 months

Left ventricular ejection fraction (LVEF) will be analyzed according to the data collected on the core lab echo CRF. At each time point, LVEF will be summarized descriptively as continuous data. Continuous change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. The endpoint will be analyzed using the Implanted set.

7.9.2.9 Change in peak global longitudinal strain (GLS) from baseline at 6 months

Peak global longitudinal strain (GLS) will be analyzed according to the data collected on the core lab echo CRF. At each time point, peak GLS will be summarized descriptively as continuous data. Change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. The endpoint will be analyzed using the Implanted set.

7.9.2.10 Change in left ventricular filling pressure (E:e') from baseline at 6 months

Left ventricular filling pressure (E:e') will be analyzed according to the data collected on the core lab echo CRF. At each time point, E:e' will be summarized descriptively as continuous data. Change from

baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. The endpoint will be analyzed using the Implanted set.

7.9.2.11 Change in stroke volume index (SVI) from baseline at 6 months

Stroke volume index (SVI) will be analyzed according to the data collected on the core lab echo CRF. At each time point, SVI will be summarized descriptively as continuous data. Change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. The endpoint will be analyzed using the Implanted set.

7.9.2.12 Change in NT-pro B-type natriuretic peptide (NT-proBNP) from baseline at 6 months

NT-proBNP will be recorded on the follow-up CRF by the investigator at each visit. At each time point, NT-proBNP will be summarized descriptively as continuous data. Additionally, the percentage of subjects with clinically-significant abnormal results (low or high) will be reported for each visit. Change from baseline will be summarized descriptively along with two-sided 95% confidence interval and p-value from a paired t-test. The endpoint will be analyzed using the Attempted Implant set.

7.9.3 Additional Outcome Measures

The following outcome measures will be also be evaluated:

1. All-cause and cardiovascular mortality annually through 5 years
2. All stroke (disabling and non-disabling) annually through 5 years
3. Cardiovascular and heart failure hospitalizations annually through 5 years
4. Heart failure events annually through 5 years
5. New York Heart Association (NYHA) functional classification at 30 days, 6 months, and annually through 5 years
6. Change in New York Heart Association (NYHA) functional classification from baseline annually through 5 years
7. Kansas City Cardiomyopathy (KCCQ) annually through 5 years
8. Hemodynamic performance metrics by Doppler echocardiography
    - Mean aortic gradient annually through 5 years
    - Effective orifice area annually through 5 years
    - Degree of total, para, and transvalvular prosthetic regurgitation annually through 5 years
    - Incidence of moderate and severe patient-prosthesis mismatch (PPM) annually through 5 years
9. Prosthetic valve thrombosis 30 days, 6 months, and annually through 5 years
10. Prosthetic valve endocarditis at 30 days, 6 months, and annually through 5 years
11. Bioprosthetic valve dysfunction (BVD) at 30 days, 6 months, and annually through 5 years
12. Bioprosthetic valve failure (BVF) at 30 days, 6 months, and annually through 5 years
13. Valve-related dysfunction requiring repeat procedure annually through 5 years

<u>Additional Outcomes Measures 1-10 and 13:</u>

Analysis for additional outcome measures 1-8 and 13 will follow the analysis methods defined for the same safety and efficacy endpoints at earlier timepoints described in Section 7.9.1 and 7.9.2, respectively. Prosthetic valve thrombosis and prosthetic valve endocarditis, additional outcome measures 9 and 10, will be analyzed with Kaplan-Meier analysis as described in Section 7.2. The analysis

of additional outcome measures 9 and 10 will be based on CEC adjudications using the Attempted Implant set.

Additional Outcome Measure 11 - Bioprosthetic valve dysfunction (BVD)[1] at 30 days, 6 months, 1 year:

Bioprosthetic valve dysfunction (BVD) is defined as meeting any of the following:

- Moderate or severe stenosis defined as any of the following:
  - Peak aortic velocity > 4 m/s OR mean aortic gradient > 40 mmHg, AND EOA < 0.8 cm^2
  - Peak aortic velocity > 4 m/s OR mean aortic gradient > 40 mmHg, AND EOA ≥ 0.8 cm^2, AND DVI < 0.25
  - Peak aortic velocity ≤ 4 m/s and mean aortic gradient ≤ 40 mmHg, AND EOA < 0.8 cm^2, AND DVI < 0.25

    Note: In the above, for subjects with BSA < 1.6 m^2, the EOA criteria for significant (moderate or severe) stenosis is < 0.6 cm^2. Additionally, for subjects with LVOT diameter > 2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is < 0.2.
- Moderate or severe paravalvular regurgitation
- Moderate or severe transvalvular regurgitation
- Moderate or severe total regurgitation

Analysis of BVD will be based on data collected on the core lab CRF. The numerator for each time point will include the number of subjects meeting any of the components of BVD. The denominator will include any subject with BVD and subjects with no evidence of BVD having evaluable data for all 4 components. BVD will be summarized with frequency counts and percentages. The components of BVD will also be summarized. The analysis will be performed using the Implanted set.

Additional Outcome Measure 12 - Bioprosthetic valve failure (BVF)[2] at 30 days, 6 months, 1 year

Bioprosthetic valve failure (BVF) is defined as meeting any of the following:

- Autopsy findings of bioprosthetic valve dysfunction, likely related to the cause of death, or valve-related death (i.e. any death caused by bioprosthetic valve dysfunction or sudden unexplained death following diagnosis of bioprosthetic valve dysfunction)
- Repeat intervention (i.e. valve-in-valve TAVI, paravalvular leak closure or SAVR following confirmed diagnosis of bioprosthetic valve dysfunction)
- Severe bioprosthetic valve dysfunction

A Kaplan-Meier analysis as described in Section 7.2 will be performed for BVF at 30 days, 6 months, and annually through 5 years. The analysis will use the Implanted set.

7.9.4 Subgroup Analysis

Subgroup analysis will be performed for the key study endpoints for exploratory purposes in the following subgroups:

1. Baseline Peak GLS ≥ median value and < median value
2. Baseline NT-proBNP ≥ median value and < median value

As the study is intended to inform the design for a future pre-market study, subgroup analyses need not be limited to those defined above and additional subgroup analyses may be performed to better understand the safety and efficacy results in these two groups of AS patients.

7.10 Safety Evaluation

Adverse events will be summarized by MedDRA System Organ Class (SOC) and High-level Term (HLT) at 30 days, 6 months, 1 year, and annually through 5 years. The number of events, number of subjects with event, and the Kaplan-Meier event rate (cumulative incidence) will be reported for each category and time point. Device related, procedure-related, and Serious Adverse Events (SAEs) will be reported similarly. A listing of adverse events will also be reported and will at minimum include the adverse event category, severity, treatment received, resolution, and investigator assessment of relationship to the device and procedure.

Additionally, listings of subject deaths, all device deficiencies, and device deficiencies which could have led to a serious adverse device effect will be reported.

7.11 Changes to Planned Analysis

This analysis plan is consistent with the CIP for which the plan was developed. Any deviations from the planned analysis in the CIP will be documented in an amended statistical analysis plan, when possible, and/or will be described with justification and rationale in the study report.

8. Validation Requirements

Level 1 validation (independent validation) will be used for the analysis datasets and for all safety and efficacy endpoints. Level 2 validation (peer review), at minimum, will be used for additional analyses, data summaries, and listings.

9. References

1. Kappetein AP, Head S,Généreux P, Piazza N, van Mieghem N, Blackstone E, Brott T, Cohen D, Cutlip D, van Es, G, Hahn R, Kirtane A, Krucoff M, Kodali S, Mack M, Mehran R, Rodes-Cabau J, Vranckx P, Webb J, Windecker S, Serruys P, Leon M. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438-54.
2. Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. (2017) 38:3382–90. doi: 10.1093/eurheartj/ehx303.