Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	Evaluation of the Valiant Mona LSA Thoracic Stent Graft System in Descending Thoracic Aortic Aneurysms and Chronic Dissections
Clinical Investigation Plan Identifier	10151194DOC
Clinical Investigation Plan Version	1F, 22 January 2019
Sponsor/Local Sponsor	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA 95403
Document Version	Version 6.0 02-SEP-2021

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted]
2.0	Add additional analysis details per study protocol Amendment from v1A to v1C, no SAP update was created from v1A to v1B.	[redacted]
3.0	Updates per protocol amendment from v1C to v1D. Remove duplication "Duration of follow-up" section. Update endoleak reporting rules. Added additional details to analysis of "Exclusion of Thoracic Lesions" for clarity. Minor formatting updates throughout.	[redacted]
4.0	Updates per protocol amendment from v1D to v1E. Updated list of abbreviations. Corrected typographical errors identified in document.	[redacted]
5.0	Updates per protocol amendment from v1E to v1F. Corrected typographical error in table 3; the lower limit of 1 year analysis time point for safety events should be aligned with lower limit of scheduled follow-up window consistent with the other analysis time points.	[redacted]
6.0	Minor format changes for new SAP template. Update image analysis reporting details to use worst-case principle according to Medtronic work instruction: Aortic Study Reporting Conventions v2.0.pdf.	[redacted]

2. List of Abbreviations and Definitions of Terms

Acronym/Abbreviation	Definition/Term
ADE	Adverse Device Effect
AE	Adverse Event
BSG	Branch Stent Graft
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Forms
CRO	Contract Research Organization
CT	Computed Tomography
CTBD	Chronic Type B Dissection
DTA	Descending thoracic aorta
EC	Ethic Committee
E-CRF	Electronic Case report Forms
FUP	Follow-Up
ICH - GCP	International Conference on Harmonization – Good Clinical Practice
IFU	Instructions for Use
ITT	Intent-to-treat
LCC	Left common carotid
LSA	Left subclavian artery
LTFU	Lost-To-Follow-Up
MAE	Major Adverse Event
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MSG	Main Stent Graft
PAU	Penetrating Aortic Ulcer
PMR	Post Market Release
QA	Quality Assurance
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
TAA	Thoracic Aortic Aneurysm
TEVAR	Thoracic Endovascular Aortic Repair

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Evaluation of the Valiant Mona LSA Thoracic Stent Graft System in Descending Thoracic Aortic Aneurysms and Chronic Dissections (short title: Evaluation of Valiant Mona LSA) study. This

document is designed for internal use as a guideline for the study Biostatistician and Statistical Programmer(s). This study was formerly titled the Valiant Mona LSA Thoracic Stent Graft System Feasibility Study, yet remains a feasibility study.

The purpose of this plan is to characterize the Valiant Mona LSA Thoracic Stent Graft System, in particular to assess the safety and effectiveness of the device acutely and at the 30 day visit in the identified subject population, as well as to report the long term effectiveness and safety observations of the device in enrolled subjects as specified in the study protocol.

As with any statistical analysis plan, the proposed methods and approaches to the data analysis should be viewed as flexible. Changes to the plan may arise if the emerging picture suggests that deviations from the original plan would provide a more reliable and valid analysis of the data. The purpose of this plan is to provide general, and in some instances, specific guidelines from which the analysis will proceed. Nonetheless, sound statistical reasoning must substantiate deviations from these guidelines.

4. Study Objectives

4.1. Study Purpose

The purpose of the clinical investigation is to assess the feasibility of the Valiant Mona LSA Thoracic Stent Graft System to repair fusiform/saccular aneurysms, penetrating ulcers, and chronic type B dissections of the DTA in patients who require coverage of the LSA, including an assessment of the safety and effectiveness of the device acutely and at the 30 day visit in the identified subject population. Procedural information will be collected in order to enhance the current instructions for use and delivery and deployment steps.

The chronic Type B Dissection expansion subjects will be prospectively enrolled in support of a future premarket approval analysis for the Valiant Mona LSA device.

Patients diagnosed with an aneurysmal descending thoracic aorta, penetrating ulcer, or chronic type B dissection who meet the eligibility criteria for the study may be enrolled (see Eligibility Criteria). Additionally, these patients must be candidates for revascularization of the LSA and anatomically appropriate for the device.

4.2. Scope and Duration of the Clinical Study

Study enrollment started in the United States in 2015. Up to ten (10) investigational sites may participate. The enrollment period is estimated to be 20 months. To ensure adequate disease state representation for analysis, a minimum of approximately 25% of the subjects will be enrolled for the treatment of aneurysms or penetrating ulcers and a minimum of approximately 25% of the subjects will be enrolled for the treatment of chronic Type B dissections.

Data from the presently treated subjects (planned up to 44) who undergo treatment with the Valiant Mona LSA Thoracic Stent Graft System in this study will be analyzed and summarized in Annual Progress Reports (APR) for FDA. Data collected in this study may be further used to submit original marketing applications for approval to commercially distribute the device system.

To permit collection of long-term safety and effectiveness data on the stent graft system, subjects will be followed for a total of 5 years under this same clinical protocol. After the scheduled 12-month study visit, patients will continue to be evaluated on an annual basis for up to 5 years post implantation. When all enrolled subjects have been followed for 5 years post index procedure, or have exited, the study will be closed.

4.3. Description of Study Observations

Study observations will also be treated and described as study endpoints in this document.

4.3.1. Primary Safety Observation

The following clinical outcomes will be collected for reporting. The initial reporting period will be all occurrences within 1 month (Day 0 – Day 30) from the index procedure. The outcome data will consist of:

- Aorta-Related Mortality
- Stroke
- Paraplegia
- Left Arm/Hand Ischemia

4.3.2. Primary Effectiveness Observation

The primary effectiveness observation is treatment success (defined below) and will be captured within the initial reporting period of 1 month from the index procedure.

Treatment success is defined as:

Technical success, which is the successful delivery and deployment of the stent graft (deployment of the Valiant Mona LSA Thoracic Stent Graft System in the planned location with no unintentional coverage of other vessels, assessed intra-operatively, and the removal of the delivery system) and successful exclusion of the aneurysm/penetrating ulcer or primary entry tear while maintaining patency of the MSG and BSG at 30 day visit.

4.3.3. Additional Observations

The following additional observations will be evaluated through the 30 day visit and at each follow up visit.

- Major adverse events (MAEs) rates within 30 days of the initial or secondary procedures, including:

  - All-Cause Mortality
  - Myocardial Infarction
  - Paraplegia
  - Renal Failure
  - Stroke
  - Left Arm/Hand Ischemia
- Secondary endovascular procedures
- Secondary endovascular procedures for primary device failures (including Type I/III endoleaks, aneurysm expansion, aneurysm/aortic rupture, and BSG occlusion)
- Rupture
- Endoleaks
- Maximum aneurysm diameter change from baseline*
- Exclusion of aneurysm
- Exclusion of penetrating aortic ulcer (PAU)
- Stent graft patency
- Stent graft integrity
- Conversion to surgery
- Surgical revascularization of the LSA
- Paraparesis
- Adverse events including serious adverse events and device, procedure, and/or disease-related Adverse Events
- For CTBD, these additional observations will be evaluated:
  - Coverage of primary entry tear (exclusion of false lumen)
  - Extension of dissection (proximally or distally) with or without complications
  - Continuing or new false lumen (FL) perfusion
    - Primary intimal tear false lumen perfusion (PIT FLP)
    - Proximal aorta false lumen perfusion (PA FLP)
    - Distal aorta false lumen perfusion (DA FLP)
    - Proximal branch false lumen perfusion (PB FLP)
    - Distal branch false lumen perfusion (DB FLP)
  - Aortic remodeling post-procedure as measured by:
    - Change from baseline* in the maximum true lumen (TL) diameter over the length of the stent graft
    - Change from baseline* in the maximum false lumen (FL) diameter over the length of the stent graft
    - Change from baseline* in the maximum total descending thoracic aortic diameter
    - FL thrombosis over the length of the stent graft

* The discharge computerized tomography angiogram (CTA) will be used as baseline to assess aortic changes. If a discharge CTA is not performed then, the one month follow-up CTA will be used for baseline purposes.

4.3.4. Periprocedural and Discharge Clinical Utility Measures

The following periprocedural through discharge clinical utility measures will be summarized using descriptive statistics.

1. Mean duration (min) of procedure.
2. Mean time (min) to implant the LSA Branch device.
3. Proportion of subjects who underwent general anesthesia.
4. Mean volume (cc) of estimated blood loss.
5. Proportion of subjects requiring blood transfusions.
6. Mean time (hours) in intensive care unit.
7. Mean time (days) of overall hospital stay (from hospital admission to discharge).

5. Investigation Plan

This study is a prospective, single-arm, non-randomized, multicenter, pre-market clinical study evaluating subjects implanted with the Valiant Mona LSA Thoracic Stent Graft System for the treatment of aneurysms, type B chronic dissections, and penetrating ulcers of the descending thoracic aorta who are candidates for revascularization of the left subclavian artery. All analyses will be descriptive in nature and no statistical comparisons are planned. This study is not a hypothesis driven study; no hypotheses testing will be carried out.

6. Determination of Sample Size

There is no sample size calculation since this study is not a hypothesis driven study; however, the number of enrolled subjects is pre-specified. This study will enroll up to 44 subjects.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

7.1.1.1. Eligibility Criteria

The study population will include those patients diagnosed with an aneurysmal thoracic aorta, penetrating ulcer, or chronic type B dissection who are candidates for revascularization of the left subclavian artery (LSA) and who meet the inclusion and exclusion criteria. Data will be recorded on the Inclusion and Exclusion Criteria Form.

Following review of the preliminary safety data of the first 18 enrolled patients, 5 additional subjects with TAA or PAU will be enrolled to further evaluate the device's safety.

The safety data for these 5 subjects will be reviewed by the investigator(s) in coordination with MDT and the DSMB to determine whether to start enrollment of the CTBD arm.

Inclusion Criteria for Thoracic Aortic Aneurysms and Penetrating Ulcers

- Subject is at least 18 years of age.
- Subject understands and has signed an Informed Consent approved by the Sponsor and by the IRB for this study.
- Subject must be considered a candidate for revascularization of the Left Subclavian Artery. Subject must be able to tolerate a surgical revascularization of the LSA.
- Subject has a TAA/PAU which will require coverage of the LSA and is:
    - a fusiform aneurysm with a diameter of ≥ 5.5 cm OR is > 2 times the diameter of the non-aneurysmal thoracic aorta;

    AND/OR

    - a saccular aneurysm or penetrating atherosclerotic ulcer (ulcer defined as ≥ 10 mm in depth and 20 mm in diameter, or symptomatic);
- Subject has a healthy, non-diseased aortic proximal seal zone of at least 20 mm from the distal end of the LCC ostium to the beginning of the disease including at least 10 mm between the LSA and the LCC.
- Subject has a non-diseased aortic proximal neck length of >0 mm distal to the LSA.
- Subject has a non-diseased aortic diameter between 25 mm and 42 mm.
- Subject has a non-diseased LSA with a diameter between 8 mm and 13 mm.
- Subject has sufficient landing zone within the LSA to accommodate the BSG without occlusion of any significant vessels.
- Brachial, iliac or femoral artery access vessel morphology (diameter, calcification, tortuosity) that is compatible with vascular access techniques, the device, or accessories.
    - Introducer sheath is required for all procedures
    - An iliac conduit is required for access if the above requirements are not met

Exclusion Criteria for Thoracic Aortic Aneurysms and Penetrating Ulcers

- Subjects will be excluded if they have conditions requiring prospective revascularization of the LSA including:

  - Dominant left vertebral artery requiring revascularization
  - Prior coronary artery bypass graft utilizing the left mammary artery requiring revascularization
  - Incomplete circle of Willis or other neurological vasculature requiring revascularization
- Subject has an aneurysmal, tortuous, or atherosclerotic LSA.
- Subject has an acute dissection of the descending thoracic aorta.
- Subject has an intramural hematoma of the descending thoracic aorta.
- Subject has prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites.
- Subject has circumferential calcification in the external iliac artery or in the common iliac artery with an intraluminal diameter (ID) less than 10mm at any point proximal to or at the access vessel site unless a surgical adjunctive procedure is planned.
- Subject requiring an aortic conduit or direct aortic access.
- Subject has an aortic atheroma classified as grade IV or grade V.
- Subject has had previous endovascular repair of the ascending and/or descending thoracic aorta <30 days of implantation of investigational device or previous repair was a non-Medtronic device.
- Treatment with the Valiant Mona LSA Thoracic Stent Graft system would require intentional coverage of the left common carotid artery with the stent graft fabric.
- Subject has significant and/or circumferential aortic mural thrombus at either the proximal or distal attachment sites that would compromise fixation and seal of the device.
- Subject is a pregnant female.
- Subject has a known allergy or intolerance to the device components.
- Subject is in acute renal failure or has renal insufficiency with a serum creatinine ≥ 2.0 mg/dL or is on dialysis.
- Subject has a body habitus which prevents adequate visualization of the aorta.
- Subject has coronary artery disease with unstable angina and who has not received treatment.
- Subject has a connective tissue disease (e.g. Marfan's syndrome, medial degeneration).
- Subject has active systemic infection and/or a mycotic aneurysm.
- Subject is currently participating in an investigational drug or device clinical trial that would interfere with the observations of this study.

- Subject has other medical, social, or psychological problems that, in the opinion of the investigator, will interfere with treatment and follow-up procedures.
- Subject has a life expectancy of less than 1 year.
- Subject requires treatment of an infrarenal aneurysm at the time of the implantation.
- Subject had previous surgical or endovascular treatment of an infra-renal aortic aneurysm < 30 days of implantation of investigational device.
- Subject has a history of bleeding diathesis, coagulopathy, or refuses blood transfusion.
- Subject has had a cerebral vascular accident (CVA) within 3 months prior to the procedure.
- Subject has had a myocardial infarction (MI) within 3 months prior to the procedure.
- Subject has a known hypersensitivity or contraindication to anticoagulants or contrast media, which is not amenable to pre-treatment.

Inclusion Criteria for Chronic Type B Dissections

- Subject is at least 18 years of age.
- Subject understands and has signed an Informed Consent approved by the Sponsor and by the IRB for this study.
- Subject must be considered a candidate for revascularization of the Left Subclavian Artery (LSA). Subject must be able to tolerate a surgical revascularization of the LSA.
- Subject has a chronic type B dissection which will require coverage of the LSA. A chronic type B dissection is defined as > 30 days from symptom onset and is complicated with an aortic diameter ≥ 5.5 cm or has progressive aortic enlargement (> 5 mm/year).
- Subject has a healthy, non-diseased aortic proximal seal zone of at least 20 mm from the distal end of the LCC ostium to the beginning of the disease, including at least 10 mm between the LSA and the LCC.
- Subject has a non-diseased aortic diameter between 28 mm to 44 mm.
- Subject has a non-diseased LSA with a diameter between 8 mm and 13 mm.
- Subject has sufficient landing zone within the LSA to accommodate the BSG without occlusion of any significant vessels.
- Brachial, iliac or femoral artery access vessel morphology (diameter, calcium, tortuosity) that is compatible with vascular access techniques, the device, or accessories.
    - Introducer sheath is required for all procedures
    - An iliac conduit is required for access if these requirements are not met

Exclusion Criteria for Chronic Type B Dissections

- Subjects will be excluded if they have conditions requiring prospective revascularization of the LSA including:
    - Dominant left vertebral artery requiring revascularization

  - Prior coronary artery bypass graft utilizing the left mammary artery requiring revascularization
  - Incomplete circle of Willis or other neurological vasculature requiring revascularization
- Subject has an aneurysmal, tortuous, or atherosclerotic LSA.
- Subject has an acute dissection of the descending thoracic aorta.
- Subject has an intramural hematoma of the descending thoracic aorta.
- Subject has prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites.
- Subject has circumferential calcification in the external iliac artery or in the common iliac artery with an intraluminal diameter (ID) less than 10mm at any point proximal to or at the access vessel site unless a surgical adjunctive procedure is planned.
- Subject requiring an aortic conduit or direct aortic access.
- Subject has an aortic atheroma classified as grade IV or grade V.
- Subject had previous endovascular repair of the ascending and/or descending thoracic aorta.
- Treatment with the Valiant Mona LSA Thoracic Stent Graft system would require intentional coverage of the left common carotid artery with the stent graft fabric.
- Subject has significant and/or circumferential aortic mural thrombus at either the proximal or distal attachment sites that would compromise fixation and seal of the device.
- Subject is a pregnant female.
- Subject has a known allergy or intolerance to the device components.
- Subject is in acute renal failure or has renal insufficiency with a serum creatinine ≥ 2.0 mg/dL or is on dialysis.
- Subject has a body habitus which prevents adequate visualization of the aorta.
- Subject has coronary artery disease with unstable angina and who has not received treatment.
- Subject has a connective tissue disease (e.g. Marfan's syndrome, medial degeneration).
- Subject has active systemic infection and/or a mycotic aneurysm.
- Subject is currently participating in an investigational drug or device clinical trial that would interfere with the observations of this study.
- Subject has other medical, social, or psychological problems that, in the opinion of the investigator, will interfere with treatment and follow-up procedures.
- Subject has a life expectancy of less than 1 year.
- Subject requires treatment of an infrarenal aneurysm at the time of the implantation.
- Subject had previous surgical or endovascular treatment of an infra-renal aortic aneurysm.
- Subject has a history of bleeding diathesis, coagulopathy, or refuses blood transfusion.
- Subject had a cerebral vascular accident (CVA) within 3 months prior to the procedure.

- Subject had a myocardial infarction (MI) within 3 months prior to the procedure.
- Subject has a known hypersensitivity or contraindication to anticoagulants or contrast media, which is not amenable to pre-treatment.

7.1.1.2. Study Disposition

The number of subjects who are enrolled, who have a clinical follow-up visit and who have imaging during the follow-up visit will be summarized. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

Subject and Imaging accountability will be summarized in the following tabulated format up to 5-years (the example only provided up to 12-month):

	Subject Follow-Up % (m/n)[1]			Subject with Imaging (at each time interval) % (m/n)[1]			Subjects with Adequate Imaging to Assess the Parameter % (m/n)[1]		Subject Events Occurring Before Next Visit[2] n					
Implant and Follow-Up	Eligible[2]	Clinical Follow-Up	Imaging Follow-Up	CT/MR Imaging	Chest X-Ray	Additional Imaging Modalities	Max Aneurysm Diameter	Endoleak	Enrolled but not Implanted	Conversion to Surgery	Death	Withdrawal	Lost to Follow-Up	Not Due for Next Visit
Implant	9													
Events Between Implant and 1-Month									0	0	0	0	0	0
1-Month	9	100.0% (9/9)	100.0% (9/9)	88.9% (8/9)	77.8% (7/9)	0.0% (0/9)	88.9% (8/9)	88.9% (8/9)						
Events Between 1-Month and 6-Months										0	0	0	0	2
6-Months	7	100.0% (7/7)	100.0% (7/7)	100.0% (7/7)	100.0% (7/7)	100.0% (7/7)	100.0% (7/7)	100.0% (7/7)						
Events Between 6-Months and 12-Months										0	0	0	0	5
12-Months	2	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)						
Total									0	0	0	0	0	
Deaths Post Conversion to Surgery											0			
Total Deaths											0			

7.1.2. Clinical Investigation Plan (CIP) Deviations

All enrolled subjects will be analyzed and reported based on evaluable data. Major and minor protocol deviations will be tabulated.

7.1.3. Analysis Set

All safety and effectiveness analyses will be performed on all enrolled subjects, according to the intention-to-treat (ITT) principle. The subject will be considered enrolled after arterial access is achieved and the Valiant Mona LSA Thoracic Stent Graft System has been introduced into the vasculature.

7.2. General Methodology

Data collected from the clinical study will be analyzed as specified in the following sub-sections. Subject data listings, tabular, and graphical representations will be provided. In general, for categorical variables, frequency and percentage will be presented as descriptive statistics. For continuous variables, number of observations, mean, standard deviation, median, minimum, and maximum will be reported.

All key study endpoints will be presented with the point estimate and the corresponding 2-sided 95% confidence interval. Confidence intervals will be included in the final clinical study report, but may not be included in other reports, such as annual progress reports.

7.2.1. Study Day

Assessments will be presented chronologically by study day, which is defined in the following:

Study day = assessment day – date of index-procedure.

Study day will be calculated from the date of index procedure, i.e. Day 0. Day 1 is the day immediately after the initial implantation. Study day of an event which occurs prior to Day 0 will be presented as a negative number, if any.

Events occurring on the day of discharge will be considered in-hospital.

7.2.2. Duration of Follow-up

If a subject is not expired, then duration of follow-up will be calculated from the last date of follow-up visit or the final assessment as indicated on the Study Exit CRF, whichever is later. If a subject is expired, then the duration of follow-up will be calculated using the date of death. If a subject withdraws from the study, the duration of follow-up will be calculated using the date of withdrawal. Data except death, if any, reported after the date of withdrawal will be excluded from reporting.

7.2.3. Time Window of an Event or Assessment

For events that can occur or are observed at any time during the study, such as an adverse event or death, no time window will be applied. For other events, an event that occurs “within 1 month” is an event that takes place between Days 0 to 30, inclusive. Similarly, an event that occurs “within 1 year” is an event occurring between Day 0 to Day 365, inclusive.

For visit-related or imaging based assessments, such as a CT scan, MRI, X-Rays, the analysis windows presented in Table 1 will be applied for by-visit data summaries:

Table 1. Time Window for Imaging Observations Analysis

Study Visit	Target Day	Scheduled Follow-Up Window	Analysis Window for Imaging Observations
Implant	0	Day 0	0
Discharge	n/a	n/a	1-14 Days
1 Month	30	15-45 Days	15-122 Days
6 Months	183	153-239 Days	123-270 Days
12 Months	365	335-421 Days	271-480 Days
24 Months	730	674-842 Days	481-913 Days
36 Months	1095	1039-1207 Days	914-1278 Days
48 Months	1460	1404-1572 Days	1279-1644 Days
60 Months	1825	1769-1937 Days	1645-2008 Days

Imaging based analyses will follow a "worst case" principle where any 'positive' finding of an undesirable outcome (e.g., fracture) or the worst measure (e.g., aneurysm diameter) in the analysis window will be used. If there are 2 or more assessments of the same subject for the same type of event within the same time window, then the following rules are applied:

1. If there are 2 or more positive findings on evaluable images for the same type of event for the same subject in the window, the earliest image showing a positive finding will be used to determine that the subject had an event in the window and this subject is only counted once for this type of event in this window.

2. If there is no positive finding for the event, the latest evaluable image showing no event will be used for analysis.

This process should be followed for each outcome, such that different images may be used for reporting on each outcome unless otherwise specified.

Table 2 shows which imaging outcomes are visible (marked with an "X") or invisible (not marked with an "X") using various imaging types. Evaluable images are images marked as "X" in the imaging matrix (Table 2) and a having response to "Was there evidence of <imaging outcome>?" of "Yes" or "No".

Images defined as 'Invisible' in the imaging matrix or any imaging assessment where the response to "Was there evidence of <imaging outcome>?" is "Not Applicable", "Not Evaluable", or blank/missing are not considered evaluable for imaging outcome analysis and are excluded.

Table 2. Imaging Matrix

Imaging Type	Migration	Endoleak	Device Integrity	Aneurysm Size Assessment	BSG/LSA Patency	MSG Patency
CTA or MR with Contrast	X	X	X	X	X	X
CTA or MR without Contrast	X		X	X	X	X
Chest Radiograph	X		X			
Doppler US					X	

7.2.4. Reporting Precisions

When applicable, P-values will be presented in the bio-statistical tables similar to what is displayed in the supporting statistical software analysis output (round to 3 decimal places for SAS output), if p-value >0.999, display as >0.999; if p-value < 0.001, then display as <0.001.

Percentages will be reported with exactly one decimal place, unless otherwise specified (e.g., in the Table, Listing, and Graphs Shell Specifications). Further discussions may be needed to determine the sensible display format if the percentage is less than 0.1% (e.g. if one decimal place rule is used for 0.04%, it will be displayed as 0.0% which is misleading); however, unless otherwise specified, two decimal places will be used.

For summary statistics, unless otherwise specified (e.g., in the Table, Listing, and Graphs Shell Specifications), means and medians will be displayed to one more decimal place than was determined above, dispersion statistics will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as the original data point defined in the Data Definition Table (DDT).

7.3. Center Pooling

No poolability analysis is planned for this study.

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

In general, imputation of missing data will not be performed for all analyses. However, in cases where the date of adverse event onset is incomplete, the 15th day of the known month or July 1st of the known year will be used unless that results in a date earlier than the date of index procedure, in which case the date of index procedure will be used. For study endpoints, missing data will be listed with subject numbers for review. The imputed AE onset date cannot be later than last known date in the study. For instances where the AE onset date is imputed after the last known date in the study, the last known date in the study will be used for the AE onset date.

7.5. Adjustments for Multiple Comparisons

Statistical hypothesis testing will not be performed for this study, therefore, no adjustments for multiple comparisons will be performed.

7.6. Demographic and Other Baseline Characteristics

All clinically relevant baseline variables will be summarized and tabulated. Descriptive statistics will be presented as follows:

- Categorical variables, including binary variables, will be reported by giving the number and percentage of patients in each category.
- Continuous variables will be reported by presenting the number of observations, mean, standard deviation, median, minimum, and maximum of each variable.

For all chosen baseline variables, patients whose assessment cannot be determined will be omitted from the respective analysis.

7.7. Treatment Characteristics

Descriptive statistics (frequency and percentage for categorical variables and number of observations; mean, standard deviation, median, minimum and maximum for continuous variables) will be displayed for the periprocedural through discharge clinical utility measures.

7.8. Interim Analyses

No interim analysis, intended to alter the study sample size, are planned for this study.

7.9. Evaluation of Objectives

7.9.1. Primary Safety Observation

The primary safety observation of this study is a composite endpoint that consists of 1) Aneurysm Related Mortality, 2) Stroke, 3) Paraplegia, and 4) Left Arm/Hand Ischemia within 1 month (0-30 days) of index procedure. Descriptive statistics (frequency and percentage) will be calculated for the primary

safety endpoint and its component events. A two-sided 95% confidence interval for the primary safety endpoint and its component will also be calculated using the exact binomial method.

7.9.2. Primary Effectiveness Observation

The primary effectiveness observation is Treatment Success that is defined as successful delivery and deployment of the stent graft (deployment of the Valiant Mona LSA Thoracic Stent Graft System in the planned location with no unintentional coverage of other vessels, assessed intra-operatively, and the removal of the delivery system) and successful exclusion of the aneurysm while maintaining patency of the MSG and BSG at the 30 day visit. Descriptive statistics (frequency and percentage) will be calculated for the primary effectiveness endpoint. A two-sided 95% confidence interval will also be calculated using the exact binomial method.

7.9.3. Additional Observations

7.9.3.1. Major Adverse Events and Major Clinical Events

The following observations will be assessed through clinical follow-up (office visit or phone contact):

- Major adverse events (MAEs) rates within 30 days of the initial or secondary procedures, including:
  - All-Cause Mortality
  - Myocardial Infarction
  - Paraplegia
  - Renal Failure
  - Stroke
  - Left Arm/Hand Ischemia
- Secondary endovascular procedures
- Rupture
- Conversion to surgery
- Surgical revascularization of the LSA
- Paraparesis

The rate of the above events will be calculated on the subject level, and for different reporting time points, the correspondent cutoff days will be used as shown in **Table 3**.

For each visit (or reporting time point), the event rate will be calculated as the proportion of the number of subjects with a certain event term over the number of evaluable subjects. The evaluable subjects at each reporting time point include all subjects who are enrolled by the snapshot date and

1) Had a clinical or safety event (e.g. MAE) within (on or before) the Reporting cutoff Days, or
2) Had a follow-up or days to last contact at or after the lower limit of the Reporting Window, or

3) The Withdrawal Consent Date /Recorded Lost-to-Follow-up Date at or after the lower limit of the Reporting Window

'Days to MAE' (date of earliest MAE – date of index procedure) and 'Days to Last Contact' (date of last contact – date of index procedure) are usually used for the determination of the eligibility of the 'evaluable subject'. *The last contact date will be calculated based on the information gathered from all available dates during the follow-ups.*

Similarly, 'Days to any AEs' and 'evaluability' of any AEs will be determined with the same principle as described above.

1. For death, Use the date of death from the CEC form, if it is not available then use Date of Death from study exit form.

2. For withdrew ("Subject withdrew consent to participate in the study" or " Physician's decision to protect the welfare of the subject") or "Subject enrolled but not implanted, completed 1 month follow-up", use Date of Exit from study exit form.

3. For patients who exited study for LTF, complete FU, or other reason, use last known date in the study from:

1) Adverse Event Form

(i) Date event started

(ii) Date of resolution

2) Secondary Procedure Form: Date of secondary procedure

3) Conversion to Open Repair Form: Date of Open Repair procedure

4) Clinical follow-up Form (including unscheduled)

(i) Date physical exam performed

(ii) Date of Labs:

5) Imaging follow-up Form: Date of diagnostic imaging (including unscheduled imaging)

6) For patients who exited study with no follow-up, use last known date in the study from:

(i) Procedure Form: Date of procedure

(ii) Discharge Form: Date of discharge

7) For Patients who did not exit study - Use last known date as above.

The 'Reporting Cutoff Days', 'Lower limit of the Reporting Window' and the correspondent visits are listed in Table 3:

Table 3. Reporting Window for MAE and Major Clinical Events

Visit	Reporting Cutoff Days	Lower Limit of the Reporting Window
1-month	30 days post-index procedure	Days to last contact: 15 days post-index procedure
6-month	183 days post-index procedure	Days to last contact: 153 days post-index procedure
12-month	365 days post-index procedure	Days to last contact: 335 days post-index procedure
24-month	730 days post-index procedure	Days to last contact: 674 days post-index procedure
36-month	1095 days post-index procedure	Days to last contact: 1039 days post-index procedure
48-month	1460 days post-index procedure	Days to last contact: 1404 days post-index procedure
60-month	1825 days post-index procedure	Days to last contact: 1769 days post-index procedure

In addition to the point estimate of the rate for each event at each time point, a two-sided 95% Confidence Interval will also be calculated for each correspondent point estimate using the exact binomial method.

7.9.3.2. Aneurysm Diameter Changes

Aneurysm Diameter change will be calculated based on the maximum measurable aneurysm diameter during the post-operative follow-up and each annual follow-up. Reference diameter is the diameter measured at first post-operative follow-up through 1 month. Change of aneurysm diameter will be defined as 1) "increased" if an aneurysm growth is strictly greater than 5 mm of the maximum measurable aneurysm diameter; 2) "decreased" when an aneurysm becomes strictly smaller in size by more than 5 mm; 3) "no change" when the change is within 5 mm.

Aneurysm diameter change rates will be calculated separately for increase, decrease and no change based on the number of subjects who had the event divided by number of implanted subjects who are evaluated for aneurysm diameter change at the time point. The analysis time window will be used to determine if an image assessment belongs to a respective time point. The analysis time window for each time point is given in Section 7.2.3.

7.9.3.3. Exclusion of Thoracic Lesions

Rate of exclusion of thoracic lesions will be reported for 1-month, 6-month and each annual follow-up. The endpoints may be analyzed using site-reported imaging assessments or core lab reported imaging assessments, separately.

- **Exclusion of Aneurysm**

Exclusion of Aneurysm is defined as the absence of a type I or III endoleak associated with the absence of growth of > 5 mm of the maximum measurable aneurysm diameter; reference diameter is the diameter measured at first post-operative imaging exam.

Rate of Exclusion of Aneurysm will be calculated for each scheduled follow-up and the calculation will be based on the number of subjects who had the event divided by number of implanted subjects that are evaluated for that event at the time point. Imaging endpoint analysis time windows will be used to determine if an image assessment belongs to a respective time point. The reporting details can be found in Section 7.2.3 (Table 1).

The endpoint will be derived as follows:

- Subjects having a Type I or III endoleak or having aneurysm growth > 5mm will be considered as failures of the endpoint [defined as k].
- Otherwise subjects without a failure event and having evaluable imaging for both endoleak and aneurysm growth will be considered as a success (i.e. Exclusion of the aneurysm) [defind as m].
- Subjects without a type I or III endoleak and without aneurysm growth > 5mm, but missing one or both imaging assessments will be excluded from the analysis.

The rate will be calculated as m/(m+k), where the numerator will consist of all subjects having success for exclusion of the aneurysm [m]. The denominator will consist of all subjects having exclusion [m] or subjects having a failure event [k].

The endoleak component will be derived according to Section 7.9.3.5.

The aneurysm growth component is based on the calculated difference between the assessments at follow-up minus the first post-operative assessment. Subjects must have the maximum aneurysm diameter reported at both the post-operative assessment and the follow-up assessment. If the subject is missing either the post-operative and/or follow-up assessment, the subject is considered to have missing data for this component. The post-operative image can be either at 1 month follow-up or discharge. At each follow-up the largest aneurysm diameter will be used in the calculation of aneurysm diameter change from baseline.

Scenarios for each possible combination of the component outcomes and the final endpoint assessment of success vs. failure are presented in Table 4. Since the exclusion of aneurysm is an assessment of success with two component events, if both component events are 'success' then the final composite endpoint will be 'success' (scenario 1); if at least one component event is 'failure' then the final composite endpoint is 'failure' (scenario 2,3,4,5 8); if one component event is success, but the other component event is missing due to unevaluable data, the final composite endpoint will be missing

(scenario 6,7); finally, if both components are missing then composite endpoint will be missing (scenario 9):

Table 4. Exclusion of Thoracic Lesion Scenarios

Scenarios	1st component	2nd component event			Composite endpoint of Exclusion of TAA/PAU
	Absence of Type I or III Endoleak	1st post-operative assessment of Maximum aneurysm/dissection/PAU diameter	assessment of Maximum aneurysm/dissection /PAU diameter at each scheduled visit	Absence of growth > 5 mm	
1	Success	evaluable	evaluable	Success	Success
2	Success	evaluable	evaluable	Failure	Failure
3	Failure	evaluable	evaluable	Success	Failure
4	Failure	evaluable	evaluable	Failure	Failure
5	Missing	evaluable	evaluable	Failure	Failure
6	Missing	evaluable	evaluable	Success	Missing
7	Success	Missing/evaluable	Evaluable/missing	Missing	Missing
8	Failure	Missing/evaluable	Evaluable/missing	Missing	Failure
9	Missing	Missing/evaluable	Evaluable/missing	Missing	Missing

- **Exclusion of Penetrating Aortic Ulcer (PAU)**

Exclusion of penetrating aortic ulcer (PAU) is defined as the absence of a type I or III endoleak associated to the absence of growth > 5 mm of the maximum measurable aortic diameter at the level of PAU; the reference diameter is the diameter measured at the first post-operative imaging exam.

The rate of the exclusion of PAU will be calculated similarly to that of the exclusion of Aneurysm;

- **Exclusion of False Lumen (dissection)**

Exclusion of false lumen (dissection) is defined as the exclusion of primary entry tear of dissection associated to the thrombosis of false lumen at the level of stent graft.

Rate of exclusion of Dissection will be calculated at the post-operative time point and at each scheduled follow-up and the calculation will be based on the number of subjects who had the event divided by the number of implanted subjects under the Dissection indication who are evaluated for that event at the time point. The imaging endpoint analysis time window will be used to determine if an image assessment belongs to a respective time point and the reporting details can be found in section 7.2.3 (Table 1).

7.9.3.4. Additional Dissection Specific Assessments

Additional dissection specific assessments include the following:

- Coverage of primary entry tear (exclusion of false lumen)
- Extension of dissection (proximally or distally) with or without complications
- Continuing or new false lumen (FL) perfusion
    - Primary intimal tear false lumen perfusion (PIT FLP)
    - Proximal aorta false lumen perfusion (PA FLP)
    - Distal aorta false lumen perfusion (DA FLP)
    - Proximal branch false lumen perfusion (PB FLP)
    - Distal branch false lumen perfusion (DB FLP)
- Aortic remodeling post-procedure as measured by:
    - Change from baseline* in the maximum true lumen (TL) diameter over the length of the stent graft
    - Change from baseline* in the maximum false lumen (FL) diameter over the length of the stent graft
    - Change from baseline* in the maximum total descending thoracic aortic diameter
    - FL thrombosis over the length of the stent graft

  * The discharge computerized tomography angiogram (CTA) will be used as the baseline to assess aortic changes. If a discharge CTA is not performed then, the one month follow-up CTA will be used for baseline purposes.

The rate of the above endpoints will be calculated at the post-operative time point and at each scheduled follow-up and the calculation will be based on the number of subjects who had the event divided by number of implanted subjects under the Dissection indication who are evaluated for that event at the time point. The imaging endpoint analysis time window will be used to determine if an image assessment belongs to a respective time point and the reporting details can be found in section 7.2.3 (Table 1).

- Thoracic dissection measurement over entire DTA and thoracic measures over endograft segment

If there are multiple images in a reporting window, the image with the largest maximum thoracic aortic centerline diameter over the entire DTA in the window will be used for reporting all related measurements (e.g., maximum thoracic aortic centerline diameter, maximum true lumen diameter, etc.)

7.9.3.5. Endoleaks

Type of endoleak includes Ia, Ib, Ic, type I combined, II, III, IV, and undetermined. The rate of these events will be reported for the 30-days visit, 6-month visit and at each annual follow-up and will be reported as the composite rate of endoleak requiring intervention or endoleak observed by imaging

assessment. The endpoint will be analyzed using the core lab imaging assessment and the site reported imaging assessment, separately.

The endpoint will be reported descriptively with frequency counts and percentages for any endoleak as well as by type.

- The numerator will include all subjects having endoleak requiring intervention within the analysis time window *or* any endoleak reported on imaging assessment within the time window.
- The denominator will include all subjects having endoleak requiring intervention within the analysis time window or having evaluable imaging assessment within the time window.

For imaging assessment, any endoleak reported during the time window will be accounted for in analysis. The secondary procedure date will be used as the basis of determining if an endoleak requiring intervention occurred within the time window.

7.9.3.6. Technical Observations

A technical observation is defined as a defect, malfunction, or failure of the device. Also, this may pertain to the device or system not functioning according to its designed intent. These might include (but are not be limited to) stent fracture, migrations, and device access difficulties. Technical observations may or may not be related to an adverse event in a subject.

Technical observations that are not associated with any untoward medical occurrence in a subject will be reported on the Imaging Exam Forms, Index Endovascular Procedure Form or Secondary Procedure Form. Technical observations that result in an Adverse Event will be considered by definition as Adverse Device effects and must also be documented in an Adverse Event form.

Technical observations may be analyzed using site-reported imaging assessments or core lab reported imaging assessments, separately.

Rate of Non-recurrent Imaging Endpoints

The following imaging assessments will be identified and reported by investigators per protocol definition - once such an event is discovered through an imaging assessment, it will likely stay noticeable on the subsequent imaging assessments at all follow-ups:

- Stent graft migration
- Stent graft separation
- Stent graft kinking
- Stent graft twisting
- Loss of stent graft integrity

The rate of these events will be reported for the 30-day visit, 6-month visit and for each annual follow-up and calculated based on the number of subjects who had the event divided by the number of implanted subjects who are evaluated for that event at the time point. The imaging endpoint analysis time window will be used to determine that an image assessment belongs to a respective time point and the reporting details can be found in section 7.2.3.

Further, if such event is observed during a time window, it will most likely be observed on all the images thereafter (if the imaging visit is completed); hence only the first observed event will be used to calculate the event rate - once one such event is reported for a subject for a time point, that subject will be excluded from that event rate reporting for that same event term for any later time points.

More detailed programming rules are described below:

a. If at least one positive (event) imaging assessment is found for an event type (e.g., fracture) – select the earliest positive assessment and then apply the visit window rules: The event will be included in the rate calculation for the corresponding visit, and for any visit after this one, that patient will be excluded from both the numerator and denominator of the event rate calculation;
b. If no positive imaging assessment is found, select the one using the 'latest evaluable image showing no event in the window rule';
c. Steps a and b need to be repeated for each specific event, such that a different image may be used for reporting each event type.
d. These observations will be assessed separately, for example, if a patient is determined to have fracture at 1-month, that patient will be excluded from fracture rate calculation for the visits after 1-month, but if no data support that the same patient has migration or kinking at 1-month, that patient will be included in the rate calculation at the later visit if the data are available until the relevant event(s) is/are determined.

Rate of Recurrent Imaging Observations

The following imaging assessments will be identified and reported by investigators per protocol definition; these events may appear or disappear through the imaging assessment from time to time:

- Loss of stent graft patency

More detailed programming rules are described below:

a. Slot all non-missing (evaluable) imaging assessments into the correspondent reporting window;
b. If multiple imaging assessments are found within the same visit window:
   i. If there is any positive finding for the event on evaluable images in the window, select the earliest image showing a positive finding e);
   ii. If there is no positive finding for the event, select the latest evaluable image showing no event.

Similar rules will be applied for the aortic artery measurement (such as diameter and length, etc.) during the follow-up visits.

7.9.4. Subset Analysis

Subset analyses of the primary safety and effectiveness observations will be created for the subjects enrolled with aneurysms, penetrating ulcers, or chronic Type B dissections. Descriptive statistics will be used to analyze the primary observations, additional observations, and periprocedural and discharge clinical utility measures.

7.10. Safety Evaluation

Any Adverse events (AEs or SAEs) other than MAEs will be summarized by relationship and time period. Relationship will be site-reported in 3 categories, device-related, procedure-related and aneurysm-related. If an AE is in 2 or more categories, it will be included in both or all summaries. All SAEs will be summarized separately. All AEs will be coded according to the Medtronic Endovascular Dictionary.

The rate of any AE will be calculated for following time periods:

- 0-30 days
- 31-365 days
- 366-730 days
- 731-1095 days
- 1096 -1460 days
- 1461 – 1825 days

The event rate is determined by number of subjects who had the event during the time period divided by number of subjects at risk at the beginning of the time period, i.e. number of subjects who are still in the study at the beginning of the time period.

Unanticipated Serious Adverse Device Effects (USADEs), Unanticipated Adverse Device Effects (UADEs) and deaths will be provided in a listing. Device malfunctions and failures will be listed.

7.11. Health Outcomes Analyses

No Health Outcomes analyses are planned for this study.

7.12. Changes to Planned Analysis

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical

underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

Version 6.0 of this document incorporated the 'worst case' principle for imaging analyses reporting rule changes requested by the FDA.[1]

8. Validation Requirements

All statistical analysis results will be validated. Level I validation will be used for all safety endpoints and efficacy endpoints defined in the Protocol as well as all analysis datasets. Validation methods for each statistical output will be documented in the validation report (GBET 019).

9. References

1. Medtronic work instruction: Aortic Study Reporting Conventions v2.0, based on discussion and agreement with FDA.

10. Statistical Appendices

None.