



# GROWTH: A Multicenter Pivotal Study of Neonatal, Infant, and Young Child Vascular Stenoses Studying the Renata Minima Stent

**Statistical Analysis Plan**

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# 3 Abbreviations and Definitions

| | |
|---|---|
| ACT | Activated Clotting Time |
| AE | Adverse Event |
| AI | Attempted Implant |
| AT | All Treated |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| CRF/eCRF | Case Report Form / electronic Case Report Form |
| CXR | Chest X-Ray |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| ECMO | Extracorporeal Membrane Oxygenation |
| EDC | Electronic Data Capture |
| EFS | Early Feasibility Study |
| FDA | United States Food and Drug Administration |
| GCP | Good Clinical Practice |
| H&P | History and Physical Examination |
| Hct | Hematocrit |
| Hgb | Hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ICU | Intensive Care Unit |
| IDE | Investigational Device Exemption |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| LAR | Legally Authorized Representative |
| PAS | Pulmonary Artery Stenosis |
| RV | Right Ventricle |
| RVOT | Right Ventricular Outflow Tract |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| TTE | Transthoracic echocardiogram |
| UADE | Unanticipated Adverse Device Effect |
| WBC | White blood cell |

# 4 Introduction

## 4.1 Preface

The use of endovascular stents in congenital heart disease was first described more than 30 years ago. Soon thereafter, pediatric cardiologists began exploring and successfully implanting stents in smaller children and infants. While these procedures have now been performed successfully for decades, there continue to be numerous important drawbacks. The current standard of care to treat pediatric and infant vascular stenosis is either open surgical plasty or off-label endovascular stent implantation. Despite the apparent benefits of stent placement, the use of stents in infants presents a unique challenge. Due to normal and expected somatic growth, when a stent is placed in an infant, there is an unavoidable risk of restenosis caused by the development of device-patient size mismatch. This risk can be largely mitigated by simple stent re-dilation over time, however, currently there are no stents available that are small enough to be safely placed in an infant vessel that can be re-dilated to adult vessel dimensions.

The Renata Minima stent was designed to address these issues by providing a lifetime stent solution for a neonate, infant, or young child with vascular stenosis through (1) the use of a specific delivery system and stent dimensions designed to safely navigate the vasculature of this unique population and (2) the design of a unique stent created to be re-dilatable to adult vessel dimensions and thereby provide the potential for stenosis relief over the course of a lifetime.

## 4.2 Scope of the analyses

These analyses will assess the efficacy and safety of the Renata Minima Stent System in comparison with a performance standard and will be included in the clinical study report.

# 5 Study Objectives and Endpoints

## 5.1 Study Objectives

The objective of the clinical investigation is to access device performance and the clinical safety and effectiveness of the Minima Stent in neonates, infants, and young children requiring intervention for coarctation of the aorta and/or pulmonary artery stenosis who are indicated for treatment.

## 5.2 Endpoints

| | |
|---|---|
| **Primary Efficacy Endpoint** | The primary efficacy endpoint will be assessed as the rate of clinical success, with the performance goal defined as a clinical success rate of greater than 77%.<br><br>Clinical success is defined as:<br>• Stenosis relief, defined by stent outer diameter ≥ 75% of the surrounding vessel immediately after deployment.<br>• Freedom from open surgical intervention required to treat Minima Stent disfunction through 6 months.<br>• Maintenance of stented vessel diameter ≥ 50% of post-implant diameter at 6 months; as measured using CT angiography and/or angiography. |

| | |
|---|---|
| **Primary Safety Endpoint** | The primary safety endpoint will be assessed as the percentage of cases with freedom from procedure- or device-related SAEs resulting in an event listed below, with the performance goal defined as greater than 78% of cases:<br>o Death<br>o Cardiac arrest and/or emergency ECMO cannulation<br>o Stroke<br>o Limb loss<br>o Vessel dissection of target lesion<br>o Device thrombosis/occlusion<br>o Cardiac perforation requiring percutaneous or open surgical intervention<br>o Persistent cardiac arrhythmia requiring a pacemaker |
| **Secondary Efficacy Endpoints** | • Peak-to-peak pressure gradient (ventricle to arterial or arterial to arterial) < 20 mmHg after stent placement, when applicable.<br>• Successful stent re-dilation (when indicated) at re-catheterization, defined as an increase in the intra stent angiographic luminal diameter within 2mm of the adjacent native vessel diameter immediately after re-dilation. |
| **Secondary Safety Endpoints** | • Freedom from stent embolization or migration through 6 months.<br>• Freedom from stent fracture that led to reintervention through 6 months<br>• Freedom from non-elective Minima Stent explant at 90-days post re-dilation<br>• Freedom from procedure- or device-related SAE during re-dilation that results in the following:<br>o Death<br>o Cardiac arrest and/or emergency ECMO cannulation<br>o Stroke<br>o Limb loss<br>o Vessel dissection of target lesion<br>o Device thrombosis/occlusion<br>o Cardiac perforation requiring percutaneous or open surgical intervention<br>o Persistent cardiac arrhythmia requiring a pacemaker |

# 6 Study Methods

## 6.1 General Study Design and Plan

This is a single-arm, prospective, non-randomized, multi-center, open-label, pivotal study. The study intends to enroll a maximum of 42 subjects within the United States. For each treatment location (pulmonary artery or aortic vascular), a minimum of 10 patients will be treated. These subjects will be enrolled at up to 8 US investigational sites, with the possibility of additional Japanese and/or European Union sites pending the appropriate regulatory approval. A minimum of 50% of patients must be treated at sites within the Unites States. As there have been no stent related design changes as a result of the EFS implants, the initial 10 patients will be included in the 36-42 patients.

## 6.2 Inclusion-Exclusion Criteria and General Study Population

The study population will be comprised of patients with a clinically relevant pulmonary artery or aortic vascular stenosis who are indicated for treatment. For each treatment location (pulmonary artery or aortic vascular), a minimum of 10 patients will be treated.

## Inclusion Criteria

Candidates must meet **all** of the following inclusion criteria:

1. The subject's legally authorized representative has been informed of the nature of the clinical investigation, agrees to its provisions, and has provided written informed consent.*
2. Requiring treatment* of:
   a. Native, acquired, or recurrent aortic coarctation, and/or
   b. Native, acquired, or recurrent pulmonary artery stenosis

   *As defined by the patient's medical team
3. Patency of at least one femoral, jugular vessel, or both carotid arteries able to accommodate the delivery system
4. Adjacent vessel to stenosis measuring > or equal to 4 mm

*This clinical investigation is enrolling neonates, infants, and young children. All local laws and governing Institutional Review Board (IRB) requirements will be followed for obtaining informed consent.

## Exclusion Criteria

Candidates will be excluded from the clinical investigation if **any** of the following are present:

1. Active bloodstream infection requiring antibiotic therapy within 7 days prior to stent implantation
2. History of or active endocarditis (active treatment with antibiotics) within 180 days prior to stent implantation
3. Aortic or pulmonary artery aneurysm in the location targeted for treatment
4. Body weight of < 1.5 kg
5. Anatomic location of lesion judged by the investigator to not lend to the safe placement of a stent
6. Target vessels larger or smaller than the Minima System balloon size ranges
7. Currently participating in an investigational drug study or another device study
8. Known genetic syndrome known to be associated with vasculopathies such as but not limited to Williams syndrome, Loeys-Dietz syndrome, etc
9. Clinical scenario requiring that more than one vessel needs stent implantation at the time of trial procedure.
10. Major or progressive non-cardiac disease resulting in a life expectancy of less than six months
11. Known hypersensitivity to aspirin or heparin and cannot be treated with other antiplatelet and/or antithrombotic medications
12. Known hypersensitivity to cobalt-chromium or contrast media that cannot be adequately pre-medicated

## Inclusion Criteria for Re-dilation

Candidates must meet **one** or more of the following inclusion criteria:

Development of an increase in the pressure gradient across the stent and/or stent lumen diameter less than the nominal adjacent vessel diameter, as defined as:

1. Peak Doppler echo gradient ≥ 30 mmHg and/or a mean Doppler gradient ≥20 mmHg across the stented vessel
2. Stented lumen diameter is ≤ 75% of adjacent native vessel

## Exclusion Criteria for Re-dilation

Candidates must not have any of the following:

1. Evidence of significant vessel wall damage (e.g.. aneurysm, dissection) in the area of planned re-dilation
2. Stent deformity or loss of structural integrity judged by the investigator to not lend to the safe re-dilation of the stent
3. Access site or patient vasculature judged by the investigator to not lend to the safe re-catheterization using a balloon catheter approved for the stent location..

## 6.3 Study Assessments

| Activity | Screening | Procedure | Post-Procedure | 1 Month (±7days) | 3 Months (±7days) | 6 Months ±14 days) | 12 Months (±30days) | Annually Years 2-5 (±45days) |
|---|---|---|---|---|---|---|---|---|
| Informed consent & HIPAA authorization | X | | | | | | | |
| Inclusion/exclusion criteria assessment | X | | | | | | | |
| Demographics | X | | | | | | | |
| Medical history | X | | | | | | | |
| Physical exam & vital signs | X | | X | X | X | X | X | X |
| WBC, Hgb, Hct, platelets | X[1] | | | | | | | |
| Serum creatinine | X[1] | | | | | | | |
| INR (if taking Warfarin) | X | | | | | | | |
| Chest X-ray | X | | X | X | X | X | | |
| Transthoracic echocardiogram | X | | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X |
| Minima stent implantation | | X | | | | | | |
| Pre-and Post-implantation angiography and hemodynamic assessments (within procedure) | | X | | | | | | |
| Adverse events / Device deficiencies[2] | | X | X | X | X | X | X | X |
| Concomitant procedures[3] | X | | X | X | X | X | | |
| CT angiography | | | | | | X[4] | | |

[1]To reduce unnecessary blood draws from patients, blood work may be performed after successful completion of all other screening activities / in the catheterization lab prior to device introduction into the bloodstream.

[2] All AEs collected for 12 months post-transplant; after 12 months, see **Section 8.2** for select AE reporting.

[3] See **Section 8.8** for reporting of select concomitant medications/procedures.

[4] Catheter-based angiography can be performed in place of CT if clinically appropriate.

The table below defines the analysis time windows that correspond to the targeted visit time frame.

Analysis Time Windows

| Visit (target day) | Lower bound (days) | Upper bound (days) |
|---|---|---|
| Month 1 (30) | 2 | 60 |
| Month 3 (90) | 61 | 135 |
| Month 6 (180) | 136 | 270 |
| Month 12 (360) | 271 | 374 |

### Missed window

For missed data collection, confidence intervals, standard deviations and other calculations dependent on sample size will be calculated using the reduced sample size, unless noted otherwise in the resolution of the protocol deviation.

### Duplicate Measurements Within Window

In the event multiple measurements are made within window (due to an unscheduled visit or other event), the implanting physician for the subject is responsible for determining which visit conducted is the scheduled visit. The unscheduled visit will still be documented within the database using an unscheduled visit form; however, the datapoints will not be used in follow-up calculations unless instructed to do so as part of a resolution of a protocol deviation.

## 7 Sample Size

Safety:

This is a one proportion study powered at 80% and a one-sided 2.5% significance. The published literature supports a Major AE rate of 12%. As there are no approved devices in the space, a non-inferiority margin of 10% was selected and is supported by the Renata Physician advisors.

Based on published data (Holzer) the incidence of device or procedure-related SAEs on the current treatment procedure is 10% in patients > 1 year of age and 14% in patients ≤1 year of age; therefore, a blended rate of 12% will be used. Clinically, it is generally believed that incidences of SAEs less than 22% are clinically acceptable. Therefore, we are adopting a performance goal of 22% for the SAE rate.

Based on the clinically acceptable rate of 22%, the hypothesis would then be written as the following:

Null Hypothesis (H0): Incidence of device or procedure-related SAE ≥ 22%
Alternative Hypothesis (HA): Incidence of device or procedure-related SAE <22%
One-Sided (H0: P ≥ P0 vs. H1: P < P0)

Assuming an SAE rate of 4% (Boe), 30 subjects will provide 80% power to meet the performance goal and reject the null hypothesis at a 2.5% one-sided significance level. The sample size calculation was based on the normal approximation to the binomial distribution.

Efficacy:
This is a one proportion study powered at 80% and a one-sided 2.5% significance. The published literature supports a procedural effectiveness rate of 87%. As there are no approved devices in the space, a non-inferiority margin of 10% was selected and is supported by the Renata Physician advisors.

Based on published data (Stanfill) the incidence of angiographic success during implantation is 87%. Clinically, it is generally believed that a procedural success rate greater than 77% is clinically acceptable. Therefore, we are adopting a performance goal of 77% for procedural effectiveness.

Based on the clinically acceptable rate of 77%, the hypothesis would then be written as the following:

Null Hypothesis (H0): Incidence of clinical success ≤77%.
Alternative Hypothesis (HA): Incidence of clinical success >77%.
One-Sided (H0: $P \leq P0$ vs. H1: $P > P0$)

Assuming a clinical success rate of 97% (Boe), 24 subjects will provide 80% power to meet the performance goal and reject the null hypothesis at a 2.5% one-sided significance level. The sample size calculation was based on the normal approximation to the binomial distribution.

Co-Primary Endpoint Power Calculation:
For the study to successfully pass, all both Safety & Efficacy Primary Endpoints must reject their null hypothesizes concurrently, using the appropriate one-sided significance level for each endpoint (2.5% and 2.5% respectively); therefore, power calculations were performed for each hypothesis statement, based on the normal approximation to the binomial distribution, and combined using the Inclusion-Exclusion Rule (shown below), assuming the two endpoints are independent, to determine the power of the study at each sample size.

$$P(A \cup B) = P(A) + P(B) - P(AB)$$

Where:

$$P(A) = \beta_{Efficacy}$$
$$P(B) = \beta_{Safety}$$
$$P(AB) = \beta_{Efficacy} \times \beta_{Safety}$$
$$P(A \cup B) = \beta_{Efficacy\ \&\ Safety}$$
$$\text{Study Power} = 1 - \beta_{Efficacy\ \&\ Safety}$$

Using the assumptions above, analysis shows a minimum of 36 subjects will provide 90% power to meet both the primary efficacy and safety performance goals. To account for approximately 15% attrition rate, a maximum of 42 United States subjects (42=36(100%+15%)) will be allowed to be implanted, prior to further authorization.

| Sample Size | Safety Power | Efficacy Power | Total Power |
|---|---|---|---|
| 20 | 0.49 | 0.66 | 0.32 |
| 21 | 0.53 | 0.70 | 0.37 |
| 22 | 0.57 | 0.75 | 0.42 |
| 23 | 0.60 | 0.78 | 0.47 |
| 24 | 0.64 | 0.82 | 0.52 |
| 25 | 0.67 | 0.85 | 0.57 |
| 26 | 0.71 | 0.87 | 0.62 |
| 27 | 0.74 | 0.90 | 0.66 |
| 28 | 0.76 | 0.91 | 0.70 |
| 29 | 0.79 | 0.93 | 0.73 |
| 30 | 0.81 | 0.94 | 0.77 |
| 31 | 0.83 | 0.95 | 0.80 |
| 32 | 0.85 | 0.96 | 0.82 |
| 33 | 0.87 | 0.97 | 0.85 |
| 34 | 0.89 | 0.98 | 0.87 |
| 35 | 0.90 | 0.98 | 0.89 |
| 36 | 0.91 | 0.99 | 0.90 |
| 37 | 0.93 | 0.99 | 0.92 |
| 38 | 0.94 | 0.99 | 0.93 |
| 39 | 0.94 | 0.99 | 0.94 |
| 40 | 0.95 | 1.00 | 0.95 |

# 8 General Analysis Considerations

## 8.1 Timing of Analyses

The first analysis will be performed when a minimum of 10 subjects have completed the 6 month visit.

Primary analysis and submission of available data will be completed after all patients have completed their 6 month follow-up visits.

Subsequent analysis will be completed annually through 5 years.

## 8.2 Analysis Populations

8.2.1 The All Treated (AT) population is defined as all subjects who signed informed consent, meet eligibility criteria and for whom a procedure was begun (defined as the initiation of vascular access).

8.2.2 The Attempted Implant (AI) population is defined as all AT subjects who continued to meet the eligibility criteria and had an attempted implant of the Minima stent. A subject is considered to have an attempted implant at the time in which the Minima Stent System is inserted into the subject.

## 8.3 Interim Analyses

There are no plans for an interim analysis at this time.

# 9 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. All summary tables will be structured with a column for treatment and will be annotated with the total population size relevant to that table, including any missing observations.

Only deviations from the general overview will be noted in the subsequent sub-sections within section 9.

## 9.1 Subject Disposition

The number of patients completing each visit from the schedule of assessments will be reported along with the reason for loss (screen failure, death, loss to follow-up, etc).

The summary statistics will be produced in accordance with section 9.

## 9.2 Protocol Deviations

All protocol deviations will be summarized.

If a stent is removed surgically during another procedure (which is unrelated to a Minima Stent malfunction/failure) the data collected prior to stent removal will be included within analysis. After stent removal, no additional data related to the stent will be collected and the sample size will be reduced accordingly in any applicable calculations.

If a patient is found to not meet eligibility criteria per the protocol inclusion/exclusion criteria, they will not be treated under the protocol and the appropriate regulatory filing must be completed prior to treating the patient outside of the protocol. All patients treated off protocol will not be included in analysis.

The summary statistics will be produced in accordance with section 9.

## 9.3 Demographic and Baseline Variables

The summary statistics will be produced in accordance with section 9.

## 9.4 Concurrent Illnesses and Medical Conditions

The summary statistics will be produced in accordance with section 9.

# 10 Efficacy Analyses

## 10.1 Primary Efficacy Analysis

The primary efficacy endpoint will be assessed as the rate of clinical success, with the performance goal defined as a clinical success rate of greater than 77%.

Clinical success is defined as:

- Stenosis relief, defined by stent outer diameter ≥ 75% of the surrounding vessel immediately after deployment.
- Freedom from open surgical intervention required to treat Minima Stent disfunction through 6 months.
- Maintenance of stented vessel diameter ≥ 50% of post-implant diameter at 6 months; as measured using CT angiography and/or angiography.

The AI patient population will be used to test the study hypothesis. The Clopper-Pearson method will be used to calculate the two-sided 95% confidence limits. If the lower limit of the resulting confidence interval exceeds 77%, then the null hypothesis will be rejected in favor of the alternative. This study hypothesis will be tested without imputation of missing data; however, additional sensitivity analyses will be performed to evaluate the effect of missing data on the study conclusions.

## 10.2 Secondary Efficacy Analyses

The secondary efficacy endpoints are as follows:

- Peak-to-peak pressure gradient (ventricle to arterial or arterial to arterial) < 20 mmHg after stent placement, when applicable.
- Successful stent re-dilation (when indicated) at re-catheterization, defined as an increase in the intra stent angiographic luminal diameter of within 2mm of the adjacent native vessel diameter immediately after re-dilation.

# 11 Safety Analyses

## 11.1 Primary Safety Analysis

The primary safety endpoint will be assessed as the percentage of cases with freedom from procedure- or device-related SAEs resulting in an event listed below, with the performance goal defined as greater than 78% of cases:

- Death
- Cardiac arrest and/or emergency ECMO cannulation
- Stroke
- Limb loss
- Vessel dissection of target lesion
- Device thrombosis/occlusion
- Cardiac perforation requiring percutaneous or open surgical intervention
- Persistent cardiac arrhythmia requiring a pacemaker

The AT patient population will be used to test this hypothesis. The Clopper-Pearson method will be used to calculate the two-sided 95% confidence limits. If the lower limit of the resulting confidence interval exceeds 78%, then the null hypothesis will be rejected in favor of the alternative. The study hypothesis will be tested without imputation of missing data; however, additional sensitivity analyses will be performed to evaluate the effect of missing data on the study conclusions.

## 11.2 Secondary Safety Analysis

The secondary safety endpoints will be assessed:

- Free from stent embolization or migration through 6 months.
- Free from stent fracture that led to reintervention through 6 months
- Free from non-elective Minima Stent explant at 90-days post re-dilation
- Free from procedure- or device-related SAE during re-dilation that results in the following:
  - Death
  - Cardiac arrest and/or emergency ECMO cannulation
  - Stroke
  - Limb loss
  - Vessel dissection of target lesion
  - Device thrombosis/occlusion
  - Cardiac perforation requiring percutaneous or open surgical intervention
  - Persistent cardiac arrhythmia requiring a pacemaker

## 11.3 Adverse Events

The summary statistics will be produced in accordance with section 9.

The following tables will be generated:

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with number and frequency of such events in each arm/group of the clinical study.
- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events
- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) grouped by organ system, with number and frequency of such events.

The number of events as well as the number of patients with each event will be summarized by time interval, The time intervals will be 0 to 30 days, 31-90 days and 91 to 180 days, 180 to 365 and annually through 5 years. The denominator will include all subjects in the AT population with follow-up data during the specific time interval.

## 11.4 Clinical Laboratory Evaluations

The summary statistics will be produced in accordance with section 9 and reported with the baseline characteristics.

## 11.5 Prior and Concurrent Medications

The summary statistics will be produced in accordance with section 9.

# 12 Subgroup Analyses

In or evaluate the consistency of the treatment results, the primary endpoints will calculated for each of the subgroups listed below. The fisher's exact test will be used to evaluate the statistical significance of any differences across subgroup levels for both primary endpoints.

Demographic/Baseline Characteristics

- Sex
- Age (<6mo; 6mo-24mo; >24mo)
- Race (Caucasian vs. Non-Caucasian)

Procedural:

- Implant location (Pulmonary vs. Aortic)

## 12.1 Geographic Region

Should patients be enrolled outside the US, the primary endpoints will be compared across geographical region (e.g. US vs. Japan vs. Europe).

## 12.2 Investigational Sites

Renata Medical will select investigators based on training and experience. Renata may select up to 8 US investigational sites, with the possibility of additional Japanese and/or European Union sites pending the appropriate regulatory approvals. These sites will enroll a maximum of 42 subjects with a minimum of 50% of the patients implanted being treated within the United States.

Results for the primary endpoints will be presented stratified by investigational site and rates will be compared using the fisher's exact test.

# 13 Missing Data Considerations

The hypothesis tests for the primary endpoints will be performed without imputation of missing data. The incidence of missing data is expected to be low and all efforts will be made to collect all required data points in the study. Should there be missing data for either primary endpoint, then sensitivity analyses will be performed to evaluate the potential effect of the missing data on the study conclusions. If the study conclusions are upheld using a worst-case scenario imputation approach, then no further missing data analyses will be required. The worst-case scenario approach would treat all missing data points as failures for the endpoint.
If the results are not upheld with the worst-case scenario approach, then two further analyses will be performed.

1) A tipping point analysis: missing data are imputed over the range of possible scenarios, from imputing all as successes to all as failures, in order to determine at what point the hypothesis is no longer met.
2) Multiple Imputation: A multiple imputation analysis will be performed using a logistic regression model. Variables in the model will include:
    a. Lesion Location (Aortic, Pulmonary)
    b. Age
    c. Weight

# 14 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.