Statistical Analysis Plan

Protocol #[redacted]
SUMMIT

CLINICAL TRIAL TO EVALUATE THE **S**AFETY AND EFFECTIVENESS OF **U**SING THE TENDYNE **M**ITRAL VALVE SYSTEM FOR THE TREATMENT OF SYMPTOMATIC **MIT**RAL REGURGITATION

Statistical Analysis Plan (SAP)

Version K

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Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Protocol CS0004-P, [redacted], the SUMMIT clinical trial.

1.2 Clinical Investigational Objectives

The objective of the trial is to evaluate the safety and effectiveness of the Tendyne™ Transcatheter Mitral Valve System for the treatment of patients with symptomatic, moderate-to-severe or severe mitral regurgitation (MR), or for patients with symptomatic mitral valve disease due to severe mitral annular calcification..

1.3 Clinical Investigational Design

This trial is a prospective, controlled, multicenter clinical investigation of the Tendyne™ Transcatheter Mitral Valve System for the treatment of eligible subjects with symptomatic, moderate-to-severe or severe mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria), or severe mitral annular calcification (MAC) for whom the site heart team deems transcatheter treatment is more appropriate than conventional mitral valve surgery.

The trial is composed of a Randomized, a Non-repairable and a Severe MAC Cohort. Subjects will be assigned to either the Randomized, the Non-repairable or the Severe MAC Cohort at the discretion of the local site heart team. Subjects must satisfy the trial inclusion/exclusion criteria and be approved by the Subject Eligibility Committee (SEC), prior to inclusion in the trial.

Randomized Cohort: Subjects suitable for transcatheter mitral valve replacement (TMVR) with Tendyne and indicated for transcatheter edge-to-edge repair (TEER) with MitraClip will be randomized in a 1:1 ratio to receive either Tendyne (Treatment) or MitraClip® (Control). Subjects with primary MR must be at prohibitive surgical risk, while subjects with secondary MR must be symptomatic despite maximally-tolerated guideline-directed medical therapy in accordance with the MitraClip Indications for Use. Randomization will be stratified by investigational site.

Non-Repairable Cohort: Subjects with valve anatomies suitable for Tendyne TMVR, but not for TEER will be eligible to enroll in the Non-repairable Cohort, in which all subjects will receive treatment with the Tendyne system.

Severe MAC Cohort: Subjects who have severe MAC rendering the subject unsuitable for mitral valve surgery will be eligible to enroll in the Severe MAC Cohort, in which all subjects will receive treatment with the Tendyne system.

Approximately 382 subjects will be included in the Randomized Cohort, with approximately 191 subjects targeted to receive the investigational device, at up to 80 sites in globally. In the Non-repairable Cohort, approximately 325 subjects will be targeted to receive the investigational device. In the Severe MAC Cohort, approximately 103 subjects will be targeted to receive the investigational device. [redacted]

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[redacted]

Following the completion of enrollment of the Severe MAC Cohort, approved subjects will be enrolled into a Severe MAC continued access plan (CAP). Details of the analysis plan for the Severe MAC CAP are included in APPENDIX VI.

An additional 160 roll-in subjects (up to 2 per site) may be treated by operators without prior or recent experience using the Tendyne system to gain hands-on experience before registering subjects in a study cohort. Roll-in subjects will not count toward the subject caps in the Randomized (382 subjects), Non-repairable (325 subjects) cohort or Severe MAC (103 subjects) cohorts.

All subjects will be followed at 30 days, 90 days, 6 months, 12 months, and annually thereafter through 5 years from the index procedure.

1.4 Endpoints

1.4.1 Primary Endpoints

For the Randomized Cohort, the primary endpoint is

- Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure.

For the Non-repairable Cohort, the primary endpoint is

- Freedom from all-cause mortality, and heart failure hospitalization at 12-months post index procedure.

For the Severe MAC Cohort, the primary endpoint is

- Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure.

1.4.2 Secondary Endpoints

For the Randomized Cohort, the secondary endpoints are:

- Freedom from MR > mild (1+) in severity at 30 days post index procedure among survivors
- Freedom from all-cause mortality and mitral valve (MV) reintervention at 12 months post index procedure
- Improvement in Quality of Life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) by at least 10 points at 12 months from baseline
- Proportion of Patients with New York Heart Association (NYHA) Functional Classification I or II at

12 months

- Improvement in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) by at least 50 meters at 12 months from baseline

For the Non-Repairable Cohort, the secondary endpoints are:

- Change in QoL, as measured by the KCCQ from baseline at 6 months and 12 months
- Improvement of NYHA Functional Classification I or II at 12 months
- Change in 6MWD from baseline at 6 months and 12 months

For the Severe MAC Cohort, the secondary endpoints are:

- Freedom from MR > mild (1+) in severity at 30 days post index procedure among survivors
- Change in QoL, as measured by the KCCQ from baseline at 6 months and 12 months
- Improvement of NYHA Functional Classification I or II at 12 months
- Change in 6MWD from baseline to 6 months and 12 months

1.4.3 Descriptive Endpoints

Additional descriptive endpoints include:

1.4.3.1 Clinical Endpoints:

- All-cause mortality, CV hospitalizations, all stroke or MV reintervention or reoperation, at 2 years post index procedure and then yearly through 5 years
- Change from baseline in distance walked on the 6MWT at each follow-up visit
- Change from baseline in QoL, as measured by the KCCQ at each follow-up visit
- Change from baseline in health outcomes, as measured by the EQ-5D questionnaire, at each follow-up visit
- Change from baseline in health outcomes, as measured by the 12-item Short Form Health Survey (SF-12), at each follow-up visit
- NYHA Functional Classification at each follow-up visit
- Number of days alive and out of hospital from the time of the index procedure to 12 months, and then yearly through 5 years
- Length of index hospitalization for procedure
- Annualized rate of heart failure hospitalizations
- Change from baseline in BNP or NT pro-BNP levels, at all follow-up visits
- All-cause mortality at 30 days, 1 year and then yearly through 5 years

1.4.3.2 MVARC Endpoints:

The following Mitral Valve Academic Research Consortium (MVARC) measures of success will be captured for the Randomized, Non-repairable and Severe MAC Cohorts.

- Technical Success
- Device Success
- Procedural Success
- Patient Success

The definitions for the above endpoints can be found in Appendix II of Protocol CS0004-P, the SUMMIT clinical trial.

1.4.3.3 Echocardiographic Endpoints:

The following echocardiographic endpoints, as adjudicated by the Echocardiography Core Laboratory, will be reported at baseline, discharge, 1 month, 6 months, 12 months, and then annually through 5 years. For continuous variables, change from baseline to each follow-up will also be reported:

- MR severity grade
- Effective Regurgitant Orifice Area (EROA)
- Regurgitant Volume
- Regurgitant Fraction
- Left Ventricle End Diastolic Volume (LVEDV)
- Left Ventricular End Systolic Volume (LVESV)
- Left Ventricular End Diastolic Dimension (LVEDD)
- Left Ventricular End Systolic Dimension (LVESD)
- Left Ventricular Ejection Fraction (LVEF)
- Right Ventricular Systolic Pressure (RVSP)
- Mitral Valve Area
- Mean Mitral Valve Gradient
- Mean Left Ventricular Outflow Tract Gradient
- Cardiac Output
- Forward Stroke Volume

1.5 Randomization

1.5.1 Randomized Cohort

Approximately 382 subjects will be randomized **1**:**1** in the primary analysis (treatment vs. control). [redacted]

An Electronic Data Capture (EDC) system will be used to randomize subjects.

1.5.2 Timing of Randomization

Subjects will be randomized after the investigational site personnel have confirmed and documented that the subject has met all eligibility criteria, the imaging core labs have confirmed anatomic suitability, and the SEC has concurred with the local site heart team that the subject has been treated per applicable standards and can be treated in the Randomized cohort of the trial.

1.6 Blinding

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Randomized Cohort

The Intention-to-Treat, modified Intention-to-Treat and Per-Protocol are defined below. For analyses of the Randomized Cohort, the duration of follow-up will be calculated from the date of registration.

2.1.1.1 Intent-to-Treat (ITT) Population

[redacted]

2.1.1.2 Modified Intention-to-Treat (mITT) Population

[redacted]

2.1.1.3 Per-Protocol (PP) Population

[redacted]

2.1.2 Non-repairable and Severe MAC Cohorts

2.1.2.1 Attempted Procedure (AP) Population

[redacted]

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, LVEF, LVEDV), results will be summarized with the numbers of observations, means, standard deviations, quartiles, minimums, maximums, and 95% confidence intervals. Differences between the treatment groups, if applicable, will be summarized with differences of the two means, and 95% confidence intervals for the difference between the means.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables, such as sex and NYHA classification, results will be summarized with subject counts and percentages/rates, and with exact 95% [redacted] confidence intervals. Differences between the two treatment groups, if applicable, will be summarized with the difference in proportions and [redacted] 95% confidence interval for the difference of two proportions.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point when they stay in the study. Survival curves will be constructed using Kaplan-Meier estimates.

2. 3 Endpoint Analysis

As the Coronavirus Disease 2019 (COVID-19) pandemic has spread around the globe, the following analysis mechanism will be implemented to minimize the potential confounding effect from this emerging infectious disease for the trial primary and secondary endpoints set forth in assessing trial success and labeling claims. In alignment with the guidance document “FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency” updated 03-June-2020, and EU “Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic” updated 28-April-2020, additional consideration was given to the impact of the COVID-19 pandemic on the primary and secondary endpoints analyses for this study. As such, prespecified methods are included in

the sections that follow to indicate the handling of any outcomes impacted by COVID-19 as well as efforts to minimize missing endpoint data during the COVID-19 pandemic.

Any subject experiencing a CEC-adjudicated COVID-19-related hospitalization or death, indicated as 'related' within the associated event adjudication by the CEC, will have any and all follow-up clinical data censored beginning with the event. That is, the follow-up data will not contribute toward any primary or secondary endpoint analysis for any of the 3 cohorts, with the exception of MR severity, which will be used for all subjects in all cohorts in whom MR data are available. Furthermore, any subject having a COVID-19 infection but not experiencing a CEC adjudicated COVID-19-related hospitalization or death, as defined above, will not be censored and their data, barring other protocol deviations, will contribute in its entirety to the analysis of all endpoints.

2.3.1 Randomized Cohort

2.3.1.1 Randomized Cohort – Primary Endpoint

The primary endpoint for the randomized cohort is freedom from all-cause mortality and heart failure hospitalization (HFH) at 12-months post index procedure. The trial is intended to demonstrate non-inferiority of the Tendyne™ Transcatheter Mitral Valve System to TEER with MitraClip for the treatment of moderate-to-severe or severe MR.

The null (H_0) and alternative (H_1) hypotheses[10] are:

$\mathbf{H_0}$: $\pi_D - \pi_C \leq -d$

$\mathbf{H_1}$: $\pi_D - \pi_C > -d$

where π_D and π_C are the true event rates for the composite of freedom from all-cause mortality and HFH at 12 months in the Treatment and Control group, respectively, and *d* is the non-inferiority margin. The non-inferiority margin is set at 12.5%.

The primary analysis for the primary endpoint will be performed on the ITT population. The analysis will also be performed on the mITT and PP populations. [redacted] using a one-sided test with a 5% significance level.

If the primary endpoint passes the non-inferiority test, it will then be tested, following secondary endpoints, for superiority of Tendyne vs. MitraClip [redacted] at two-sided 5% significance level.

The justification of the non-inferiority margin *d* of 12.5% will be provided in the Appendix. Additional analysis populations and sensitivity analyses to address missing data are described in **Sections 2.8 and 2.13**.

2.3.1.2 Randomized Cohort – Secondary Endpoints

The following secondary endpoints will be evaluated. These endpoints will be evaluated for labeling claims if the primary endpoint for the Randomized cohort is met. The primary analysis population for all secondary endpoints of the Randomized cohort is ITT.

2.3.1.2.1 Freedom from MR > mild (1+) at 30 days post index procedure among survivors

Subjects treated with the Tendyne device are expected to experience greater reduction in MR severity than subjects in the Control group. The proportion of subjects with MR ≤ mild (1+) at 30 days will be compared between the Treatment and Control groups.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_D - P_C \leq 0$

$\mathbf{H_1}$: $P_D - P_C > 0$

where P_D and P_C represent the proportion of subjects with MR ≤ mild (1+) at 30 days post index procedure in the Treatment and Control groups, respectively. [redacted] at one-sided 2.5% significance level.

In the case that the 1-month follow-up visit is missed, or the subject's MR measurement is not available from this visit for some reason, the chronologically nearest post-procedure MR measurement obtained from the core lab, within 365 days of the scheduled 1-month follow-up visit, will be used instead.

2.3.1.2.2 Freedom from all-cause mortality and MV reintervention at 12 months

The Tendyne device may reduce the risk for surgical reintervention and subjects in the Treatment group are expected to experience greater reduction in MR severity than subjects in the Control group. The proportion of subjects alive and without MV reintervention at 12 months will be compared between the Treatment and Control groups.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $\pi_D - \pi_C \leq -d$

$\mathbf{H_1}$: $\pi_D - \pi_C > -d$

where π_D and π_C are the true event rates for the composite of freedom from all-cause mortality and MV reintervention at 12 months in the Treatment and Control group, respectively, and d is the non-inferiority margin of 10%. [redacted] using a one-sided test with a 2.5% significance level, as described above in **Section 2.3.1.1.**

2.3.1.2.3 Improvement in KCCQ by at least 10 points at 12 months from baseline

To evaluate the benefit of the Tendyne device, the improvement in Quality of Life as measured by change in the KCCQ scores at 12 months from baseline will be compared between the Treatment and Control

groups.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_D - P_C \leq - d$

$\mathbf{H_1}$: $P_D - P_C > - d$

where P_D and P_C represent the proportion of subjects who improve at least 10 points in KCCQ score at 12 months from baseline in the Treatment and Control groups, respectively, and *d* is the non-inferiority margin of 15%. [redacted]

[redacted]

2.3.1.2.4 Proportion of Patients with NYHA Functional Classification I or II at 12 months

To evaluate improvement in heart failure symptoms, the proportion of NYHA Functional Classification I or II at 12 months will be compared with that at baseline.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_D - P_C \leq - d$

$\mathbf{H_1}$: $P_D - P_C > - d$

where P_D and P_C represent the proportion of subjects with NYHA Classification I/II at 12 months for treatment and control, respectively, and *d* is the non-inferiority margin of 15%. [redacted]

[redacted]

2.*3*.1.2.5 Improvement in Six-Minute Walk Test Distance by at least 50 meters at 12 months from baseline

To evaluate the benefit of the Tendyne device, the increase in the Six-Minute Walk Test distance will be compared between the Treatment and Control groups.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_D - P_C \leq - d$

$\mathbf{H_1}$: $P_D - P_C > - d$

where P_D and P_C represent the proportion of subjects increasing their Six-Minute Walk Test distance by at least 50 feet from baseline at 12 months in the Treatment and Control groups, respectively, and d is the non-inferiority margin of 15%. [redacted]

[redacted]

2.3.2 Non-Repairable Cohort

2.3.2.1 Non-Repairable Cohort – Primary Endpoint

The primary endpoint for the Non-repairable cohort is freedom from all-cause mortality and heart failure hospitalization at 12-months post the index procedure. The trial is intended to demonstrate that the primary endpoint event rate in subjects treated with the Tendyne™ Transcatheter Mitral Valve System does not exceed a pre-specified performance goal.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $\pi_D \leq \pi_{PG}$

$\mathbf{H_1}$: $\pi_D > \pi_{PG}$

where π_D is the true event rate of freedom from all-cause mortality and heart failure hospitalizations at 12-months post the index procedure, and π_{PG} is the performance goal. The performance goal (PG) is set at 45% (Justification of the PG is provided in the Appendix). [redacted] The null hypothesis will be tested at the one-sided 2.5% level of significance [redacted].

[redacted]

The primary analysis population for the primary endpoint is the AP population. The primary endpoint will be considered met if the null hypothesis is rejected.

2.3.2.2 Non-Repairable Cohort – Secondary Endpoints

The following secondary endpoints will be evaluated. These endpoints will be evaluated for labeling claims if the primary endpoint for the Non-repairable cohort is met. The primary analysis population for the secondary endpoint of the Non-repairable cohort is the AP population.

2.3.2.2.1 Change in KCCQ from Baseline at 12 months

To evaluate the benefit of the Tendyne device, the Quality of Life as measured by the KCCQ scores at 12 months will be compared with those from baseline.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $D_{12M} \leq 0$

$\mathbf{H_1}$: $D_{12M} > 0$

Where D_{12M} is the average change in KCCQ score from baseline at 12 months. [redacted] one-sided 2.5% significance level.

[redacted]

2.3.2.2.2 Improvement of NYHA Functional Classification I or II at 12 months

The proportion of subjects with NYHA Functional Classification I or II at 12 months will be evaluated at two-sided 5% level of significance [redacted].

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_{M12} = P_B$

$\mathbf{H_1}$: $P_{M12} \neq P_B$

where P_{M12} and P_B represent the proportion of NYHA Classification I or II at 12 months and baseline, respectively.

[redacted]

2.3.2.2.3 Change in Six-Minute Walk Test Distance from Baseline at 12 months

To evaluate the benefit of the Tendyne device, the distance walked at 12 months as measured by the 6MWT will be compared with those from baseline.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $D_{12M} \leq 0$

$\mathbf{H_1}$: $D_{12M} > 0$

Where D_{12M} is the average change in 6MWT distance from baseline at 12 months. [redacted] one-sided 2.5% significance level.

[redacted]

[redacted]

2.3.2.2.4 Change in KCCQ from Baseline at 6 months

To evaluate the benefit of the Tendyne device, the Quality of Life as measured by the KCCQ scores at 6 months will be compared with those from baseline.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $D_{6M} \leq 0$

$\mathbf{H_1}$: $D_{6M} > 0$

Where D_{6M} is the average change in KCCQ score from baseline at 6 months. [redacted] at the one-sided 2.5% significance level.

2.3.2.2.5 Change in Six-Minute Walk Test Distance from Baseline at 6 months

To evaluate the benefit of the Tendyne device, the distance walked at 6 months as measured by the 6MWT will be compared with those from baseline.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $D_{6M} \leq 0$

$\mathbf{H_1}$: $D_{6M} > 0$

Where D_{6M} is the average change in 6MWT distance from baseline at 6 months. [redacted] the one-sided 2.5% significance level. [redacted]

2.3.3 Severe MAC Cohort

2.3.3.1 Severe MAC Cohort – Primary Endpoint

The primary endpoint for the Severe MAC Cohort is freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $\pi_D \leq \pi_{PG}$

$\mathbf{H_1}$: $\pi_D > \pi_{PG}$

where π_D is the true event rate for the composite of freedom from all-cause mortality and heart failure hospitalization at 12 months and π_{PG} is the performance goal. The performance goal is set at 43% [redacted] The null hypothesis will be tested at the one-sided 2.5% level of significance [redacted].

[redacted]

The primary analysis population for the primary endpoint is AP population. The primary endpoint will be considered met if the null hypothesis is rejected.

2.3.3.2 Severe MAC Cohort – Secondary Endpoints

The following secondary endpoints will be evaluated. These endpoints will be evaluated for labeling claims if the primary endpoint for the Severe MAC Cohort is met. The primary analysis population for the secondary endpoints of the Severe MAC Cohort is AP population.

2.3.3.2.1 Freedom from MR > mild (1+) at 30 days post index procedure

The proportion of subjects with MR ≤ mild (1+) at 30 days post the index procedure will be compared to a pre-specified performance goal.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $P_D \leq P_{PG}$

$\mathbf{H_1}$: $P_D > P_{PG}$

where P_D is the proportion of subjects with MR ≤ mild (1+) at 30 days post the index procedure and P_{PG} is the performance goal. The P_{PG} is set at 75%. [redacted] one-sided 2.5% significance level. [redacted]

[redacted]

2.3.3.2.3 Change in KCCQ from Baseline at 12 months

To evaluate the benefit of the Tendyne device, the Quality of Life as measured by the KCCQ scores at 12 months will be compared with those from baseline.

The null and alternative hypotheses are:

$\mathbf{H_0}$: $D_{12M} \leq 0$

H_1: $D_{12M} > 0$

Where D_{12M} is the average change in KCCQ score from baseline at 12 months. [redacted] at the one-sided 2.5% significance level.

[redacted]

2.3.3.2.3 Improvement of NYHA Functional Classification I or II at 12 months

The proportion of subjects with NYHA Functional Classification I or II at 12 months will be evaluated at two-sided 5% level of significance [redacted].

The null and alternative hypotheses are stated as:

H_0: $P_{M12} = P_B$

H_1: $P_{M12} \neq P_B$

where P_{M12} and P_B represent the proportion of NYHA Classification I or II at 12 months and baseline, respectively.

[redacted]

2.3.3.2.4 Change in Six-Minute Walk Test Distance from Baseline at 12 months

To evaluate the benefit of the Tendyne device, the distance walked at 12 months as measured by the 6MWT will be compared with those from baseline.

The null and alternative hypotheses are:

H_0: $D_{12M} \leq 0$

H_1: $D_{12M} > 0$

Where D_{12M} is the average change in 6MWT distance from baseline at 12 months. [redacted] at the one-sided 2.5% significance level.

[redacted]

2.3.4.2.5 Change in KCCQ from Baseline at 6 months

To evaluate the benefit of the Tendyne device, the Quality of Life as measured by the KCCQ scores at 6 months will be compared with those from baseline.

The null and alternative hypotheses are:

H_0: $D_{6M} \leq 0$

H_1: $D_{6M} > 0$

Where D_{6M} is the average change in KCCQ score from baseline at 6 months. [redacted] one-sided 2.5% significance level.

2.3.3.2.6 Change in Six-Minute Walk Test Distance from Baseline at 6 months

To evaluate the benefit of the Tendyne device, the distance walked at 6 months as measured by the 6MWT will be compared with those from baseline.

The null and alternative hypotheses are:

H_0: $D_{6M} \leq 0$

H_1: $D_{6M} > 0$

Where D_{6M} is the average change in 6MWT distance from baseline at 6 months. [redacted] at the one-sided 2.5% significance level. [redacted]

2.4 Sample Size Calculations

[redacted]

2.4.1 Sample Size Calculation – Randomized Cohort

2.4.1.1 Sample Size Calculation – Randomized Cohort – Primary Endpoint

The sample size, for the Randomized Cohort, is determined based on the primary endpoint of freedom from all-cause mortality and heart failure hospitalizations (HFH) at 12 months. The primary endpoint will be analyzed based on ITT population in which the Tendyne group tested against the MitraClip group for non-inferiority. The null and alternative hypotheses are stated in Section 2.3.1.1. [redacted]

[redacted]

2.4.1.2 Sample Size Calculation – Randomized Cohort – Secondary Endpoint

2.4.1.2.1 Freedom from MR > mild (1+) at 30 days Post Procedure

The power of the secondary endpoint for the Randomized Cohort, freedom from MR > mild (1+) at 30 days post procedure is also evaluated. The secondary endpoint will be analyzed based on the ITT population in which the Tendyne group tested against the MitraClip. The null and alternative hypotheses are stated in Section 2.3.1.2. [redacted]

[redacted]

2.4.2 Sample Size Calculation – Non-Repairable Cohort

The sample size, for the Non-repairable cohort, is determined based on the primary endpoint of freedom from all-cause mortality and heart failure hospitalization at 12 months. [redacted] The null and alternative hypotheses are stated in Section 2.3.2.1. [redacted]

[redacted]

2.4.3 Sample Size Calculation – Severe MAC Cohort

The sample size, for the Severe MAC Cohort, is determined based on the primary endpoint of freedom from all-cause mortality and heart failure hospitalizations (HFH) at 12 months. [redacted] The null and alternative hypotheses are stated in Section 2.3.3.1. [redacted]

2.5 Interim Analysis

No interim analysis is planned for this study.

2.6 Timing of the Analysis

The analysis of the primary endpoints and secondary endpoints of the Randomized, Non-repairable and Severe MAC Cohorts will be assessed when all registered subjects in the corresponding cohorts complete 12 months of follow-up.

2.7 Trial Success

2.7.1 Trial Success - Randomized Cohort

The Randomized Cohort will be considered successful if the primary composite endpoint meets non-inferiority test. Additional labeling claims may be made based on the secondary endpoints.

2.7.2 Trial Success - Non-Repairable Cohort

The Non-repairable Cohort will be considered successful if the primary composite endpoint meets the pre-specified performance goal. Additional labeling claims may be made based on the secondary endpoints.

2.7.3 Trial Success - Severe MAC Cohort

The Severe MAC Cohort will be considered successful if the primary endpoint meets the pre-specified performance goal. Additional labeling claims may be made based on the secondary endpoints.

2.8 Subgroups for Analysis

For a comprehensive understanding of the device performance and safety profile in specific subgroups, the following subgroup analyses of the primary endpoint are planned:

- Age: ≥ Median baseline age, < Median baseline age,
- Sex: Male, Female
- Baseline NYHA: II, III/IV

- Etiology of Heart Failure: Ischemic, Non-ischemic
- MR Etiology: Primary MR, Secondary MR

[redacted]

2.8.1 Subgroup Analysis – Randomized Cohort

[redacted]

2.8.2 Subgroup Analysis – Non-Repairable Cohort

[redacted]

2.8.3 Subgroup Analysis – Severe MAC Cohort

[redacted]

2.9 Handling of Missing Data

Analysis will be performed on all evaluable data. [redacted]

2.10 Poolability Issue

All analyses will be performed by pooling data across study sites for the Randomized, Non-repairable and

Severe MAC Cohorts, respectively. Analysis will be conducted within each cohort to assess poolability of the primary endpoint across clinical trial sites.

[redacted]

2.11 Multiplicity Issues

The SUMMIT trial will be considered as three independent Cohorts: a Randomized cohort, a Non-repairable cohort and a Severe MAC Cohort. There is no multiplicity adjustment among the three cohorts.

2.11.1 Multiplicity – Randomized Cohort

For the Randomized cohort, hypothesis testing is planned for one primary endpoint and five secondary endpoints. If the primary endpoint is met, secondary endpoints will be evaluated for labeling claims. The first two and the group of the last three secondary endpoints will each be tested at the one-sided significance level of 2.5% and sequentially in the following order:

[redacted]

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[redacted]

2.11.2 Multiplicity – Non-Repairable Cohort

For the Non-repairable Cohort, hypothesis testing is planned for one primary endpoint and five secondary endpoints. If the primary endpoint is met, the secondary endpoints will be evaluated for labeling claims. The five secondary endpoints will each be tested sequentially, as described in Section 2.3.2.2 above, in the following order:

1. Improvement in KCCQ at 12 months from baseline
2. Proportion of NYHA Functional Classification of I or II at 12 months
3. Improvement in Six-Minute Walk Test Distance at 12 months from baseline
4. Improvement in KCCQ at 6 months from baseline
5. Improvement in Six-Minute Walk Test Distance at 6 months from baseline

2.11.3 Multiplicity – Severe MAC Cohort

For the Severe MAC Cohort, hypothesis testing is planned for one primary endpoint and six secondary endpoints. If the primary endpoint is met, secondary endpoints will be evaluated for labeling claims. The six secondary endpoints will each be tested sequentially, as described in Section 2.3.3.2 above, in the following order:

1. Freedom from MR > mild (1+) at 30 days post index procedure
2. Improvement in KCCQ at 12 months from baseline
3. Proportion of NYHA Functional Classification of I or II at 12 months
4. Improvement in Six-Minute Walk Test Distance at 12 months from baseline
5. Improvement in KCCQ at 6 months from baseline
6. Improvement in Six-Minute Walk Test Distance at 6 months from baseline

2.12 Adjustment for Covariates

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

2.13 Sensitivity Analysis

2.13.1 COVID-19

To understand the impact of the COVID-19 pandemic on the clinical outcomes, sensitivity analysis for the primary endpoints in all cohorts will be conducted by including all follow-up data and all the CEC adjudicated events, regardless of COVID-19 relatedness.

[redacted]

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, ethnicity, race, height, weight, medical history, health status, quality of life, functionality, MR classification and quantification, echocardiographic measures, medications, etc.

3.2 Adverse Events

All serious adverse device or procedure effects and UADEs will be summarized for all subjects who are randomized (ITT population of Randomized cohort) or underwent an attempted procedure (AP population for Non-repairable or Severe MAC Cohorts) in this trial in terms the number of events, the percentage of subjects with events. All CEC adjudicated adverse events will also be summarized similarly for all mITT, PP and AP populations. Moreover, COVID-19 related AEs will be summarized in terms of number of events, the percentage of subjects with events per MedDRA code.

3.3 Subject Early Termination

Subject early termination reasons including death, withdrawal, lost-to-follow-up, etc. will be summarized by treatment group at all scheduled visits

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects with reported protocol deviations in the Randomized, Non-repairable, and Severe MAC Cohorts, separately. COVID-19 related protocol deviations will also be summarized.

3.5 Descriptive Endpoints or Additional Data

The following descriptive endpoint will be analyzed for Randomized, Non-repairable and Severe MAC Cohorts.

3.5.1 Clinical Endpoints

The clinical endpoints, described in **Section 1.4.3**, will be reported using descriptive statistics as described in **Section 2.2**.

3.5.2 MVARC Endpoints

The MVARC endpoints, Technical Success, Procedure Success, Device Success, and Patient Success, described in **Section 1.4.3**, will be reported using descriptive statistics as described in **Section 2.2**.

3.5.3 Echocardiographic Endpoints

The echocardiographic endpoints, as described in **Section 1.4.3,** will be reported at baseline, discharge, 3 months, 6 months, 12 months, and then annually through 5 years using descriptive statistics as described in **Section 2.2**.

3.5.4 Device and Procedure-Related Endpoints

The following device and procedure-related acute endpoints will be reported:

- Implant Rate: defined as the rate of successful delivery and deployment of Tendyne device with retrieval of the delivery catheter
- Device Time: defined as the time elapsed from the start of the apex penetration to the time the tether tensioning ends

- Device Procedure Time: defined as the time elapsed from the first incision to the time of skin closure
- Total Procedure Time: defined as the time elapsed from the start time of anesthesia to time of skin closure
- Fluoroscopy duration: defined as the duration of exposure to fluoroscopy during the procedure

3.5.5 Analysis of Roll-In Subjects

Data from roll-in subjects will be analyzed using similar descriptive statistics as described for the Non-repairable cohort. [redacted]

3.5.6 Analysis of Tendyne GEN II Subjects

[redacted]

3.5.7 Analysis of Subjects Excluded from Non-repairable Cohort

[redacted]

4.0 DOCUMENTATION AND OTHER CONSIDERATIONS

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

5.0 ACRONYMS AND ABBREVIATIONS

Acronym	Definition	Acronym	Definition
6MWD/T	Six Minute Walk Distance/Test	LVESD	Left Ventricular End Systolic Dimension
AE	Adverse Event	LVESV	Left Ventricular End Systolic Volume
CABG	Coronary Artery Bypass Grafting	LVOT	Left Ventricular Outflow Tract
CEC	Clinical Events Committee	MI	Myocardial Infarction
CIP	Clinical Investigational Plan	MR	Mitral Regurgitation
COPD	Chronic Obstructive Pulmonary Disease	MV	Mitral Valve
CRT	Cardiac Resynchronization Therapy	MVARC	Mitral Valve Academic Research Consortium
CT	Computerized Tomography	MVRR	Mitral Valve Repair / Replacement
CV	Cardiovascular	NYHA	New York Heart Association
CVA	Cerebrovascular Accident	PAS	Pulmonary Artery Systolic pressure
DD	Device Deficiency	PCI	Percutaneous Coronary Intervention
DSMB	Data and Safety Monitoring Board	PROM	Predicted Risk of Mortality
EROA	Effective Regurgitant Orifice Area	QoL	Quality of Life
FDA	U.S. Food and Drug Administration	RCT	Randomized Control Trial
HF	Heart Failure	RVSP	Right Ventricular Systolic Pressure
HFH	Heart Failure Hospitalization	SAE	Serious Adverse Event
ICD	Implantable Cardioverter Defibrillator	SEC	Subject Eligibility Committee
KCCQ	Kansas City Cardiomyopathy Questionnaire	STS	Society of Cardiothoracic Surgeons
LV	Left Ventricle	TEE	Transesophageal Echocardiogram
LVEDD	Left Ventricular End Diastolic Dimension	TTE	Transthoracic Echocardiogram
LVEDV	LVEDV Left Ventricle End Diastolic Volume	TMVI	Transcatheter Mitral Valve Implantation
LVEF	Left Ventricular Ejection Fraction	UADE	Unanticipated Adverse Device Effect

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7.0 APPENDICES

APPENDIX I. JUSTIFICATION OF NON-INFERIORITY MARGIN AND PERFORMANCE GOAL IN THE HYPOTHESIS TESTS

A. Randomized Cohort: Non-inferiority Margin for Primary Endpoint

[redacted]

Statistical Analysis Plan

[redacted]

B. Randomized Cohort-Secondary Endpoints:

Non-inferiority Margin for Freedom from All-cause Mortality and MV reintervention at 12 months

[redacted]

Non-inferiority Margin for Improvement in KCCQ by at least 10 points at 12 months from baseline; NYHA I/II at 12 months and Improvement in 6MWD by at least 50 meters at 12 months from baseline

[redacted]

[redacted]

Statistical Analysis Plan

[redacted]

C. Non-Repairable Cohort: Performance Goal for the Primary Endpoint

[redacted]

D. Severe MAC Cohort: Performance Goal for the Primary Endpoint

[redacted]

E. Severe MAC Cohort-Secondary Endpoints

Performance Goal for Freedom from MR > mild (1+) at 30 days post procedure

[redacted]

Statistical Analysis Plan

APPENDIX II. LITERATURE REVIEW ON 12-MONTH MORTALITY AND HOSPITALIZATION DATA

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[redacted]	[redacted]	[redacted]

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Table 2. One-Year Mortality and Heart Failure Hospitalizations in Patients Treated with Optimal Medical Therapy (OMT)

Statistical Analysis Plan

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Statistical Analysis Plan

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[redacted]					
[redacted]					
[redacted]					

Table 3. One-Year Mortality and Heart Failure Hospitalizations in Randomized Patients

Reference	Therapy	N	1-Year Mortality	1-Year HF Hospitalizations	Notes
[redacted]					
[redacted]					

[1] Report on file. Abbott Vascular 2017.

Statistical Analysis Plan

APPENDIX III: DIAGRAM OF TRIAL DESIGN AND ENDPOINTS

[redacted]

Statistical Analysis Plan

APPENDIX IV: R-CODE FOR SAMPLE SIZE CALCULATIONS

[redacted]

Statistical Analysis Plan

[redacted]

Statistical Analysis Plan

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Statistical Analysis Plan

[redacted]

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[redacted]

Statistical Analysis Plan

APPENDIX V: TIPPING POINT ANALYSIS

[redacted]

Statistical Analysis Plan

[redacted]

Statistical Analysis Plan

[redacted]

Statistical Analysis Plan

APPENDIX VI: STATISTICAL ANALYSIS PLAN FOR MAC CONTINUED ACCESS Plan (CAP)

Vi.1.0 SYNOPSIS OF STUDY DESIGN

VI.1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Protocol CS0004-P, [redacted], the SUMMIT Severe MAC clinical trial continuous access plan (CAP).

VI.1.2 Clinical Investigational Objectives

The objective of the SUMMIT Severe MAC CAP is to ensure continued access to the Tendyne™ Transcatheter Mitral Valve System for subjects with severe MAC rendering the subject unsuitable for mitral valve surgery, while also providing additional experience for operators and supplementary safety and effectiveness data on the Tendyne™ Transcatheter Mitral Valve System.

1.3 Clinical Investigational Design

This SUMMIT Severe MAC CAP is a prospective, single armed, multicenter clinical investigation of the Tendyne™ Transcatheter Mitral Valve System for the treatment of eligible subjects with severe mitral annular calcification (MAC) for whom the site heart team deems transcatheter treatment is more appropriate than conventional mitral valve surgery, in which all subjects will receive treatment with the Tendyne system.

The Severe MAC CAP will begin once the Severe MAC cohort of the SUMMIT trial (CS0004-P, [redacted]) has completed enrollment.

All subjects will be followed at 30 days, 90 days, 6 months, 12 months, and annually thereafter through 5 years from the index procedure.

VI.1.4 Endpoints

VI.1.4.1 Primary Endpoints

Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure.

VI. 1.4.2 Secondary Endpoints

- Freedom from MR > mild (1+) in severity at 30 days post index procedure among survivors
- Change in QoL, as measured by the KCCQ from baseline at 6 months and 12 months
- Improvement of NYHA Functional Classification I or II at 12 months

- Change in 6MWD from baseline to 6 months and 12 months

VI.1.4.3 Descriptive Endpoints
Additional descriptive endpoints include:

VI.1.4.3.1 Clinical Endpoints:

- All-cause mortality, CV hospitalizations, all stroke or MV reintervention or reoperation, at 2 years post index procedure and then yearly through 5 years
- Change from baseline in distance walked on the 6MWT at each follow-up visit
- Change from baseline in QoL, as measured by the KCCQ at each follow-up visit
- Change from baseline in health outcomes, as measured by the EQ-5D questionnaire, at each follow-up visit
- Change from baseline in health outcomes, as measured by the 12-item Short Form Health Survey (SF-12), at each follow-up visit
- NYHA Functional Classification at each follow-up visit
- Number of days alive and out of hospital from the time of the index procedure to 12 months, and then yearly through 5 years
- Length of index hospitalization for procedure
- Annualized rate of heart failure hospitalizations
- Change from baseline in BNP or NT pro-BNP levels, at all follow-up visits
- All-cause mortality at 30 days, 1 year and then yearly through 5 years

VI.1.4.3.2 MVARC Endpoints:

- Technical Success
- Device Success
- Procedural Success
- Patient Success

The definitions for the above endpoints can be found in Appendix II of Protocol CS0004-P, the SUMMIT clinical trial.

VI.1.4.3.3 Echocardiographic Endpoints:
The following echocardiographic endpoints, as adjudicated by the Echocardiography Core Laboratory, will be reported at baseline, discharge, 1 month, 6 months, 12 months, and then annually through 5 years. For continuous variables, change from baseline to each follow-up will also be reported:

- MR severity grade
- Effective Regurgitant Orifice Area (EROA)

- Regurgitant Volume
- Regurgitant Fraction
- Left Ventricle End Diastolic Volume (LVEDV)
- Left Ventricular End Systolic Volume (LVESV)
- Left Ventricular End Diastolic Dimension (LVEDD)
- Left Ventricular End Systolic Dimension (LVESD)
- Left Ventricular Ejection Fraction (LVEF)
- Right Ventricular Systolic Pressure (RVSP)
- Mitral Valve Area
- Mean Mitral Valve Gradient
- Mean Left Ventricular Outflow Tract Gradient
- Cardiac Output
- Forward Stroke Volume

VI.2.0 ANALYSIS CONSIDERATIONS

VI.2.1 Analysis Populations

VI.2.1.2. Attempted Procedure (AP) Population

The Attempted Procedure population will consist of subjects in whom a Tendyne procedure is attempted.

VI.2.2 Statistical Methods

There is no pre-specified hypothesis test for the Severe MAC CAP. Descriptive analysis will be performed to summarize baseline characteristics and endpoints, described in section VI.1.4 above, of the Severe MAC CAP.

VI.2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables, such as sex and NYHA classification, results will be summarized with subject counts and percentages/rates, and with exact 95% [redacted] confidence intervals. Differences between the two treatment groups, if applicable, will be summarized with the difference in proportions and [redacted] 95% confidence interval for the difference of two proportions.

VI.2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. [redacted]

VI.2.3 Endpoint Analysis

As the Coronavirus Disease 2019 (COVID-19) pandemic has spread around the globe, the following analysis mechanism will be implemented to minimize the potential confounding effect from this emerging infectious disease for the trial primary and secondary endpoints set forth in assessing trial success and labeling claims. In alignment with the guidance document "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency" updated 03-June-2020, and EU "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" updated 28-April-2020, additional consideration was given to the impact of the COVID-19 pandemic on the primary and secondary endpoints analyses for this study. As such, prespecified methods are included in the sections that follow to indicate the handling of any outcomes impacted by COVID-19 as well as efforts to minimize missing endpoint data during the COVID-19 pandemic.

Any subject experiencing a CEC-adjudicated COVID-19-related hospitalization or death, indicated as 'related' within the associated event adjudication by the CEC, will have any and all follow-up clinical data censored beginning with the event. That is, the follow-up data will not contribute toward any primary or secondary endpoint analysis, with the exception of MR severity, which will be used for all subjects in all cohorts in whom MR data are available. Furthermore, any subject having a COVID-19 infection but not experiencing a CEC adjudicated COVID-19-related hospitalization or death, as defined above, will not be censored and their data, barring other protocol deviations, will contribute in its entirety to the analysis of all endpoints.

All endpoints described in section VI.1.4 above will be descriptively summarized as described in section VI.2.2 and no formal hypothesis testing will be performed. [redacted]

VI.2.4 Sample Size Calculations

Up to 150 subjects will be enrolled in the Severe MAC CAP cohort. [redacted]

VI.2.5 Timing of Analysis

An annual report will be planned as needed and a final report will be submitted when all the subjects enrolled in the Severe MAC CAP have completed the follow up. The primary and secondary endpoints in the Severe MAC CAP will be analyzed when all registered subjects in the corresponding cohorts complete 12 months of follow-up.

VI.2.6 Subgroups for Analysis

For a comprehensive understanding of the device performance and safety profile in specific subgroups, the following subgroup analyses of the primary endpoint are planned:

- Age: ≥ Median baseline age, < Median baseline age,
- Sex: Male, Female
- Baseline NYHA: II, III/IV
- Etiology of Heart Failure: Ischemic, Non-ischemic
- MR Etiology: Primary MR, Secondary MR

[redacted]

VI.2.7 Handling of Missing Data

Analysis will be performed on all evaluable data. [redacted]

VI.2.8 Poolability Issue

Unless otherwise specified, no site poolability analyses is planned for the Severe MAC CAP.

VI.2.9 Multiplicity Issues

There is no hypothesis testing for the Severe MAC CAP study. Thus multiplicity issues are not applicable.

VI.2.10 Adjustments for Covariates

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

VI.2.11 Sensitivity Analysis

COVID-19

To understand the impact of the COVID-19 pandemic on the clinical outcomes, sensitivity analysis for the primary endpoints will be conducted by including all follow-up data and all the CEC adjudicated events, regardless of COVID-19 relatedness.

Subjects who do not experience any primary endpoint event and are alive will be censored on the date of their last information available. Subjects who exit from the study without experiencing any primary endpoint

event will be censored on the date of exit. Duration of follow-up will be calculated from the date of index procedure.

VI.3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

VI.3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, ethnicity, race, height, weight, medical history, health status, quality of life, functionality, MR classification and quantification, echocardiographic measures, medications, etc.

VI.3.2 Adverse Events

All serious adverse device or procedure effects and UADEs will be summarized for all subjects who underwent an attempted procedure in the Severe MAC CAP in terms the number of events, the percentage of subjects with events. Moreover, COVID-19 related AEs will be summarized in terms of number of events, the percentage of subjects with events per MedDRA code.

VI.3.3 Subject Early Termination

Subject early termination reasons including death, withdrawal, lost-to-follow-up, etc. will be summarized at all scheduled visits.

VI.3.4 Protocol Deviation

Protocol deviations will be summarized for subjects with reported protocol deviations in the Severe MAC CAP cohort. COVID-19 related protocol deviations will also be summarized.

Statistical Analysis Plan

APPENDIX VII: STATISTICAL ANALYSIS PLAN REVISIONS

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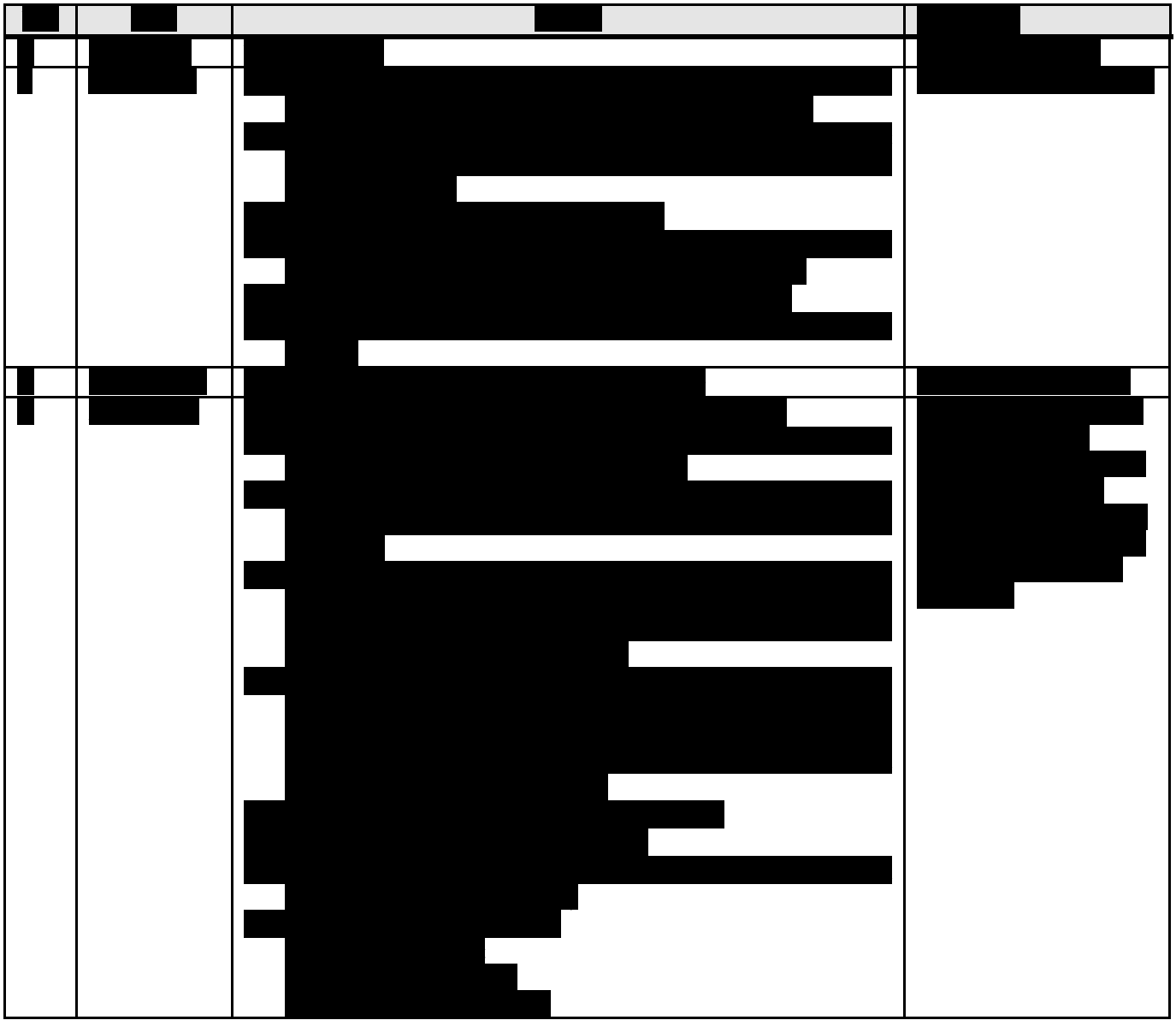

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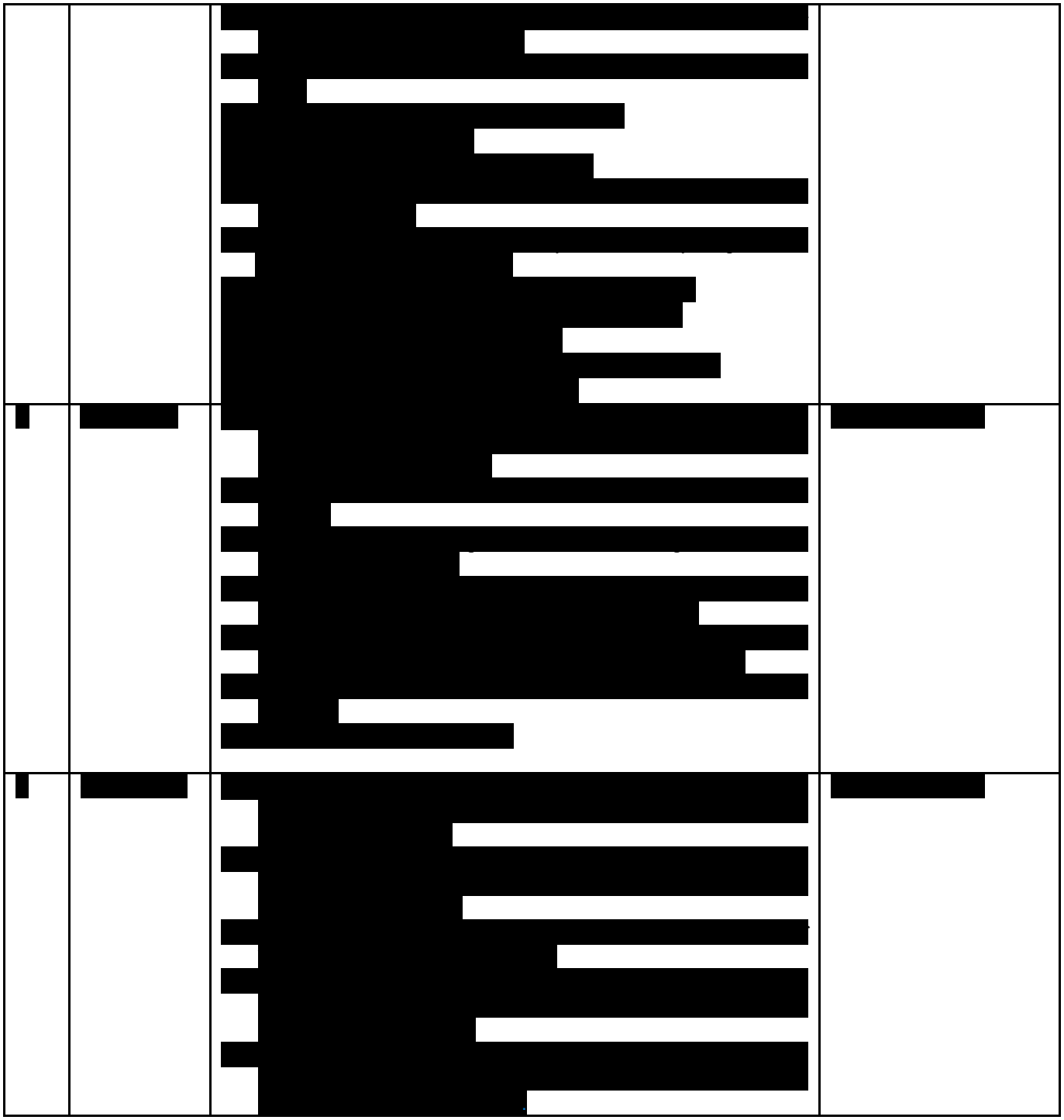

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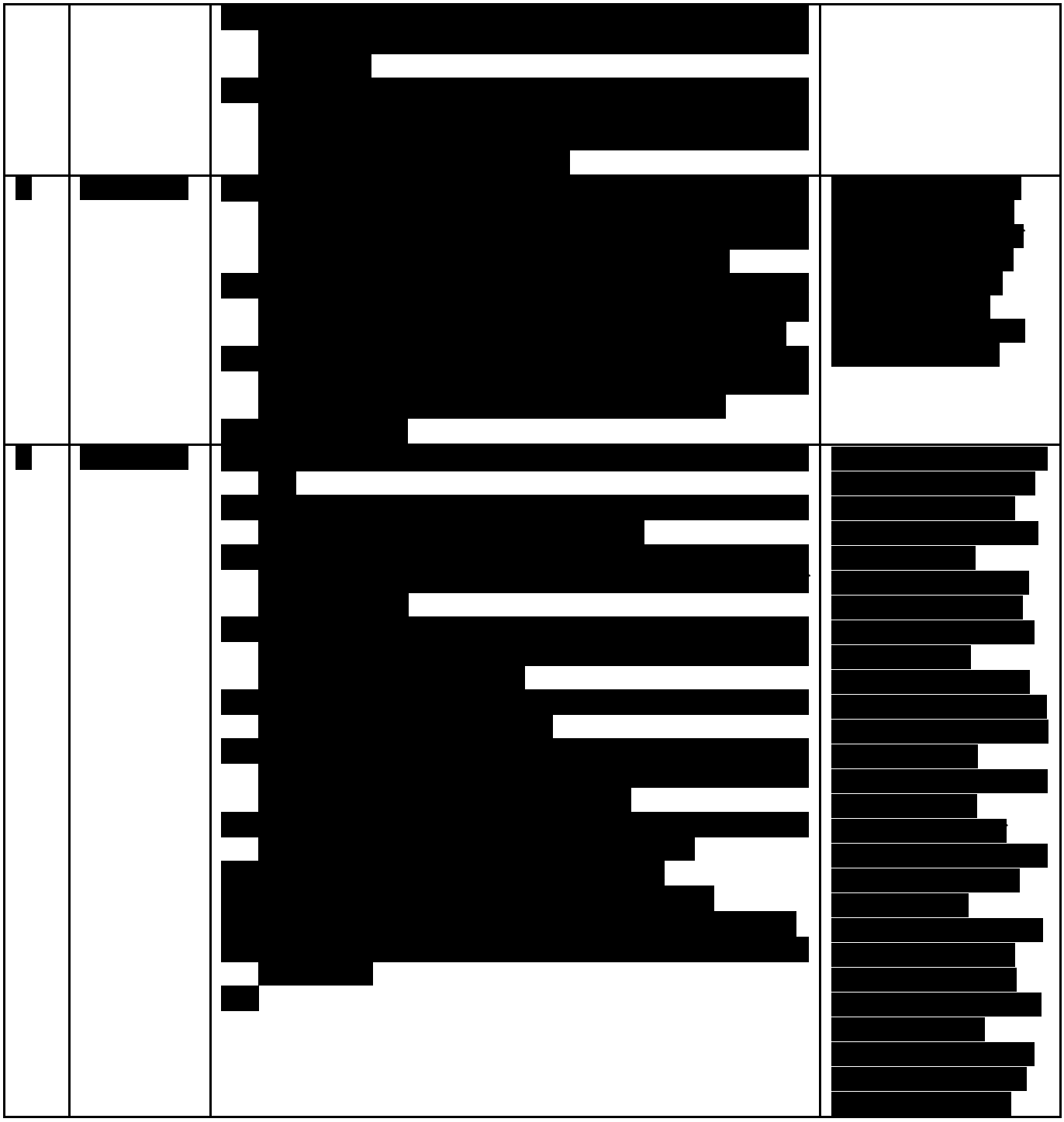

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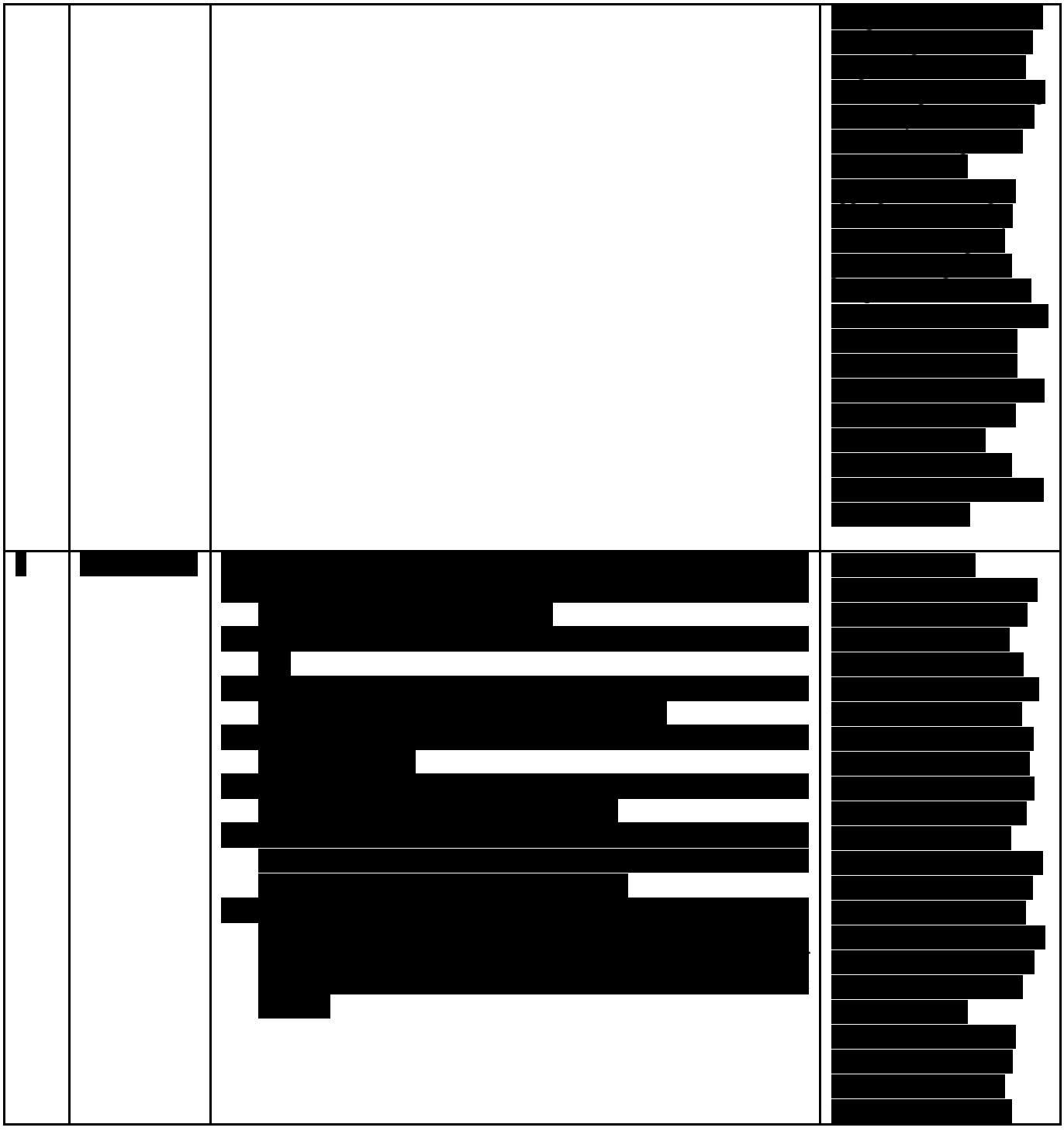

Statistical Analysis Plan

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