Statistical Analysis Plan

Prospective, Multi-Center, All-Comer MANTIS Endoscopic Clipping Study

MANTIS Clip Study

E7170

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

Lead Biostatistician – [Insert Name and Title]	Date (dd-mon-yyyy)
Clinical Project/Trial Manager – [Insert Name and Title]	Date (dd-mon-yyyy)
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Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
1	B	1, 3.1.3	Changed alpha level from 0.05 to 0.025	This was a typo in the protocol that was transferred to SAP. The sample size calculation was performed using 0.025 alpha, so nothing else changed.
2	C	1, 3, 5.5	Match protocol version C	Updating to match version C of the protocol

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1 PROTOCOL SUMMARY

MANTIS Clip Study	
Objectives	Initial Cohort To document performance of the MANTIS™ Clip in all indications for endoscopic clipping. Continued Enrollment Cohort To evaluate the procedural and clinical merit of specific attributes of the MANTIS™ Clips, specifically the ability of this new endoscopic clipping device: o to provide prophylaxis to reduce the risk of delayed bleeding post lesion resection o to close post mucosal resections/polypectomy ulcers, post submucosal dissection ulcers, or mucosal incisions made in conjunction with endoscopic myotomy procedures o to close lumenal perforations, fistulas, or leaks o to close perforations after full thickness resection of lesions in the gastrointestinal (GI) tract
Indications for Use	Resolution™ Clip family is indicated for clip placement within the GI tract for the purpose of: 1. Endoscopic marking 2. Hemostasis for: o Mucosal/sub-mucosal defects < 3 cm o Bleeding ulcers o Arteries < 2 mm o Polyps < 1.5 cm in diameter o Diverticula in the colon o Prophylactic clipping to reduce the risk of delayed bleeding post lesion resection 3. Anchoring to affix jejunal feeding tubes to the wall of the small bowel 4. As a supplementary method, closure of GI tract luminal perforations < 20 mm that can be treated conservatively
Study Device	MANTIS™ is a clip in the Resolution 360 Clip product family.

MANTIS Clip Study	
Study Procedure	The portion of the endoscopic procedure where the MANTIS™ Clip is used for hemostasis, closure, anchoring or marking.
Study Design	Prospective, multi-center, open label • Group A: Hemostasis • Group B: Closure • Group C: Anchoring • Group D: Endoscopic Marking • Group E: Other
Number of Subjects and Sites	• Initial Cohort: Up to 50 cases • Continued Enrollment Cohort: 240 cases • Up to 15 sites globally
Primary Effectiveness Endpoint	Initial Cohort Ability to complete the indication for the use of endoscopic clipping Continued Enrollment Cohort Clinical success defined as, where applicable, o Absence of delayed bleeding o Sustained closure of the targeted leasion up to 30 days after the endoscopic clipping procedure
Primary Safety Endpoint	Rate of serious adverse events (SAEs) related to the MANTIS™ clip or the endoscopic study portion of the procedure. NOTE: If providing hemostasis to an active bleed requires possible additional hemostasis after the index study procedure for management of bleeding SAEs within 7 days[36] of the index study procedure, then such bleeding SAEs are not counted for the Primary Safety Endpoint.
Additional Endpoints	1. Technical success at placement defined as ability to deploy the endoscopic clips in satisfactory position. 2. Ability to anchor device, mobilize the tissue, and approximate defect edges for secured closure. (Group B only).

MANTIS Clip Study	
	3. Post procedural bleeding, defined as a severe bleeding event that required hospitalization, a blood transfusion (>5 units), or another invasive intervention (angiographic or surgery) within 30 days after the study clip placement. 4. For active bleeding hemostasis cases only a. Rate of patients requiring additional modalities of hemostasis. b. Report of hemostasis of active bleeding 7 days after the index study procedure, defined as ability to stop the active bleed at the time of the study procedure and/or with additional clipping procedures to provide hemostasis of continued or recurrent bleeding within 7 days of the index study procedure
Follow-up Schedule	• Baseline • Procedure • 30 day follow up (both Initial and Continued Enrollment Cohort)
Study Duration	Enrollment is expected to be completed in approximately 18 months; therefore the total study duration is estimated to be approximately 19 months as Subjects will be on the study for up to 30 days.
Key Inclusion Criteria	1. Subject indicated for endoscopic clipping per local standard of practice. 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study. NOTE: Hemostasis and closure can be needed in the setting of complications such as perforations or acute bleeding that are typically rare and sometimes emergent. In such circumstances consenting the patient before the procedure is not feasible and consent shall be obtained from the patient after the procedure but before any study data is collected.
Key Exclusion Criteria	1. Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor. 2. Subjects who the investigator deems at risk for study device or procedure related complications per the Instructions for Use (IFU), where commercially available or the Investigator Brochure (IB) for countries where the study device is not approved.

MANTIS Clip Study	
Statistical Methods	Initial cohort: No hypotheses will be tested, only observational, summary statistics will be performed. Continued enrollment cohort: A systematic literature search was conducted on PubMed and Embase from January 1, 2016 to September 2022 to identify studies that evaluated the safety and effectiveness of an endoscopic clip device for closing various types of incisions, lesions, or defects in the gastrointestinal tract resulting from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), polypectomy of polyps or adenomas, perforations, and fistulas. The primary objective of the search strategy was to identify studies that examined the closure of large mucosal defects by endoscopic clipping. Twenty studies were identified through a post-market literature review activity were included to the analysis with a total of 2257 patients. We hypothesize that the **clinical success rate** of MANTIS™ clip will be greater than the performance goal of **89%** with expected clinical success rate of **94%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect: • 20 publications representing 2257 patients: 93.9% (95% CI 88.6%-97.6%) We hypothesize that the **serious adverse event (SAE) rate** related to MANTIS™ clip or the endoscopic clipping portion of the procedure will be lower than the performance goal of **19%** with expected related SAE rate of **10%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect: • 9 publications representing 1019 patients: 9.8% (95% CI 3.7%-18.5%) Using an exact test with an alpha level of 0.05, **240 subjects** enrolled will provide at least 80% power for the performance and safety metrics. These tests will only be performed for cases in the continued enrollment cohort.

2 INTRODUCTION

This statistical plan addresses the planned analyses for the study on the MANTIS Clip Study based on the protocol dated February 17, 2023 Version C. Specified analyses may be used for scientific presentation and/or manuscripts and may not all be provided to Competent Authorities.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoints

3.1.1 Primary Effectiveness Endpoint

Clinical Initial Cohort

Ability to complete the indication for the use of endoscopic clipping

Continued Enrollment Cohort

Clinical success defined as, where applicable,

- Absence of delayed bleeding
- Sustained closure of the targeted lesion (up to 30 days after the endoscopic clipping procedure)

3.1.2 Primary Safety Endpoint

Rate of serious adverse events (SAEs) related to the MANTIS™ clip or the endoscopic study portion of the procedure.

NOTE: If providing hemostasis to an active bleeding in Group A requires possible additional hemostasis after the index study procedure for management of bleeding SAEs within 7 days of the index study procedure, then such bleeding SAEs are not counted for the Primary Safety Endpoint.

3.1.3 Hypotheses and Sample Size

Initial cohort:

No hypotheses will be tested, only observational, summary statistics will be performed.

Continued enrollment cohort:

A systematic literature search was conducted on PubMed and Embase from January 1, 2016 to September 2022 to identify studies that evaluated the safety and effectiveness of an endoscopic clip device for closing various types of incisions, lesions, or defects in the gastrointestinal tract resulting from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), polypectomy of polyps or adenomas, perforations, and fistulas. The primary objective of the search strategy was to identify studies that examined the closure of large mucosal defects by endoscopic clipping. Twenty studies

were identified through a post-market literature review activity were included to the analysis with a total of 2257 patients.

We hypothesize that the **clinical success rate** of MANTIS™ clip will be greater than the performance goal of **89%** with expected clinical success rate of **94%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect:

- 20 publications representing 2257 patients: 93.9% (95% CI 88.6%-97.6%)

The null and alternative hypotheses for the primary effectiveness endpoint are as follows:

$$Ho: \pi_1 \leq 89\%$$

$$Ha: \pi_1 > 89\%$$

where π_1 is the probability of clinical success.

We hypothesize that the **serious adverse event (SAE) rate** related to MANTIS™ clip or the endoscopic clipping portion of the procedure will be lower than the performance goal of **19%** with expected related SAE rate of **10%**. These assumptions are based in the following meta-analyses of clinical success for closure of a defect:

- 9 publications representing 1019 patients: 9.8% (95% CI 3.7%-18.5%)

The null and alternative hypotheses for the primary endpoint are as follows:

$$Ho: \pi_1 \geq 19\%$$
$$Ha: \pi_1 < 19\%$$

where π_1 is the probability of an related SAE.

Using an exact test with an alpha level of 0.05, 217 subjects enrolled will provide at least 80% power for the performance and safety metrics. An additional 10% will be added for attrition, so total enrollment will be 240 subjects. These tests will only be performed for cases in the continued enrollment cohort

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

Enrolled Cohort

A subject is considered enrolled after signing the study-specific ICF. Subjects who sign the ICF, but subsequently do not meet one or more of the eligibility criteria provided in Section 8.1 and Section 8.2 will be considered screen failures and excluded from the study.

Intent-to-Treat Cohort (ITT)

This cohort consists of enrolled subjects who are planned to have a MANTIS™ clip placed regardless if they met I/E criteria.

Treated Cohort

The treated cohort is a subset of the ITT subjects who have a MANTIS™ clip placed.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

- Technical success at placement defined as ability to deploy the endoscopic clips in satisfactory position.
- Ability to anchor device, mobilize the tissue, and approximate defect edges for a secured closure.
- Post procedural bleeding, defined as a severe bleeding event that required hospitalization, a blood transfusion (>5 units) , or another invasive intervention (angiographic or surgical) within 30 days after completion of the study clip placement procedure.
- For active bleeding hemostasis cases only
    - Rate of patients requiring additional modalities of hemostasis.
    - Report of hemostasis of active bleeding 7 days after the index study procedure, and/or with additional clipping procedures to provide hemostasis of continued or recurrent bleeding within 7 days of the index study procedure

5.2 Baseline Data

Subject demographics and medical history will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

5.3 Procedure Data

Procedure data including qualitative evaluation will be collected and reported using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

5.4 Post-Procedure Data

Post-procedure information will be collected as detailed in Table 10-1.1 Data Collection Schedule from the protocol and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency statistics for discrete variables.

5.5 Interim Analyses

There will be no formal interim analyses performed.

5.6 Subgroup Analyses

Stratified analyses will include tabulating the primary and select secondary endpoints by gender, polyp location, polyp size, or use of periprocedural antithrombotic medications.

5.7 Justification of Pooling

The analyses will be performed using data pooled across institutions. An assessment of the poolability of patients across sites will be made by fitting generalized linear models with site as the factor of interest and the primary endpoints as the outcome variable.

5.8 Multivariable Analyses

Multivariable analyses may be performed to assess the effect of potential predictors on the primary endpoints and select secondary endpoints.

5.9 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

7 PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

All statistical analyses will be done using The SAS System software, version 8 or higher (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

7.2 Format of output

Results of analysis will be output programmatically to Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Rules and Definitions

- Binary event rates (proportions) will be reported on a per-patient basis.
- The last follow-up date will be the latest of the following dates for each patient: date of an adverse event, procedure date, follow-up visit date, and device event date.
- Serious Adverse Event will be defined as an adverse event that:
    - Led to death
    - Led to a serious deterioration in the health of the subject that either resulted in:
        - a life-threatening illness or injury, or
        - a permanent impairment of a body structure or a body function, or

        - in-patient hospitalization or prolonged hospitalization (of an existing hospitalization), or
        - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
- When calculating rates of adverse events, missing and partial dates will be handled as follows:

Partial Date Description	**Action Taken**
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.