AXIOS™ for Gallbladder Drainage as an Alternative to Percutaneous Drainage IDE

NCT03767881

Statistical Analysis Plan

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A Multicenter, Prospective Study of EUS-Guided Transluminal Gallbladder Drainage in Patients with Acute Cholecystitis as an Alternative to Percutaneous Gallbladder Drainage

AXIOS™ for Gallbladder Drainage as an Alternative to Percutaneous Drainage IDE

E7108

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:

TABLE OF CONTENTS

1. PROTOCOL SUMMARY

Objective(s)	To evaluate the safety and effectiveness of the AXIOS™ Stent with Electrocautery Enhanced Delivery System in the management of symptoms of acute cholecystitis as an alternative to percutaneous gallbladder drainage. It is anticipated that a transluminal EUS drainage approach with the AXIOS™ stent will provided benefits in time to resolution of acute cholecystitis as well as a lower the fraction of patients whom would require additional interventions compared to those treated with percutaneous cholecystostomy; study endpoints will be used to further evaluate.
Test Device	AXIOS™ Stent and Electrocautery Enhanced Delivery System
Control Device	None
Study Design	Prospective, single arm, multi-center trial
Planned Number of Subjects	30
Planned Number of Investigational Sites	Up to 7 centers (US and OUS)
Primary Endpoints	Primary Effectiveness Endpoint: Time to resolution of acute cholecystitis measured in days. Note: Resolution is defined as either a fever of less than 100.5°F, or at least a 4-point decrease in the pain score, or WBC count less than 12,000/cc, with improvement in at least two of these categories without the deterioration of the third category. Secondary Effectiveness Endpoint: Rate of re-interventions including but not limited to stent migration, stent occlusion by gallbladder stones, and luminal debridement.
Additional Endpoints	1. Stent patency (ability to facilitate gallbladder drainage) defined indirectly as resolution of acute cholecystitis or, in the absence of resolution of acute cholecystitis, endoscopic observation of unobstructed AXIOS™ stent lumen 2. Technical stent placement success: Successful stent placement, defined as transmural placement of the AXIOS™ stent with confirmed stent patency via (i) drainage visualized through the stent or fluoroscopically,

	or (ii) ability to endoscopically observe the inner walls of the gallbladder through the AXIOS™ stent 3. Technical stent removal success: Successful stent removal, defined as ability to remove the AXIOS™ stent endoscopically without stent removal related serious adverse events 4. Rate of recurrence of acute cholecystitis and its management 5. Number of cumulative hospital and ICU days from initial stent placement to resolution of symptoms of acute cholecystitis

2. INTRODUCTION

This statistical plan addresses the planned analyses for the Axios Gallbladder Drainage IDE Study based on protocol # 92147168. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

IMPORTANT NOTE: This SAP documents changes to the Statistical Methods outlined in the protocol. This SAP shall be following where there are any differences between the Statistical Methods in the protocol and this SAP. ***Differences to the Statistical Methods between the protocol and this SAP will be in bold, italics.***

3. ENDPOINT ANALYSIS

3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the time to resolution of acute cholecystitis measured in days.

Note: Resolution is defined as either a fever of less than 100.5°F, or at least a 4-point decrease in the pain score, or WBC count less than 12,000/cc, with improvement in at least two of these categories without the deterioration of the third category.

3.1.1 Hypothesis

The analysis of the primary effectiveness endpoint is to compare the days to clinical resolution using an AXIOS™ stent to a performance goal (PG).

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

H_0: $\mu_{days} \geq PG$

H_1: $\mu_{days} < PG$

where μ_{days} is the mean days to clinical resolution for patients in the AXIOS™ Gallbladder Drainage Study and PG is a performance goal of 3.5 days based on a literature review of percutaneous drainage studies.

3.1.2 Sample Size Calculation

This analysis of the primary effectiveness endpoint is to compare the observed days to clinical resolution for AXIOS™ stents from this study to a PG.

- Expected AXIOS™ stent (test) mean days to clinical resolution = 2.35 days with standard deviation 2 days (point estimate of days to clinical resolution based on historical rates reported in literature [1] with median days to clinical response of 1 day, range 0 to 3 days)
- PG = 3.5 days (mean days to resolution for percutaneous gallbladder (GB) drainage (PC-GBD) based on historical rates reported in literature [2])
- Test significance level (α) = ***0.025*** (1-sided)
- Power (1-β) = ***82%***
- Evaluable number of patients needed = 27
- Expected rate of attrition = 10%
- Enrolled number of patients = 30

The historical time to cholecystitis resolutions comes from 2 studies that report time to cholecystitis for endoscopic ultrasound-guided transmural gallbladder drainage (EUS-GBD) [1] and PC-GBD [2] (Table 3.1-1).

Table 3.1-1. Time to Cholecystitis Resolution (in days)

Reference	EUS-GBD	PC-GBD
Irani (2015) [1]	Median=1 (0-3) [N=15]	N/A
Kedia (2015) [2]	N/A*	Mean 4.6 [N=43]

* Endoscopic drainage was not transmural and therefore was not included in the analysis

3.1.3 Analysis

The primary effectiveness endpoint will be evaluated for all ITT patients regardless of whether an AXIOS^{TM} stent is implanted. Patients for whom an AXIOS^{TM} stent is implanted and cholecystitis is resolved will be considered a success for the endpoint and the days to resolution will be the date of resolution minus the date of the index procedure. If a patient does not receive an AXIOS^{TM} stent, the patient will be considered a failure for the endpoint with censoring at 60 days. If a subject receiving an AXIOS^{TM} stent does not achieve resolution of cholecystitis for any reason, the patient will be treated as censored in the Kaplan-Meier analysis and the days to censoring will be the date of censoring minus the date of the index procedure. The date of censoring will be the earliest of the following:

- date of the patient receiving a cholecystectomy,
- date of the patient dying,
- date of last contact for patients who withdraw from the study or are lost to follow-up, or
- date of the AXIOS^{TM} stent removal.

The mean time to resolution and standard error of the mean will be estimated from a Kaplan-Meier analysis so that subjects for whom resolution is not obtained can be included in the analysis.

The estimated mean, $\hat{\mu}_T$, from the Kaplan-Meier analysis will be calculated as:

$$\hat{\mu}_T = \int_0^T \hat{S}(t)dt$$

where $\hat{S}(t)$ is the estimated survival function from the Kaplan-Meier analysis and T is time of longest days to resolution or days to censoring. The variance of $\hat{\mu}_T$, $\hat{V}(\hat{\mu}_T)$, is estimated as:

$$\hat{V}(\hat{\mu}_T) = \sum_{i=1}^{D} \left[\int_{t_i}^{T} \hat{S}(t)dt\right]^2 \frac{d_i}{Y_i(Y_i - d_i)}$$

where D is the number of distinct times (days to resolution), t_i is the i-th time, Y_i is the number of patients at risk at time t_i, and d_i is the number of events at time t_i. The 100(1 - α)% upper bound of the confidence interval of the mean will be calculated as:

$$\hat{\mu}_T + Z_{1-\alpha}\sqrt{\hat{V}(\hat{\mu}_T)}$$

For the primary effectiveness endpoint of days to clinical resolution, testing will be performed as described below.

The estimated mean and standard error from the Kaplan-Meier analysis will be used to construct a one-sided ***97.5%*** upper confidence bound of the mean. If the upper ***97.5%*** confidence bound of the mean days to clinical resolution for the AXIOS™ group is less than the performance goal of 3.5 days, the null hypothesis will be rejected in favor of the alternative hypothesis and the mean days to resolution for the AXIOS™ group will be considered to be significantly less than the performance goal of 3.5 days.

As a worst-case scenario sensitivity analysis, the Kaplan-Meier analysis for the primary effectiveness endpoint will be re-analyzed with 60 days as the time to censoring for all censored patients with time to censoring <60 days.

3.2 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is the rate of re-interventions including but not limited to stent migration, stent occlusion by GB stones, and luminal debridement.

3.2.1 Hypothesis

The analysis of the secondary effectiveness endpoint is to compare the rate of reintervention using an AXIOS™ stent to a PG.

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

H_0: $\pi_{reint} \geq PG$

H_1: $\pi_{reint} < PG$

where π_{reint} is the rate of reintervention for patients in the AXIOS™ Gallbladder Drainage Study and PG is a performance goal of 46.2% based on reintervention rates associated with percutaneous drainage reported in literature [3, 4].

3.2.2 Sample Size Calculation

This analysis of the secondary effectiveness endpoint is to compare the observed rate of reintervention for AXIOS™ stents from this study to a PG.

- Expected AXIOS™ stent (test) rate of reintervention = 8.0% (point estimate of rate of reintervention based on historical rates reported in literature [3, 4])
- PG = 46.2% (rate of reintervention for percutaneous GB drainage based on historical rates reported in literature [3, 4])
- Test significance level (α) = ***0.025*** (1-sided)
- Power (1-β) = 99%

- Evaluable number of patients needed = 27
- Expected rate of attrition = 10%
- Enrolled number of patients = 30

The historical rates of reintervention come from 2 studies that compare the use of the AXIOS™ stent to percutaneous drainage [3, 4] (Table 3.2-1). The combined rate of reintervention from the AXIOS™ arms is 8.0% (7/87) and for the percutaneous drainage arms is 46.2% (73/158).

Table 3.2-1. Proportion of Patients with a Reintervention

Reference	EUS-GBD	PC-GBD
Irani (2017)* [3]	3/45 (6.7%)	45/45 (100.0%)
Tyberg (2016)** [4]	4/42 (9.5%)	28/113 (24.8%)
Total	7/87 (8.0%)	73/158 (46.2%)

*Reintervention defined as any procedure required to replace, check, or remove the previously placed drain or stent
**Reintervention defined as repeat procedure

3.2.3 Analysis

For the secondary effectiveness endpoint of rate of reintervention, testing will be performed as described below.

If the *P* value from the one-group binomial test comparing the rate of reintervention from the AXIOS™ stent to the performance goal is ***<0.025***, the rate of reintervention for the AXIOS™ group will be concluded to be significantly less than the performance goal for the analysis set being tested. This corresponds to the one-sided Clopper-Pearson upper ***97.5%*** confidence bound on the rate of reintervention for the AXIOS™ group being less than the performance goal of 46.2%. A sensitivity analysis (ie tipping point analysis) will be done to assess the robustness of results in the case where subjects do not have resolution of cholecystitis and no reintervention was required.

3.3 Study Success Criteria

To declare overall study success, the null hypotheses for both the primary and secondary effectiveness endpoints must be rejected in favor of the alternative hypotheses. ~~***Since the type I errors for the primary and secondary effectiveness endpoints are 2.2% and 0.3%, respectively, the type I error for the entire study is 2.5%.***~~

4. GENERAL STATISTICAL METHODS

4.1 Description of Statistical Methods

Descriptive statistics will be presented for all intent to treat (ITT) and treated patients. The primary analysis for the primary and secondary effectiveness endpoints and the additional endpoints will be assessed for the ITT cohort. The primary and secondary effectiveness endpoints and the additional endpoints will also be assessed for the Treated cohort and for the PP cohort if the PP cohort is different from the Treated cohort. The mean, standard deviation, minimum, and maximum will be used to describe continuous variables; the median (and interquartile range) will be calculated where appropriate. Frequency tables will be used to

summarize discrete variables. Proportions of subjects with adverse events and SAEs will be reported for the ITT cohort.

4.2 Analysis Sets

Enrolled Cohort - A subject will be considered enrolled when the ICF is signed.

Intent-to-treat Cohort - The intent-to-treat (ITT) cohort is defined as all subjects who signed the ICF, were evaluated for inclusion/exclusion criteria, and in whom the endoscopic procedure was initiated. Subjects in the ITT cohort will be counted towards the enrollment ceiling and this cohort will be considered the primary analysis cohort.

Treated Cohort - The treated cohort is defined as all ITT subjects who have an AXIOS™ stent implanted for the purpose of gallbladder drainage.

Per Protocol Cohort - The per-protocol cohort is defined as all treated subjects for whom an AXIOS™ stent was implanted for the purpose of gallbladder drainage and met all eligibility criteria.

4.3 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria and have signed the ICF will be eligible for enrollment in the study. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

4.4 Number of Subjects per Investigative Site

There will be no limit to the number of subjects enrolled at each investigative site.

5. ADDITIONAL DATA ANALYSES

5.1 Additional Endpoints

1. Stent patency (ability to facilitate gallbladder drainage) defined indirectly as resolution of acute cholecystitis or, in the absence of resolution of acute cholecystitis, endoscopic observation of unobstructed AXIOS™ stent lumen
2. Technical stent placement success: Successful stent placement, defined as transmural placement of the AXIOS™ stent with confirmed stent patency via (i) drainage visualized through the stent or fluoroscopically, or (ii) ability to endoscopically observe the inner walls of the gallbladder through the AXIOS™ stent
3. Technical stent removal success: Successful stent removal, defined as ability to remove the AXIOS™ stent endoscopically without stent removal related serious adverse events
4. Rate of recurrence of acute cholecystitis and its management
5. Number of cumulative hospital and ICU days from initial stent placement to resolution of symptoms of acute cholecystitis.

5.2 Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early. Informal interim analysis may be conducted for the purpose of submissions of abstracts to major professional meetings.

5.3 Subgroup Analyses

No subgroup analysis is planned.

5.4 Justification of Pooling

The analyses will be performed using data pooled across institutions. An assessment of the poolability of subjects across sites for the primary and secondary effectiveness endpoints will be made by fitting an analysis of variance (ANOVA) model and logistic regression model, respectively, with site as a factor and the primary endpoint as outcome. The following baseline variables will also be explored for pooling: region (US or outside US), acalculous/calculous cholecystitis, grade I or II cholecystitis, and prior sphincterotomy.

If the P value for the site from the pooling analysis is ≥0.15, it will be concluded that the primary endpoint is not different across sites, and the data can be pooled. If the P value for site from the ANOVA model is <0.15, site differences will be explored.

5.5 Multivariable Analyses

No multivariable analyses are planned for this study.

5.6 Other Analyses

5.6.1 Baseline Characteristics

Baseline data will be summarized to assess subject demographics, clinical history, risk factors, and pre-procedure characteristics. Data will be summarized as described in Section 4.1.

5.6.2 Post-procedural Information

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study event schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. No formal statistical testing will be performed. Data will be summarized as described in Section 4.1.

5.6.3 Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables for each visit.

5.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior will be documented in an amended Statistical Analysis Plan. Changes from the planned statistical methods after performing the analysis will be documented in the clinical study report along with a reason for the deviation.

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

Statistical data review will be performed by the sponsor. Statistical analyses will be performed using SAS System software, version 9.2 or later (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.

8. BIBLIOGRAPHY

1. Irani S, Baron TH, Grimm IS, Khashab MA. EUS-guided gallbladder drainage with a lumen-apposing metal stent (with video). Gastrointest Endosc 2015; 82: 1110-1115.
2. Kedia P, Sharaiha R, Kumta N, Widmer J, Jamal-Kabani A, Weaver K, Benvenuto A, Millman J, Barve R, Gaidhane M, Kahaleh M. Endoscopic gallbladder drainage compared with percutaneous drainage. Gastrointest Endosc 2015; 82: 1031-1036
3. Irani, Shayan, et al. "Similar Efficacies of Endoscopic Ultrasound Gallbladder Drainage with a Lumen-Apposing Metal Stent vs Percutaneous Transhepatic Gallbladder Drainage for Acute Cholecystitis." Clinical Gastroenterology and Hepatology (2017).
4. Tyberg, Amy, et al. "EUS-guided Versus Percutaneous Gallbladder Drainage: Isn't It Time to Convert?." Journal of Clinical Gastroenterology (2017).

9. REVISION HISTORY

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
A	90702621, AE	All	Original version of the SAP	