E7116

A Multicenter, Single-Arm Study of Endoscopic Ultrasound-Guided Drainage of Walled-off Pancreatic Necrosis with Lumen-Apposing Metal Stents

AXIOS WON Drainage IDE

NCT03525808

Statistical Analysis Plan

May 18, 2018

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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)
Medical Director – [Insert Name and Title]	Date (dd-mon-yyyy)

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1. PROTOCOL SUMMARY

Objective(s)	To demonstrate safety and effectiveness of lumen-apposing metal stents for resolution of walled off pancreatic necrosis (WONs) in patients with WONs with solid component >30%
Test Device	AXIOS™ Stent and Electrocautery Enhanced Delivery System
Control Device	None
Study Design	Prospective, single arm, multi-center trial
Planned Number of Subjects	40
Planned Number of Investigational Sites	Up to 6 centers
Primary Endpoints	Primary Effectiveness Endpoint: Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI Primary Safety Endpoint: AXIOS™ stent related or WON drainage procedure related serious adverse events
Additional Endpoints	1. Reduction of WON-related clinical symptoms. *Note: WON-related symptoms as defined in Inclusion Criteria #4 in the protocol* 2. Technical AXIOS™ stent placement success, defined as placement in desired location using endoscopic/EUS techniques per standard of practice. 3. Technical AXIOS™ stent removal success, defined as ability to remove the AXIOS™ stent using an endoscopic snare or forceps or graspers without AXIOS™ stent removal related serious adverse events. 4. Drainage procedural time: Time elapsed between initial puncture of the WON with electrocautery to endoscope retrieval. 5. Resolution of WON with or without necrosectomy by 6 months post AXIOS™ stent removal. 6. Time to WON resolution using same definition as for primary endpoint, namely:

	• Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI 7. Recurrence of WON after initial resolution and up to 6 months post AXIOS™ stent removal. 8. Stent lumen patency, evaluated via imaging or direct visual inspection with endoscope, and defined as one or both of the following: • Drainage through AXIOS™ stent visualized from the stomach or bowel, and/or • Visual confirmation of AXIOS™ stent lumen patency 9. Fluoroscopy (time) per endoscopic procedure. 10. Incidence of new organ failure from drainage procedure to WON resolution. 11. Change in Quality of Life score (SF-12 questionnaire) from baseline to stent removal and end of study
Primary Effectiveness Endpoint Assessment	*Note: Success will be based on the number of WONs resolved, not on the number of AXIOS™ Stents required to achieve resolution.* • If it is determined that the fluid collection is actually two separate collections, and each collection is drained via an AXIOS™ stent, then each collection will be assessed individually via the drainage success criteria of ≤3cm. • If it is determined that the fluid collection is a single collection but the drainage is inadequate via a single AXIOS™ stent, then the success of the AXIOS™ drainage will be assessed as follows: o If a second AXIOS™ stent is used at a new drainage site/original drainage site and the entire fluid collection is drained to meet the success criteria of ≤3cm then the collection will be considered to be a single collection drainage success. o If a second AXIOS™ stent is used at a new drainage site and the entire fluid collection does not drain adequately to meet the drainage success criteria of ≤3cm then the fluid drainage of the collection will be considered to be a single drainage failure. o If a plastic stent is used at a new drainage site and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered indeterminate. o If a plastic stent is used at a new drainage site and the entire fluid collection does not drain to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single drainage failure.

2. INTRODUCTION

This statistical plan addresses the planned analyses for the Axios WON Drainage IDE Study based on protocol # 92153943. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

3. ENDPOINT ANALYSIS

3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is the resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI.

Primary Effectiveness Endpoint Assessment:

Note: Success will be based on the number of WONs resolved, not on the number of AXIOS™ Stents required to achieve resolution.

- If it is determined that the fluid collection is actually two separate collections, and each collection is drained via an AXIOS™ stent, then each collection will be assessed individually via the drainage success criteria of ≤3cm.
- If it is determined that the fluid collection is a single collection but the drainage is inadequate via a single AXIOS™ stent, then the success of the AXIOS™ drainage will be assessed as follows:
  - If a second AXIOS™ stent is used at a new drainage site/original drainage site and the entire fluid collection is drained to meet the success criteria of ≤3cm then the collection will be considered to be a single collection drainage success.
  - If a second AXIOS™ stent is used at a new drainage site and the entire fluid collection does not drain adequately to meet the drainage success criteria of ≤3cm then the fluid drainage of the collection will be considered to be a single drainage failure.
  - If a plastic stent is used at a new drainage site and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered indeterminate.
  - If a plastic stent is used at a new drainage site and the entire fluid collection does not drain to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single drainage failure.

3.1.1 Hypothesis

As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement in the original IDE is 76.7% (23/30) [95% CI (57.7%, 90.0%)] patients. Given that the WONs in the proposed IDE will have an estimated necrotic material content above 30%, namely larger than in IDE #G130264, a slightly lower success rate of 70% is expected in this study. This success rate is within the range of reported WON resolution rates in several recent publications [1-7] representing 448 patients for which a random effects meta-analysis yields a mid-point WON resolution rate of 67.0% [95% CI (60.0%, 73.4%)] for WON

drainage with plastic stents (Table 1), an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [8].

Table 1. Plastic Stent WON Resolution Rates from Recent Publications [1-7]

Study	% Resolution (x/N)	95% Confidence Interval
Bapaye (2017)	73.8% (45/61)	(60.9%, 84.2%)
Gardner et al (2009)	68.9% (31/45)	(53.4%, 81.8%)
Papachristou (2007)	52.8% (28/53)	(38.6%, 66.7%)
Schmidt (2015)	61.7% (50/81)	(50.3%, 72.3%)
Smoczynski (2015)	75.9% (85/112)	(66.9%, 83.5%)
Abu Dayyeh (2017)	75.0% (27/36)	(57.8%, 87.9%)
Varadarajulu (2011)	60.0% (36/60)	(46.5%, 72.4%)
Random-Effects Meta-Analysis	**67.0%**	**(60.0%, 73.4%)**

3.1.2 Analysis

The primary effectiveness endpoint will be summarized as the proportion of patients who have resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤3cm evaluated by CT scan or MRI out of all patients who have an AXIOS™ stent successfully implanted. A Clopper-Pearson exact 95% confidence interval will also be calculated.

3.2 Primary Safety Endpoint

The primary safety endpoint is AXIOS™ stent related or WON drainage related serious adverse events for AXIOS subjects.

3.2.1 Hypothesis

As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with AXIOS™ stent related or WON drainage procedure related serious adverse events in the original IDE is 10.0% (3/30) [95% CI (2.1%, 26.5%)] patients. A similar rate of AXIOS™ stent related or WON drainage procedure related serious adverse events is expected in this study. This event rate is within the range of reported stent related or WON drainage procedure related serious adverse event rates in several recent publications [2-4, 9] representing 306 patients for which a random effects meta-analysis yields a mid-point related SAE rate of 16.7% [95% CI (10.1%, 26.3%)] for WON drainage with plastic stents (see Table 2 and Table 3 (categorized events from Table 2)), an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [8].

Table 2. Plastic Stent-related or WON Drainage-procedure related Serious Adverse Events Rates from Recent Publications [2-4, 9]

Study	% Related SAEs (x/N)	95% Confidence Interval
Papachristou (2007)	20.8% (11/53)	(10.8%, 34.1%)
Schmidt (2015)	12.3% (10/81)	(6.1%, 21.5%)
Smoczynski (2015)	25.9% (29/112)	(18.1%, 35.0%)

Study	% Related SAEs (x/N)	95% Confidence Interval
Varadarajulu (2011)	8.3% (5/60)	(2.8%, 18.4%)
Random-Effect Meta-Analysis	**16.7%**	**(10.1%, 26.3%)**

Table 3. Categorized Plastic Stent-related or WON Drainage-procedure related Serious Adverse Events Rates from Recent Publications [2-4, 9]

SAE	% (x/N)
Bleeding	11.1% (34/306)
Perforation	2.6% (8/306) [5 GI; 2 Collections; 1 Undefined]
Pneumoperitoneum	1.3% (4/306)
Sepsis	0.7% (2/306)*
Stent migration	1.0% (3/306)
Multiple organ failure	1.0% (3/306)
Other - loss of access to the collection (due to hypertension)	0.3% (1/306)

*Note: 1 patient with septic shock also had multiple organ failure (death)

3.2.2 Analysis

The primary safety endpoint will be summarized as the proportion of patients who have AXIOS™ stent related or WON drainage procedure related serious adverse events out of all patients who have an AXIOS stent successfully implanted. A Clopper-Pearson exact 95% confidence interval will also be calculated.

3.3 Sample Size and Success Criteria

The WON resolution rates and related SAE rates reported in the above provided study references are similar to those reported for WON drainage using plastic stents in a recent systematic review and meta-analysis comparing plastic stents to metal stents, including lumen-apposing metal stents (LAMS) for the management of WONs [10]. Appendix I in Section 21 of the protocol provides a few key points from this systematic review.

Although reported effectiveness and safety event rates from different sources appear similar, 95% confidence intervals are fairly wide, mostly due to small sample sizes and heterogeneity in WONs and in detailed procedural WON drainage steps. Therefore we chose to increase the sample size of the present study to be slightly larger than in the original IDE study #G130264, which was 30 patients.

We will conduct the present study in 40 patients.

3.3.1 Effectiveness Endpoint Success Criteria

An observed rate of 67% or higher for the proportion of AXIOS patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement is required for success.

This rate is the same as the point estimate of the random-effect meta-analysis of WON resolution rates for plastic stents provided in Table 1. Note that in the recent systematic review and meta-

analysis [10] (Appendix I in Section 21 of the protocol) WON resolution rates were higher and the number of procedures required to reach WON resolution were lower when using LAMS compared to plastic stents for WON drainage. Thus, the proposed success criteria for effectiveness seems reasonable.

3.3.2 Safety Endpoint Success Criteria

An observed rate of 17.5% or lower for the proportion of AXIOS patients with AXIOS™ stent related or WON drainage procedure related serious adverse events is required for success.

This rate is similar to the point estimate of the random-effect meta-analysis of AXIOS stent related or WON drainage related serious adverse events for plastic stents provided in Table 2. Note that in the recent systematic review and meta-analysis [10] (Appendix I in Section 21 of the protocol) the complication rates that showed statistically significant differences between plastic stents and LAMS for drainage of WONs were bleeding and stent occlusion, both in favor of LAMS. These findings are particularly important given that (a) bleeding is the most commonly reported serious adverse event, and (b) stent occlusion almost always requires reintervention. It should also be noted that of the plastic stent WON drainage references provided above, even the one reporting the highest complication rates, namely Smoczynski et al [4] conclude that the benefits outweigh the risks: "*In a large group of selected patients with symptomatic walled-off necrosis, endoscopic drainage enables high success rate with acceptable complication rate and low procedure-related mortality*." Thus, the proposed success criteria for safety seems reasonable and acceptable.

4. GENERAL STATISTICAL METHODS

4.1 Description of Statistical Methods

Descriptive statistics will be presented for all intent to treat (ITT) and treated patients. If the treated and per-protocol (PP) cohorts are different, the primary effectiveness and safety endpoints will also be assessed for the PP cohort. The mean (± standard deviation) will be used to describe continuous variables with a normal distribution and the median (and interquartile range) will be used to describe continuous variables with a skewed distribution. Frequency tables will be used to summarize discrete variables. Proportions of patients with adverse events and SAEs will be reported. No hypothesis testing will be performed.

4.2 Analysis Sets

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

Intent-to-treat Cohort - The 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.

Treated Cohort - The treated cohort is defined as all ITT subjects who have an AXIOS™ stent implanted for the purpose of WON drainage. Subjects in the treated cohort will be counted towards the enrollment ceiling and this cohort will be considered the primary analysis cohort.

Per Protocol Cohort - The PP cohort is defined as all treated subjects for whom an AXIOS™ stent was implanted for the purpose of WON 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. Reduction of WON-related clinical symptoms. *Note: WON-related symptoms as defined in Inclusion Criteria #4 of the protocol.*
2. Technical AXIOS^{TM} stent placement success, defined as placement in desired location using endoscopic/EUS techniques per standard of practice.
3. Technical AXIOS^{TM} stent removal success, defined as ability to remove the AXIOS^{TM} stent using an endoscopic snare or forceps or graspers without AXIOS^{TM} stent removal related serious adverse events.
4. Drainage procedural time: Time elapsed between initial puncture of the WON with electrocautery to endoscope retrieval.
5. Resolution of WON with or without necrosectomy by 6 months post AXIOS^{TM} stent removal.
6. Time to WON resolution using same definition as for primary endpoint, namely:
    - Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI.
7. Recurrence of WON after initial resolution and up to 6 months post AXIOS^{TM} stent removal.
8. Stent lumen patency, evaluated via imaging or direct visual inspection with endoscope, and defined as one or both of the following:
    - Drainage through AXIOS^{TM} stent visualized from the stomach or bowel, and/or
    - Visual confirmation of AXIOS^{TM} stent lumen patency
9. Fluoroscopy (time) per endoscopic procedure.
10. Incidence of new organ failure from drainage procedure to WON resolution.
11. Change in Quality of life score (SF-12 questionnaire) from baseline to stent removal and end of study

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 effectiveness and safety endpoints will be made by fitting logistic regression models with site as a factor and the primary effectiveness and safety endpoints as outcomes. Certain baseline variables may also be explored for pooling.

If the P value for the site is ≥0.05, it will be concluded that the endpoint is not different across sites, and the data can be pooled. If the P value for site from the logistic model is <0.05, 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).

SF-12 survey data will be evaluated using the PRO CoRE software version 1.2 (April, 2018, Optum Inc., Johnston, Rhode Island 02919, USA).

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.

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9. REVISION HISTORY

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