Statistical Analysis Plan

Version AA

Randomized Multi-Center Study Comparing No Drainage to Preoperative Biliary Drainage Using Metal Stents in Patients with Resectable Pancreatic or Periampullary Cancer

Preoperative Biliary Drainage RCT

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Revision History

Version AA - Initial Release

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Revision History

Revision Number/Release Date	Section	Change	Reason for Change

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1 PROTOCOL SUMMARY

Full Title	**Randomized Multi-Center Study Comparing No Drainage to Preoperative Biliary Drainage Using Metal Stents in Patients with Resectable Pancreatic or Periampullary Cancer**
Short Title	Preoperative Biliary Drainage RCT
Objective(s)	To demonstrate that preoperative biliary drainage using self-expanding metal stents (SEMS) improves overall surgical outcomes in patients undergoing pancreaticoduodenectomy for treatment of pancreatic or periampullary cancer.
Test Device	Devices: WallFlex Biliary RX Fully Covered stent Note: WallFlex Biliary RX Uncovered stents may be used in in some cases as outlined in the protocol Cleared Indication: The WallFlex Biliary stents are indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms; the WallFlex FC stent is also indicated for the treatment of benign biliary strictures per CE Mark.
Study Design	• Prospective, multi-center, randomized, post-market (on label) • Patients will be block randomized at baseline in a 1:1 ratio between **Group 1:** No Pre-Operative Biliary Drainage and **Group 2:** Pre-Operative Biliary Drainage with a SEMS.
Planned Number of Subjects	**294 total number of subjects:** • Group 1: 147 • Group 2: 147
Planned Number of Centers / Countries	7-12 sites Countries: Australia, Belgium, China, France, Germany, India, Italy, Japan (this list of countries may change)
Primary Endpoint	Serious pre-operative, operative and post-operative adverse events to 120 days post randomization or to 30 days post-surgery, whichever comes last

Secondary Endpoints	1. Adverse events: rate, severity, seriousness, relatedness to stent or endoscopic or surgical procedure, impact on time of surgery, length of hospitalization and ICU stay 2. Time to surgery 3. Curative Intent Surgery details pertaining to intraoperative assessment of resectability, surgical resection and reconstruction techniques 4. Intraoperative blood loss and blood transfusions, duration of surgery 5. Biliary obstructive symptoms assessment (Week 2, surgery/transition to palliation, 30 day post-operative follow up and 120 day follow up) 6. Improvement of LFT levels as relative to baseline (Week 2, surgery/transition to palliation, 30 day post-operative follow up and 120 day follow up) 7. Stent placement success: ability to deploy the stent in satisfactory position across the stricture **(Group 2)** 8. **Stent removal success:** successful SEMS removal, either *en bloc* at time of surgery or endoscopically prior to surgery without stent removal related SAEs 9. Number, type, reason and timing of biliary re-interventions 10. Number and duration of hospital and ICU admissions
Follow-up Schedule and Assessments	• **Screening:** Count all consecutive patients seen at investigational site presenting with biliary obstructive symptoms and suspicion of pancreatic cancer, distal common bile duct cholangiocarcinoma or peri-ampullary cancer. Of those, a subset will be invited to participate in trial: Informed Consent (enrollment) and Eligibility Criteria Assessment • **Baseline Visit (Day 0):** Demographics, Medical History, Tumor Diagnosis, Staging and Characteristics, Assessment of Biliary Obstructive Symptoms, Laboratory Tests, Randomization • **Stent Placement Procedure Visit (Group 2 only, Day 0):** Stent Details, Procedure Details, Adverse Events (AEs) • **Pre-Operative Visit (Week 2):** Assessment of Biliary Obstructive Symptoms, Laboratory Tests**,** AEs ***Group 1 (No Pre-Operative Biliary Drainage):*** Patients will undergo resection per institutional standard of practice. Time to surgery is not to exceed 4 weeks unless there is a need to delay

	planned surgery due to a complication, biliary obstructive symptoms, decline in patient physiologic status, or other factors that preclude surgery. ***Group 2 (Pre-Operative Biliary Drainage with a SEMS):*** Patients will undergo resection after resolution of jaundice is achieved (defined as Bilirubin below 100μmol per liter), or at 4 weeks, whichever comes first. • **Biliary Reintervention Visit (as needed):** Timing, Reason for Biliary Reintervention, Type of Biliary Reintervention, AEs Group 1 patients who fail their treatment algorithm by requiring biliary drainage prior to surgery will receive a study SEMS. Group 2 patients who require re-stenting or placement of a stent for a new stricture, will receive a study SEMS. • **Curative Intent Surgery: Assessment of Biliary Obstructive Symptoms,** Laboratory Tests**,** Operative Details, Stent Removal, Blood Loss, Intra- and Post-Operative Transfusion, Post-Operative Course, Specimen Pathology, AEs • **Transition to Palliative Management Visit (as needed): Assessment of Biliary Obstructive Symptoms,** Laboratory Tests**, AEs** • **Post-Operative Follow up Visit (30 days Post-Surgery, if applicable): Assessment of Biliary Obstructive Symptoms,** Laboratory Tests**, AEs** • **Long Term Follow-up Visit (120 days--150 days post randomization): Assessment of Biliary Obstructive Symptoms,** Laboratory Tests**, AEs** Patients who undergo surgery as planned will be evaluated at 30 days post-surgery and will be followed up to 120 days after randomization. Patients with delay in planned surgery may require follow up longer than 120 days to allow for a 30 day post-surgery follow up visit but follow up is not to exceed 150 days post-randomization. Patients with a delay in planned surgery whose rescheduled surgery is unable to occur within 120 days will be followed up to 120 days after randomization. Patients who do not undergo surgery as planned due to conversion to palliative management or patient choice will be followed up to 120 days after randomization. If patient's course of treatment requires placement of a biliary stent, stenting will be done per

	standard of care at each institution. If a metal stent is required, a study WallFlex Biliary FC stent will be placed.
Key Inclusion Criteria	1. Age 18 or older 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study 3. Diagnosis of probable pancreatic cancer, distal common bile duct (CBD) cholangiocarcinoma and other periampullary cancers (histology not required) 4. Biliary obstructive symptoms or signs 5. Bilirubin level at/above 100 μmol per liter (5.8 mg/dL) 6. Distal biliary obstruction consistent with pancreatic cancer, distal CBD cholangiocarcinoma or other periampullary malignancy 7. Location of distal biliary obstruction is such that it would allow the proximal end of a stent to be positioned at least 2 cm from the hilum 8. Patients deemed as resectable by pancreatic protocol CT or MRI 9. Surgical candidate per pancreatobiliary surgeon after multi-disciplinary discussion 10. Surgery intent within 4 weeks 11. Endoscopic and surgical treatment to be provided by same team
Key Exclusion Criteria	1. Biliary strictures caused by confirmed benign tumors 2. Biliary strictures caused by malignancies other than pancreatic, cancer, distal CBD cholangiocarcinoma and other periampullary cancers 3. Surgically altered biliary tract anatomy, not including prior cholecystectomy 4. Neoadjuvant chemotherapy for current malignancy 5. Palliative indication due to reasons other than surgical candidate status 6. Previous biliary drainage by ERCP/PTC 7. Patients for whom endoscopic techniques are contraindicated 8. Participation in another investigational trial within 90 days

	9. Pregnancy
Primary Statistical Hypothesis	A literature search of preoperative biliary drainage with self-expanding metal stents in patients with pancreatic or periampullary cancer yielded eight articles with 305 patients.[1-8] A meta-analysis of the probability for pre-operative, operative and peri-operative complications was performed. A rate of 24.2% [95% CI: 13.2%, 37.2%] was calculated using the eight articles. Statistical testing will be performed to determine if the rate of complications for the *Pre-Operative Biliary Drainage with SEMS* group is non-inferior to the *No Pre-Operative Biliary Drainage* group. The null hypothesis is that the complication rate is inferior in the *Pre-Operative Biliary Drainage with SEMS* versus the *No Pre-Operative Biliary Drainage* group: $Ho: \pi_{test} - \pi_{control} \geq \Delta$ (Inferior) $Ha: \pi_{test} - \pi_{control} < \Delta$ (Non-inferior) where π_{test} and $\pi_{control}$ are the probabilities of having pre-operative, operative and peri-operative complications in the *Pre-Operative Biliary Drainage with SEMS* arm and *No Pre-Operative Biliary Drainage* arm respectively, and Δ is defined as the non-inferiority margin. The sample size was calculated for a one-sided 0.050 exact Farrington-Manning test using StatXact 9®. If the P value from the exact Farrington-Manning test is <0.05 then the *Pre-Operative Biliary Drainage with SEMS* group will be considered non-inferior to the *No Pre-Operative Biliary Drainage* group. The expected probability of complications in the *Pre-Operative Biliary Drainage with SEMS* arm and *No Pre-Operative Biliary Drainage* arm is 37.2%, which was taken from the upper limit of the 95% CI from the meta-analysis described above and from the only available Level 1 study comparing no drainage to preoperative stenting in which the complication rate was reported to be 39% in the no drainage arm.[9] The non-inferiority margin (Δ) is 15%. Given these assumptions and a one-sided 5% significance level, 2 x 132 = 264 subjects will provide 80% power to reject the null hypothesis, that the *Pre-Operative Biliary Drainage with SEMS* group is inferior to the *No Pre-Operative Biliary Drainage* group. To compensate for possible loss of subjects after enrollment and

	complete assessment of inclusion/exclusion criteria, an additional 10% of subjects will be enrolled, for a total of 2 x 147 = 294 subjects.

2 INTRODUCTION

This statistical plan addresses the planned analyses for the WallFlex Biliary Preoperative Biliary Drainage RCT based on the protocol dated 17 October 2012, Version AC. All of the specified analyses may not be provided in reports to Competent Authorities but may be used for scientific presentations and/or manuscripts. The primary analysis will be based on the data through 120 days post-randomization or 30 days post-surgery whichever comes last.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

The rate of serious adverse events is the primary endpoint for the study.

3.1.1 Hypotheses

Statistical testing will be performed to determine if the rate of complications for the Pre-Operative Biliary Drainage with SEMS group is non-inferior to the No Pre-Operative Biliary Drainage group. The null hypothesis is that the complication rate is inferior in the Pre-Operative Biliary Drainage with SEMS versus the No Pre-Operative Biliary Drainage group:

Ho: $\pi_{\text{test}} - \pi_{\text{control}} \geq \Delta$ (Inferior)

Ha: $\pi_{\text{test}} - \pi_{\text{control}} < \Delta$ (Non-inferior)

where π_{test} and π_{control} are the probabilities of having pre-operative, operative and peri-operative complications in the Pre-Operative Biliary Drainage with SEMS arm and No Pre-Operative Biliary Drainage arm respectively, and Δ is defined as the non-inferiority margin.

3.1.2 Sample Size

A literature search of preoperative biliary drainage with self-expanding metal stents in patients with pancreatic or periampullary cancer yielded 8 articles with 305 patients.[21-24, 27-31]

The following meta-analysis of the probability for pre-operative, operative and post-operative complications was done:

- A rate of 24.2% [95% CI: 13.2%, 37.2%] was calculated using the 8 articles.

The sample size was calculated for a one-sided 0.050 exact Farrington-Manning test using StatXact 9®. If the P value from the exact Farrington-Manning test is <0.05 then the *Pre-Operative Biliary Drainage with SEMS* group will be considered non-inferior to the *No Pre-Operative Biliary Drainage* group. The expected probability of complications in the *Pre-Operative Biliary Drainage with SEMS* arm and *No Pre-Operative Biliary Drainage* arm is 37.2%, which was taken from the upper limit of the 95% CI from the meta-analysis described above and from the only available Level 1 study comparing no drainage to preoperative stenting in which the complication rate was reported to be 39% in the no drainage arm.[9] The non-inferiority margin (Δ) is 15%. Given these assumptions and a one-sided 5% significance level, 2 x 132 = 264 subjects will provide 80% power to reject the null hypothesis, that the *Pre-Operative Biliary Drainage with SEMS* group is inferior to the *No Pre-Operative Biliary Drainage* group.

To compensate for possible loss of subjects after enrollment and complete assessment of inclusion/exclusion criteria, an additional 10% of subjects will be enrolled, for a total of 2 x 147 = 294 subjects.

3.1.3 Statistical Methods

For calculating the rate of serious adverse events after randomization, patients with insufficient follow-up will be excluded from the calculation; that is, only patients that have at least follow-up through the long term visit (120/150 day follow-up) will be included unless the subject has already had a serious adverse event. All patients with a serious adverse will be counted in the analysis. Sensitivity analyses, such as a tipping point analysis will be performed to assess the impact of the missing data, assuming extremes of either no SAEs or all SAEs for the primary endpoint, if the data support such analysis.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

Primary endpoint and selected secondary endpoints will be done for the following cohorts.

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 the synopsis above will be considered screen failures and excluded from the study.

Intent-to-Treat Cohort (ITT)

This cohort consists of those "enrolled" subjects who meet all inclusion/exclusion criteria and are subsequently randomized.

Per-Protocol Cohort (PP)

The per-protocol cohort is a subset of the ITT subjects who are treated per protocol after randomization (Group 1 no stent, and Group 2 received a study stent) and who had no major protocol deviations (ICH E9 definitions).

5 ADDITIONAL DATA ANALYSES

5.1 Secondary Endpoints

1. Adverse events: rate, severity, seriousness, relatedness to stent or endoscopic or surgical procedure, impact on time of surgery, length of hospitalization and ICU stay
2. Time to surgery
3. Curative Intent Surgery details pertaining to intraoperative assessment of resectability, surgical resection and reconstruction techniques
4. Intraoperative blood loss and blood transfusions, duration of surgery
5. Biliary obstructive symptoms assessment (Week 2, surgery/transition to palliation, 30 day post-operative follow up and 120 day follow up)
6. Improvement of LFT levels as relative to baseline (Week 2, surgery/transition to palliation, 30 day post-operative follow up and 120 day follow up)
7. Stent placement success: ability to deploy the stent in satisfactory position across the stricture (Group 2)
8. Stent removal success: successful SEMS removal, either *en bloc* at time of surgery or endoscopically prior to surgery without stent removal related SAEs
9. Number, type, reason and timing of biliary re-interventions and time to first re-intervention.
10. Number and duration of hospital and ICU admissions

5.2 Baseline Data

Baseline data will be summarized. Subject demographics, clinical history, risk factors, LFTs, tumor diagnosis, and obstruction symptoms 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 Post-Procedure Endpoints

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.

5.4 Subgroup Analyses

The subgroup analyses will include tabulating the primary endpoint and select secondary endpoints by gender.

5.5 Justification of Pooling

The analyses will be presented using pooled data across institutions. An analysis of the poolability will be made using logistic regression for binary outcomes, proportional hazards regression for time-to-event outcomes, or analysis of variance for continuous outcomes, to assess differences between study institutions and to justify pooling data across institutions.

5.6 Multivariable Analysis

Univariate and multivariate analyses will be performed to assess possible predictors of the rate of serious adverse events. Possible predictors may include any but not limited to demographic/baseline data and medical history data. Factors from the univariate model with $p \leq 0.20$ will also be modeled multivariately using a stepwise procedure in a generalized linear model or Cox proportional hazards regression model. The significance thresholds for entry and exit into the model will be set to $p < 0.10$.

5.7 Analysis of LFT's and Obstruction symptoms

For analysis of LFT's and obstruction symptoms, a paired t-test and McNemar's Test will be used to test differences from baseline. The data will also be analyzed using a generalized linear model, including treatment group and baseline covariates as predictors. Interactions between time and treatment group will be explored. Other possible predictors may include any but not limited to demographic/baseline data and medical history data. Different correlation structures will be fit to determine the best model fit.

5.8 Analysis of Impact of Adverse Events on Endpoints

For an analysis on the effect of the adverse events impact on time of surgery, length of hospitalization, and ICU stay, subjects with and without AEs will be analyzed to determine if any differences occur. Appropriate testing will be done to determine this, i.e. a 2x2 ANOVA analysis with a treatment interaction.

5.9 Baseline Tumor Stage vs. Pathology Tumor Stage

A frequency table will be conducted to look for the differences between the baseline tumor stage and the pathology tumor stage diagnosis. This table will include all stages including a missing category for both time points.

5.10 Changes to Planned Analyses

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

6 VALIDATION

All clinical data reports generated per this plan will be validated per 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, index procedure date, follow-up visit date, any stent procedure/reintervention date, surgery date, stent removal 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.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

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.

Partial Date Description	Action Taken
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.

Definitions of complication criteria (per van der Gaag article):

Specific PBD (ERCP, PTC) related:

- **Acute pancreatitis** Abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase) three or more times the upper limit of normal, that required more than one night of hospitalization
- **Acute cholecystitis** No suggestive clinical or radiographic signs of acute cholecystitis before the procedure and if emergency cholecystectomy is subsequently required
- **Perforation** Retroperitoneal or bowel-wall perforation documented by any radiographic technique or direct visual evidence
- **Stent Occlusion** Recurring obstructive jaundice with necessary stent replacement

Specific surgery related:

- **Pancreaticojejunostomy leakage** Drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity, graded according to clinical course (ISGPS grade A, B, C), or direct visual evidence of defect at anastomosis
- **Delayed gastric emptying** Gastric stasis requiring nasogastric intubation for 10 days or more, or the inability to tolerate a regular (solid) diet on or before the fourteenth postoperative day, not due to sequelae of intra-abdominal complications (i.e. abscess, anastomotic leakage)
- **Biliary leakage** Bilirubin in abdominal drain or dehiscence found at laparotomy
- **Gastro/-duodenojejunostomy leakage** Conclusive radiographic or direct visual evidence of a defect of the anastomosis
- **Intra-abdominal abscess formation** Intra-abdominal fluid collection with positive cultures identified by ultrasonography or computed tomography, associated with persistent fever and elevations of white blood cells
- **Wound infection** Requiring intervention otherwise considered as minor complication
- **Portal Vein Thrombosis** Conclusive radiologic evidence of thrombosis

Following either procedure:

- **Cholangitis** Elevation in temperature more than 38°C, thought to have a biliary cause, without concomitant evidence of acute cholecystitis, requiring intervention
- **Hemorrhage** Bleeding after the index procedure requiring transfusion of ≥4 units of packed cells within a 24-hour period, or leading to relaparotomy/intervention
- **(Emergency) (re)laparotomy** Any (other) reason following either preoperative biliary drainage or another surgical procedure
- **Pneumonia** Pulmonary infection with radiological confirmation and requiring antibiotic treatment
- **Mortality** In-hospital death, due to protocol complications or any cause, including progression of disease, within the study period