Pre-operative Biliary SEMS RCT During Neoadjuvant Therapy

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Statistical Analysis Plan

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Statistical Analysis Plan

Version AA

Randomized Controlled Trial Comparing Covered and Uncovered Biliary Self Expanding Metal Stents (SEMS) for Pre-operative Drainage During Neoadjuvant Therapy in Patients with Pancreatic Cancer

Pre-operative Biliary SEMS RCT During Neoadjuvant Therapy

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Revision History

Version AA - Initial Release

Original Release: January 23, 2015

Revision History

Revision Number/Release Date	Section	Change	Reason for Change
01	1	Changes to I/E Criteria and labs	I/E Criteria and labs updated due to PI feedback

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1 PROTOCOL SUMMARY

Full Title	Randomized Controlled Trial Comparing Covered and Uncovered Biliary Self Expanding Metal Stents (SEMS) for Pre-operative Drainage During Neoadjuvant Therapy in Patients with Pancreatic Cancer
Abbreviated Title	Pre-operative Biliary SEMS RCT During Neoadjuvant Therapy
Primary Objective	To demonstrate non-inferiority of Fully Covered biliary SEMS to Uncovered biliary SEMS in biliary drainage for the pre-operative management of biliary obstructive symptoms caused by pancreatic cancer in patients undergoing neoadjuvant therapy.
Devices	Stent Type: FC Arm: WallFlex Biliary RX Fully Covered Stent UC Arm: WallFlex Biliary RX Uncovered Stent Stent Diameter: 8mm or 10mm Stent Length: 40mm, 60mm, or 80mm The stent length will be selected to be such that the stent length should be long enough to cover the stricture completely but to leave sufficient length of normal bile duct for subsequent anastomosis.
Device Indication	The WallFlex Biliary RX Fully Covered Stent is indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms, relief of malignant biliary obstruction prior to surgery, and for treatment of benign biliary strictures. The WallFlex Biliary RX Uncovered Stent is indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms and relief of malignant biliary obstruction prior to surgery.

Study Design	Prospective, multi-center, randomized, post-market
Primary Endpoint	Successful pre-operative biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms. • For patients undergoing surgery: from stent placement until surgery • For patients transitioning to palliative management: from stent placement until transition to palliation
Secondary Endpoints	1. Occurrence and severity of adverse events related to the stent and/or stenting procedure 2. Occurrence and severity of surgical complications 3. Occurrence and severity of peri-surgical complications (up to 30 days after surgery) 4. Ability to deploy the stent in a satisfactory position across the stricture (Stent Placement Success) 5. Improvement of biliary obstructive symptoms during stent indwell at Week 1 and Monthly until surgery or transition to palliation as applicable, compared to Baseline 6. Improvement of Laboratory Liver Function Tests (LFTs) until surgery for patients undergoing surgery, and at Week 1 and Monthly until transition to palliation, and at 1 year after stent placement for patients not undergoing surgery. 7. Biliary Reintervention rate 8. Ability to complete neoadjuvant therapy as intended without stent related interruptions of neoadjuvant therapy 9. Stent migration rate 10. Assessment by surgeon of interference, if any, of SEMS on time to surgery and/or success of pancreaticoduodenectomy 11. For patients transitioning to palliative management: Successful biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms from stent placement to 1 year after stent placement

Hypothesis	Statistical testing will be performed to determine if the rate of success when using the Fully Covered SEMS is non-inferior to the rate of success when using the Uncovered SEMS. The following hypothesis will be tested: Ho: $\pi_{UC} - \pi_{FC} \geq \Delta$ (Inferior) Ha: $\pi_{UC} - \pi_{FC} < \Delta$ (Non-inferior) where π_{FC} and π_{UC} are the probabilities of having success in the WallFlex Fully Covered Stent and WallFlex Uncovered Stent arms respectively, and Δ is defined as the non-inferiority margin. The sample size was calculated for the test using an exact non-inferiority test. The assumed success rates for both study arms and the non-inferiority margin are guided by the following analysis of literature: The success rate estimate is extracted from a full literature search which yielded nine articles (377 patients) [2, 7, 21, 24, 25, 27, 29-31] on the use of metal stents for pre-operative biliary drainage. The nine articles yielded a success rate estimate of 84.6% with a 95% CI of (80.5% - 87.9%). Each arm is assumed to have a success rate of 80.5%. The non-inferiority margin (Δ) is set at 20%. Given these assumptions a sample size of 51 x 2 = 102 patients provide 80% power to reject the null hypothesis. If the p-value calculated for the test is below 0.05 it will be concluded that the test is significant, and that the WallFlex Fully Covered stent is non-inferior to the WallFlex Uncovered stent. An additional 20% of patients will be enrolled to compensate for possible loss of patients to follow-up, giving a total sample size of 122 patients.
Planned Number of Patients	122

Planned Number of Sites	6-12
Key Inclusion Criteria	1. Age 18 or older 2. Patient indicated for biliary metal stent placement for the treatment of jaundice and/or cholestasis 3. Willing and able to comply with the study procedures and provide written informed consent to participate in the study 4. Suspicion of pancreatic adenocarcinoma 5. Likely indicated for neoadjuvant treatment 6. Distal biliary obstruction consistent with pancreatic cancer 7. Location of distal biliary obstruction such that it would allow the proximal end of a stent to be positioned at least 2 cm from the hilum 8. Endoscopic and surgical treatment to be provided at the same institution
Key Exclusion Criteria	1. Benign biliary strictures 2. Malignancy secondary to Intraductal Papillary Mucinous Neoplasm 3. Surgically altered anatomy where ERCP is not possible 4. Previous biliary drainage using a SEMS or multiple plastic stents 5. Contraindications for endoscopic techniques 6. Patients who are currently enrolled in another investigational trial that would directly interfere with the current study 7. Pregnancy
Visits	• Screening • Baseline • Stent Placement Procedure Visit • Pre-Operative Follow-Up Visit (Week 1 and Monthly until Surgery or Transition to Palliation) • Biliary Reintervention Visit (as needed) • Curative Intent Surgery • Transition to Palliative Management Visit (as needed)

	• Post-Operative Follow-Up Visit (30 day Post-Surgery visit) • Long Term Follow-Up Visit (1 year after initial treatment for patients that have transitioned to palliation or 1 year post-stent placement for patients that have not undergone surgery or transitioned to palliation (with or without Neoadjuvant Therapy))

2 INTRODUCTION

This statistical plan addresses the planned analyses for the Preoperative Biliary SEMS RCT in Neoadjuvant Therapy based on the protocol dated 17 November 2014, Version AD. All of the specified analyses may not be provided in reports to Competent Authorities but may be used for scientific presentations and/or manuscripts.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

Successful pre-operative biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms.

- For patients undergoing surgery: from stent placement until surgery
- For patients transitioning to palliative management: from stent placement until transition to palliation

3.1.1 Hypotheses

Compared to the use of an Uncovered SEMS, use of a Fully Covered SEMS may present a higher risk of migration, but offers the ability to remove the stent were this deemed indicated by the treating endoscopist. Statistical testing will be performed to determine if the rate of success when using the Fully Covered SEMS is non-inferior to the rate of success when using the Uncovered SEMS. The following hypothesis will be tested:

$Ho: \pi_{UC} - \pi_{FC} \geq \Delta$ (Inferior)
$Ha: \pi_{UC} - \pi_{FC} < \Delta$ (Non-inferior)

where π_{FC} and π_{UC} are the probabilities of having success in the WallFlex Fully Covered Stent and WallFlex Uncovered Stent arms respectively, and Δ is defined as the non-inferiority margin.

3.1.2 Sample Size

The sample size was calculated for the test using an exact non-inferiority test in StatXact 9® software. The non-inferiority margin (Δ) is set at 20%. Each arm is assumed to have a success rate of 80.5%, which is the lower 95% CI boundary from the meta-analysis, which is done below. Given these assumptions a sample size of 51 x 2 = 102 patients provides 80% power to reject the null hypothesis listed above. If the p-value calculated for the test is below 0.05 it will be concluded that the test is significant and that the WallFlex Fully Covered stent is non-inferior to the WallFlex Uncovered stent.

In order to compensate for possible loss of patients to follow-up or per Endoscopist's decision to select the Uncovered stent based on ductal anatomy, namely stricture involving the lower cystic duct confluence, but randomized to Fully Covered, an additional 20% of patients will be enrolled giving a total sample size of 122 patients.

The success rate estimate is extracted from a full literature search which yielded nine articles (377 patients) [2, 7, 21, 24, 25, 27, 29-31] on the use metal stents for pre-operative biliary drainage. The nine articles yielded a success rate estimate of 84.6% with a 95% CI of (80.5%, 87.9%).

3.1.3 Statistical Methods

The distribution of prognostic factors between patients with and without data will be examined on the primary endpoint. Statistical models that account for censored data may be employed in appropriate circumstances, e.g. for time-to-event outcomes. Sensitivity analyses will be conducted to assess the impact of missing data on the interpretation of the results, e.g. a tipping point analysis.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

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

Enrolled Cohort

A patient is considered "enrolled" after signing the study-specific ICF. Patients who sign the ICF but subsequently do not meet one or more of the eligibility criteria provided in Section 5.1 and Section 5.2 of the protocol 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 patients who are treated per protocol and have no major protocol deviations (per ICH E9 definitions).

5 ADDITIONAL DATA ANALYSES

5.1 Secondary Endpoints

1. Occurrence and severity of adverse events related to the stent and/or stenting procedure
2. Occurrence and severity of surgical complications
3. Occurrence and severity of peri-surgical complications (up to 30 days after surgery)
4. Ability to deploy the stent in satisfactory position across the stricture (Stent Placement Success)
5. Improvement of biliary obstructive symptoms during stent indwell at Week 1 and Monthly until surgery or transition to palliation as applicable, compared to Baseline
6. Improvement of Laboratory Liver Function Tests (LFTs) until surgery for patients undergoing surgery, and at Week 1 and Monthly until transition to palliation, and at 1 year after stent placement for patients not undergoing surgery
7. Biliary Reintervention rate
8. Ability to complete neoadjuvant therapy as intended without stent related interruptions of neoadjuvant therapy
9. Stent migration rate
10. Assessment by surgeon of interference, if any, of SEMS on time to surgery and/or success of pancreaticoduodenectomy
11. For patients transitioning to palliative management: Successful biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms from stent placement to 1 year after stent placement

5.2 Baseline Data

Patient demographics, clinical history, risk factors, obstructive symptoms, LFTs, tumor diagnosis, patient overall health, neoadjuvant therapy, and assessment of tumor invasion will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables 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

Stratified analyses will include tabulating the primary endpoint and select secondary endpoints by patients that undergo potentially curative surgery versus transition to palliation, by bilirubin level above or below 3 mg/dL, and gender.

5.5 Justification of Pooling

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

5.6 Multivariable Analysis

Univariate and multivariate analyses may be performed to assess the effect of potential predictors on the primary endpoint using logistic regression or Cox Proportional Hazards regression.

Variables from the following categories will be considered as possible predictors: demographics, tumor diagnosis, baseline LFTs, neoadjuvant therapy protocol, obstructive symptoms, baseline health status, and medical history. Factors from the univariate model 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 $p \leq 0.10$, with treatment assignment being manually kept in the model regardless of p-value.

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 by AE interaction.

5.9 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). For the primary endpoint analysis, StatXact 9® software can be used since SAS does not provide exact non-inferiority analysis as of the writing of this SAP.

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.

Successful pre-operative biliary drainage defined as absence of reinterventions for the management of biliary obstructive symptoms.

- For patients undergoing surgery: from stent placement until surgery
- For patients transitioning to palliative management: from stent placement until transition to palliation

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