STATISTICAL ANALYSIS PLAN

PROTOCOL: PP PLR 03

A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes with PINPOINT® Near Infrared Fluorescence Imaging in Low Anterior Resection (PILLAR III).

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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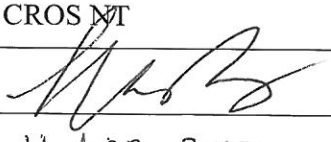
Signature:		
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Contents

Abbreviations

ADE	Adverse device effect
AE	Adverse event
AR	Anterior Resection
ASA	American Society of Anesthesiologists
AT	As-Treated
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computerized Tomography
DSMC	Data and Safety Monitoring Committee
DRSI	Disposable Rigid Scope Introducer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HD	High Definition
IA	Imaging Agent
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
ICG	Indocyanine Green
IMA	Inferior Mesenteric Artery
IMV	Inferior Mesenteric Vein
IPAA	Ileal Pouch – Anal Anastomosis
IR	Independent Radiologist
IRB	Institutional Review Board
IV	Intravenous
LAR	Low Anterior Resection
MELD	Model for End-Stage Liver Disease
mITT	Modified Intent-to-Treat
NGT	Nasogastric Tube
NIR	Near-Infrared
NPO	Nil per Os
PFN	Perfusion
PILLAR II	Perfusion Assessment in Laparoscopic Left Anterior Resection Multicenter study
PINPOINT	PINPOINT Endoscopic Fluorescence Imaging System
PO	Per Os

POD	Post-operative Day
PP	Per-Protocol
PSG	PILLAR III Study Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STD	Standard
US	United States
UADE	Unanticipated Adverse Device Effect
VIS	Visible

Revision History

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0.1	Original based on Protocol version 1.4	07 Nov 2016
1.0	Final	10 Apr 2017

1. Introduction

This study will investigate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT endoscopic fluorescence imaging (PINPOINT) or SPY Elite intraoperative imaging in reducing the post-operative anastomotic leak rate in low anterior resection (LAR).

2. Study Objectives

Primary objective is to demonstrate an improvement in post-operative anastomotic leak rate in low anterior resection procedures where colon and rectal tissue perfusion is evaluated using PINPOINT® endoscopic fluorescence imaging or SPY Elite® Intraoperative Imaging as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone.

Secondary objectives are the following:

- To evaluate the ability of the PINPOINT system or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure.
- To evaluate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT or SPY Elite in reducing the rate of post-operative abscess requiring surgical management.

3. Study Design

3.1 General design and plan

This is a randomized, controlled, parallel, multicenter study to determine the reduction in post-operative anastomotic leak rate in low anterior resection (LAR) procedures where colon and rectal tissue perfusion is evaluated using PINPOINT or SPY Elite as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone. Subjects will be enrolled at up to 40 centers in North America through March 31, 2017. The study sample size will depend on the number of subjects enrolled.

3.2 Visit Schedule and Visit Windows

Baseline/Screening Procedures (Day -30 to Day 0)

After signing the informed consent form, subjects will be assigned a screening and be evaluated for eligibility into the study.

The following procedures will be conducted during the baseline assessment:

- Collection of demographics, surgical risk factors, pre-operative diagnosis.
- Vital signs (heart rate and blood pressure), height and weight.
- Serum tests (bilirubin,sodium,creatinine and INR) for MELD Score.
- Pregnancy test (urine test or institution standard of care) for females of childbearing potential.

Day 0 Procedures

On Day 0, the following will be completed before randomization and surgery:

- Serum hemoglobin, prealbumin, and albumin measurement.

During anesthesia, subjects will be randomized. Subjects are considered enrolled upon randomization.

According to the randomization assignment, subjects in the PERFUSION arm will receive perfusion assessment with PINPOINT and/or SPY Elite during surgery and undergo surgery according to the surgeon's standard practice. Subjects randomized to the Standard arm will undergo the surgery according to the surgeon's standard practice only. All subjects will receive the hospital/institution and surgeon's standard pre-operative and post-operative care with the addition of any study specific requirements.

An intra-operative measurement of hemoglobin should be performed at the time of anastomosis if the subject experiences a hypotensive event requiring intraoperative management (e.g. use of vasopressors) or blood loss greater than 500 ml at the time of anastomosis.

Post-operative Follow-up Visits (Day 1 to Last Study Visit)

Subjects will have standard of care assessments throughout the study according to the hospital/institutions standard procedures as well as study specific visits on postoperative Day 1, the date of discharge, Week 8 (56 ±14 days) and the date of ileostomy closure, if applicable. Subjects will be assessed for the following throughout the study:

- Serum hemoglobin measurement (Day 1).
- Evidence of anastomotic leak.
- Assessment and grading of post-operative complications.
- Concomitant medications and procedures.
- Adverse events/adverse device effects.

Subjects with a discharge date later than Week 8, who did not have an ileostomy, will have the last study visit on Week 8 ±14 days.

Diverted patients should receive routine endoscopic and/or contrast enema evaluation of the anastomotic region, between 3 weeks post-surgery and the Week 8 visit.

Subjects who present with a clinical suspicion of anastomotic leak during the study will have a CT scan with PO and, if necessary (e,g., presence of a diverting ileostomy), rectal contrast to confirm.

Table 1 below presents the schedule of events for this study.

Table 1: Schedule of Assessments

Procedure	Baseline (Day -30 to Day 0)	Day 0 (Operative Phase)			Post-Operative Follow-Up			
		Pre-Op	Intra-Op	Post-Op	Day 1 (24±12 hrs.)	Date of Discharge[a]	Ileostomy Endoscopy/ Contrast Enema (Week 3 to Week 8 ±14d)	Week 8 (56±14d)
Informed consent	X							
Demography	X							
Vital signs, height, weight	X							
Surgical risk factors	X							
Pre-operative diagnosis	X							
Pregnancy test (record in source only)	X							
Inclusion/exclusion criteria	X							
Serum sodium, bilirubin, creatinine and INR for MELD Score	X							
Hemoglobin, Albumin, Pre-albumin		X	X[c]		X			
Randomization (in OR, during anesthesia)			X					
LAR surgical procedure			X					
Imaging agent administration (treatment group only)			X					
Perfusion Assessment (Perfusion arm only) Proximal transection margin Mucosal aspect of completed anastomosis			X					
Document actual surgical technique				X				
Anastomotic leak assessment				X	X	X		X
Surgical Complication assessment/grading			X	X	X	X		X
Endoscopy and/or contrast enema - Ileostomy subjects (between 3 & 8 wks.)							X[b]	
Concomitant medications and procedures	X	X	X	X	X	X		X
Adverse events/adverse device effects		X	X	X	X	X		X[d]

a Subjects with a discharge date later than Week 8, who did not have an ileostomy, will be followed until Week 8 ±14d.
b All subjects with a diverting ileostomy must have endoscopy and/or contrast enema between 3 weeks post-surgery and the Week 8 visit.
c Hemoglobin measurement at time of anastomosis if subject had any hypotensive events or blood loss over 500 ml at time of anastomosis
d All subjects with adverse events thought to be related to the LAR will be followed until resolution or deemed chronic.

3.3 Sample size justification

The sample size for this study will include all subjects enrolled through March 31, 2017. No formal sample size calculations were carried out for this study.

3.4 Randomization and blinding

Patients will be prospectively randomized into the PILLAR III Clinical Trial. Randomization will occur at the time of surgery, just after induction of anesthesia. Prior to surgery the patient will have provided written informed consent, completed all baseline procedures and met the requirements of the study inclusion and exclusion criteria. Randomization should be performed as closely as possible to the point of resection to minimize the incidence of dropout.

Patients will be randomly assigned on a one to one (1:1) basis to either the PERFUSION group (PFN) or the STANDARD group (STD). Randomization will be stratified by study site and within site by the patients history of prior neoadjuvant therapy (chemotherapy and/or radiation vs. non-neoadjuvant therapy) to ensure a more even distribution of baseline neoadjuvant therapy between treatment groups. Permuted block randomization will be performed within strata. To minimize the opportunity for the sequence to be predicted, the block size will be variable and randomly chosen from small multiples of 2 (i.e. 2, 4 or 6). The randomization schedules for all strata will be generated in advance by the contracted study statistician or designee using a computerized random number generator. Investigational sites and the Study Sponsor will not have access to the randomization schedules.

Randomization will be accomplished using a sequential numbered sealed envelope system. Due to stratification for prior neoadjuvant therapy, a box of envelopes will be supplied for each strata (one for subjects who have received prior neoadjuvant therapy and another for subjects who have not received prior neoadjuvant therapy). Envelope seals are broken and treatment assignment is made only after verification of proper informed consent execution and study eligibility. In order to prevent any attempts to subvert the randomization process, the subject's initials, date of birth, and date of randomization will be written on the randomization card. The randomization card will be signed by the study coordinator performing the randomization procedure and a second researcher who will witness the randomization procedure.

In the event of the subjects not following the randomization plan, selection bias would occur. In this situation, a conservative approach would be taken, where safety analyses would be carried out using actual treatment while efficacy analyses carried out using planned treatment. Such subjects will be documented.

In the event of subjects opting out of randomization in favor of the investigational product, sampling bias would occur. These subjects would not be included in the analyses, thus, skewing the results such that they would not be representative of the true population. If sicker patients were to select the investigational product and not be included in the analysis, the results would represent a less sick population than that of the true population.

3.5 Efficacy endpoints

3.5.1 Primary endpoint

Incidence of post-operative anastomotic leak in each study arm.

3.5.2 Secondary efficacy endpoints

- Proportion of PERFUSION arm subjects in whom the PINPOINT or SPY Elite system provided sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure.
- Incidence of post-operative abscess in each study arm.

3.6 Safety endpoints

- Incidence of treatment related adverse device events and surgical complications.
- Clavien-Dindo grading of post-operative complications.
- Concomitant medications and procedures.

4. Statistical Analysis

4.1 General

Categorical variables will be summarized with the number and percent of subjects in each group. Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum values. 95% confidence intervals will be calculated for the primary and secondary endpoints.
All data collected in the CRF will be presented in the listings.

4.2 Analysis sets

4.2.1 Screened

Subjects considered potential candidates for the study based on pre-screening will sign an IRB/EC approved Informed Consent Form (ICF) prior to any study activities. The Investigator or delegated study research staff may then complete the first study visit with the subject.

4.2.2 Randomized

The randomized population includes all randomized subjects.

4.2.3 Modified Intent-to-Treat (mITT)

The mITT analysis population includes all randomized subjects in whom a low anterior resection surgical procedure is initiated or at least one injection with ICG was performed. Subjects who have the surgical resection procedure aborted due to circumstances such as a higher stage cancer than initially anticipated will not be included in the mITT population. Subjects will be analyzed according to their randomized group assignment. The mITT population will be used for all efficacy analyses.

4.2.4 As-Treated (AT)

The As-Treated (AT) analysis population includes all randomized subjects in whom the intended open, or minimally invasive low anterior resection surgical procedure and, if assigned to the PERFUSION arm, PINPOINT or SPY Elite NIR fluorescence imaging with at least one perfusion assessment using ICG was successfully performed. Subjects in whom the intended surgical procedure is not performed or imaging with PINPOINT or SPY Elite was not successful are excluded from the AT population. mITT subjects not included in the AT population will be followed in the same manner as mITT subjects who do meet AT population inclusion criteria. Subjects will be analyzed according to the treatment actually received.

The AT population will be used for a secondary analysis of the primary endpoint.

4.2.5 Per-protocol (PP)

The Per-protocol (PP) population will consist of all AT subjects that: [1] meet critical study eligibility criteria; [2] have no significant protocol deviations; and [3] have evaluable assessment for the primary study endpoint.

The PP population will be used for subset analysis of the primary endpoint.

4.2.6 Safety

The safety analysis population includes all randomized subjects. Secondary safety endpoints including the summary of adverse events in the trial will be analyzed using this analysis population, divided into groups according to actual use or non-use of PINPOINT and SPY Elite.

4.3 Pooling of sites

The homogeneity of effectiveness results across study sites will be examined and if no significant heterogeneity is found, the results will be pooled. A logistic regression will be employed modeling the proportion of subjects with post-operative anastomotic leak with treatment, center, and treatment by center interaction as fixed effects. If treatment by center interaction is not significant when compare to an alpha of .05, it can be determined that there is no heterogeneity of treatment effect across centers. It is not anticipated that any individual study site will dominate the study results. Therefore, it is believed that the data from these study sites can be combined and analyzed as if generated at a single site.

4.4 Handling of missing and incomplete data

The number of patients with missing data will be presented under the "Missing" category, if present. Missing values will be included in the denominator count when computing percentages.

When continuous data are being summarized, only the non-missing values will be evaluated for computing summary statistics.

A sensitivity analysis will also occur for the primary endpoint via a tipping point analysis. All missing data in the treatment group will be counted as failures while all missing data in the control group will be counted as successes. The p-values will be compared to the primary efficacy analysis to see if there is a difference in interpretation of results.

In general partial dates will be imputed as follows:

- if only the day is missing, the first day of the month will be assumed;
- if the day and the month are missing, January 1st will be assumed;
- if a date is completely missing or unknown the patient's data will not be included for analysis

4.5 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.2) on a Windows 7 or later operating system.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

The number of patients included in the randomized population, mITT, PP, safety, and AT populations will be also summarised.

5.2 Protocol violations

A protocol deviation is an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol.
Deviations will be collected in the CRF and assessed according to the following categories:

- Intentional change to eliminate immediate hazard;
- Consent deviation (oral or written);
- Drug/device administration deviation 8dosage, operation, schedule etc.);
- Enrollment deviation (inclusion/exclusion criteria, recruitment, etc.);
- Procedural deviation (research activities, research reporting etc);
- Subject non-compliance;
- Complaint from research subject;
- Audit finding that require corrective action;
- Failure to report AE and/or follow data/safety reporting procedures;

- Breach of confidentiality
- Other.

During data review process before the database lock, protocol deviations will be classified as major protocol deviation and minor protocol deviation.
Major and minor protocol deviations will be summarized for each treatment arm and overall. Major deviations from the protocol will lead to the exclusion of the patient from the PP population.

5.3 Study discontinuations

Patients discontinued from the study prematurely will be presented for the randomized patients, with a breakdown of the reasons for discontinuation as reported in the CRF.

5.4 Demographics and baseline characteristics

The demographic and baseline characteristics will be summarised by treatment arm and overall by means of descriptive statistics.
The following demographic characteristics will be provided for the randomized patients:

- Age, gender, race, surgical risk factors, pre-operative diagnosis.
- Vital signs (heart rate and blood pressure), height and weight.
- Serum tests (total bilirubin, creatinine, serum sodium and INR) for MELD Score.
- Pregnancy test (urine test or institution standard of care) for females of childbearing potential.

5.5 Medical History

Medical history and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary (version 18.0) and frequency distributions and percentages will be summarised by treatment and overall for the randomised patients by SOC and PT.

5.6 Prior and concomitant medications

Any concomitant medications the subject is receiving at the start of the study (Day 0) or given for any reason during the study will be summarised by treatment and overall for the safety population through frequency distributions and percentages by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (2nd level of ATC classification) and Preferred Name.

6. Evaluation of Efficacy

6.1 Analysis of primary endpoint

The primary objective is to demonstrate an improvement in post-operative anastomotic leak rate in low anterior resection procedures where colon and rectal tissue perfusion is evaluated using PINPOINT or SPY Elite near infrared fluorescence imaging as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone.

$$H_0: p_t = p_c$$
$$H_1: p_t < p_c$$

Where p_t and p_c represent the expected population incidences of post-operative anastomotic leaks in the treatment (PERFUSION) and control groups, respectively. Within their respective treatment groups, p_t and p_c will be estimated as the number of subjects who experience a post-operative anastomotic leak divided by the number of subjects who either are included in the numerator or are known to be free of such leaks as of the 8 weeks visit. Subjects without a known anastomotic leak but with less than 6 weeks of follow-up (i.e., insufficient follow-up to declare them "leak-free") will not be included in these estimates.

Analysis of these hypotheses will be conducted using a z-test (i.e., normal approximation to the binomial distribution, using a pooled variance estimate and without continuity correction), using a (one-sided) significance level of 0.025.

A secondary analysis of the primary endpoint will be carried out on the As-treated population as well as on the PP population.

6.2 Analysis of secondary efficacy endpoints

The secondary efficacy endpoints are:

- To evaluate the ability of the PINPOINT system or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure.
    - This will be analyzed by comparing the PERFUSION-group proportion of subjects for whom there was sufficient visualization for assessment of blood flow and related tissue perfusion to a predetermined proportion, eg. 0.9.
- To evaluate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT or SPY Elite in reducing the rate of post-operative abscess requiring surgical management.
    - This will be analyzed by comparing the treatment group and control group incidence of post-operative operative abscess requiring surgical management

These objectives are intended to support product labeling and will be tested in sequential fashion, i.e., if and only if the primary objective passes, testing will proceed to the first secondary objective below (proportion of PERFUSION arm subjects in whom the PINPOINT or SPY Elite system provided sufficient visualization for assessment of blood flow and related tissue perfusion during

the procedure). If and only if that objective passes, testing will proceed to the second secondary objective (incidence of abscess requiring surgical management). The standard for "passing" the secondary objectives will be a p-value less than 0.025 one sided.

To evaluate the ability of the PINPOINT or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure:

The statistical threshold for study success will be sufficient visualization for assessment of blood flow and related tissue perfusion in greater than 90% of subjects. Letting p_t represent the PERFUSION-group proportion of subjects for whom there was sufficient visualization for assessment of blood flow and related tissue perfusion, the following hypotheses will be tested:

$$H_0: p_t \leq 0.9$$
$$H_1: p_t > 0.9$$

The statistical test will be a one-sided exact binomial test of proportions. Descriptive statistics and 95% confidence intervals will be calculated for p_t.

To evaluate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT or SPY Elite in reducing the incidence of post-operative abscess requiring surgical management:

Letting p_t and p_c respectively represent the treatment-group and control-group incidence of post-operative abscess requiring surgical management, the following hypotheses will be tested:

$$H_0: p_t = p_c$$
$$H_1: p_t < p_c$$

The statistical test will be a z-test using pooled variance estimate and no continuity correction. In the case of small counts, an exact procedure will be used. Descriptive statistics and 95% confidence intervals will be calculated for p_t, p_c, and $(p_t - p_c)$.

Then secondary efficacy endpoints will be analyzed on the mITT population.

7. Evaluation of Safety

The number of AEs, ADEs, SAEs, UADEs, and the number and the percentage of patients experiencing AEs, SAEs, ADEs, UADEs will be presented for the safety set.

AEs will be coded using the MedDRA dictionary (version 18.0). The SOCs and PTs will be used for tabulation.

The number of AEs and the number and the percentage of patients with at least one AE will be presented by SOC and PT for AEs, SAEs.

All adverse events and post-operative complications occurring during the study period will be graded according to the Clavien-Dindo classification system.

The number and the percentage of patients with at least one AE and ADE will be presented by SOC, PT and Clavien-Dindo classification system.

7.1 Adverse events (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in subjects whether or not related to the investigational medical device.

7.2 Adverse Device Effect (ADE)

Any adverse event related to the use of PINPOINT or SPY Elite (includes imaging agent and all hardware components).

7.3 Serious Adverse Event (SAE)

Any adverse event that:
a. Led to a death.

b. Led to a serious deterioration in health that either:

i. Resulted in a life-threatening illness or injury,

ii. Resulted in a permanent impairment of a body structure or a body function,

iii. Required in-patient hospitalization or prolongation of existing hospitalization,

iv. Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

7.4 Unanticipated Adverse Device Effect (UADE)

Any ADE that meets the following:

- By its nature, incidence, severity or outcome has not been identified in the current version of the PINPOINT (or SPY Elite if applicable) risk analysis report.

- On health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or

degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.